

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020759/020760

Trade Name: TROVAN TABLETS AND TROVAN I.V.

**Generic Name: TROVAFLOXACIN MESYLATE AND
ALATROFLOXACIN MESYLATE INJECTION**

Sponsor: PFIZER CENTRAL RESEARCH

Approval Date: 12/18/97

Indication(s): TREATMENT OF INFECTIONS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: : 020759/020760

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology	X			
Biopharmaceutics Review(s)				
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020759/020760

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-759
NDA 20-760

20-759
20-760

DEC 18 1997

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Ronald I. Trust, Ph.D., M.B.A.
Associate Director
Regulatory Affairs - Liaison
Pfizer Central Research
Eastern Point Road
Groton, CT 06340

Dear Dr. Trust:

Please refer to your new drug applications (NDAs) submitted December 27, 1996 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TROVAN® Tablets (trovafloxacin mesylate) 100 mg and 200 mg, NDA 20-759; and TROVAN® I.V. (alatrofloxacin mesylate injection) 200 mg and 300 mg, NDA 20-760.

We acknowledge receipt of your amendments dated January 13, 20, and 28, February 10, March 17, April 3, 25, and 28, July 23, August 15 and 26, September 18, 22, and 25, October 9, 10, 13, 17, 21, 23, and 29, November 14, 19, 20, and 21, December 2, 3, 4, 5, 9, 11, and 12, 1997.

The user fee goal date is December 30, 1997.

We also acknowledge receipt of your letter dated October 13, 1997 requesting withdrawal of the

These new drug applications request approval of the following indications:

1. Nosocomial pneumonia
2. Community-acquired pneumonia
3. Acute bacterial exacerbation of chronic bronchitis
4. Acute sinusitis
5. Uncomplicated skin and skin structure infections
6. Complicated skin and skin structure infections, including diabetic foot infections
7. Complicated intra-abdominal infections, including post-surgical infections
8. Complicated gynecologic and pelvic infections, including post-surgical infections
9. Surgical prophylaxis - elective colorectal surgery
10. Surgical prophylaxis - elective abdominal and vaginal hysterectomy

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11. Acute uncomplicated gonorrhea
12. Non-gonococcal urethritis and cervicitis
13. Bacterial prostatitis
14. Uncomplicated urinary tract infections including cystitis

16. Pelvic inflammatory disease

We have completed the review of these applications, including the submitted draft labeling as amended on December 18, 1997, and have concluded that adequate information has been presented to demonstrate that these drug products are safe and effective for use as recommended in the revised draft labeling dated December 18, 1997 (enclosed). Accordingly, these applications are approved effective on the date of this letter.

The data submitted are inadequate to support the use of TROVAN in the treatment of patients with

Before these indications may be approved, under 21 CFR 314.725(b)(5) and 314.126, you need to submit data from adequate and well controlled studies demonstrating that the drug is safe and effective for these uses.

The final printed labeling (FPL) for these drug products must be identical to the enclosed labeling. Marketing these products with FPL that is not identical to this labeling may render these products misbranded and unapproved new drugs.

Please submit 25 copies of the FPL to each application as soon as they are available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes these submissions should be designated "**FINAL PRINTED LABELING**" for approved NDA 20-759, NDA 20-760. Approval of these submissions by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of these drugs become available, revision of the labeling may be required.

We remind you of your Phase 4 commitments specified in your letter dated December 18, 1997. These commitments, along with any completion dates agreed upon, are listed below:

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Protocols, data, and final reports should be submitted to the appropriate INDs for these products and a copy of the cover letter sent to the corresponding NDAs. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to these NDAs as correspondence. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to the appropriate applications (NDAs) a status summary of each commitment. The status summary should include information on each study, expected completion and submissions dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, resulting to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

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In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Special Pathogens and Immunologic Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the methods have not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

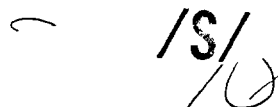
Please submit one market package of each drug product when available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have questions, please contact:

Ms. Pauline Fogarty
Regulatory Health Manager
(301) 827-2125

Sincerely yours,


David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

12-18-97

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020759/020760

FINAL PRINTED LABELING

(FINAL: 18-DEC-1997)
 [insert package insert code here]
 TROVAN™ Tablets
 (trovafloxacin mesylate)
 TROVAN™ I.V.
 (alatrofloxacin mesylate injection)
 For Intravenous Infusion

DEC 18 1997

APPROVED

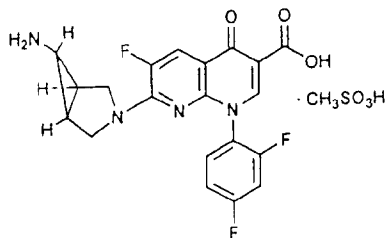
TROVAN is available as TROVAN Tablets (trovafloxacin mesylate) for oral administration and as TROVAN I.V. (alatrofloxacin mesylate injection), a prodrug of trovafloxacin, for intravenous administration.

DESCRIPTION

TROVAN Tablets

TROVAN Tablets contain trovafloxacin mesylate, a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, trovafloxacin mesylate, a fluoronaphthyridone related to the fluoroquinolone antibacterials, is (1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate. Trovafloxacin mesylate differs from other quinolone derivatives by having a 1,8-naphthyridine nucleus.

The chemical structure is:



Its empirical formula is $C_{20}H_{15}F_3N_4O_3 \cdot CH_3SO_3H$ and its molecular weight is 512.46.

Trovafloxacin mesylate is a white to off-white powder.

Trovafloxacin mesylate is available in 100 mg and 200 mg (trovafloxacin equivalent) blue, film-coated tablets. TROVAN Tablets contain microcrystalline cellulose, crosslinked sodium carboxymethylcellulose and magnesium stearate. The tablet coating is a mixture of hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol and FD&C blue #2 aluminum lake.

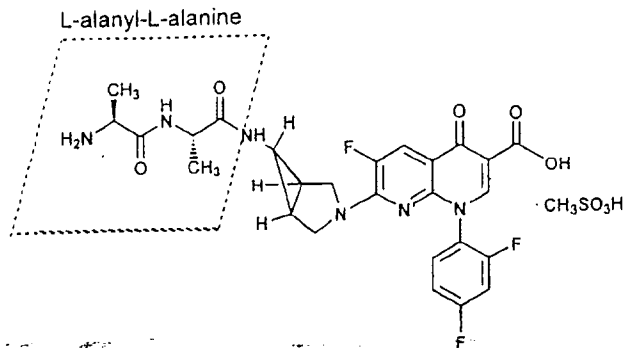
TROVAN I.V.

TROVAN I.V. contains alatrofloxacin mesylate, the L-alanyl-L-alanyl prodrug of trovafloxacin mesylate. Chemically, alatrofloxacin mesylate is (1 α , 5 α , 6 α)-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate. It is intended for administration by intravenous infusion.

Following intravenous administration, the alanine substituents in alatrofloxacin are rapidly hydrolyzed *in vivo* to yield trovafloxacin. (See CLINICAL PHARMACOLOGY)

The chemical structure is:

47



48

49

Its empirical formula is C₂₆H₂₅F₃N₆O₅ • CH₃SO₃H and its molecular weight is 654.62.

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Alatrofloxacin mesylate is a white to light yellow powder.

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TROVAN I.V. is available in 40 mL and 60 mL single use vials as a sterile, preservative-free aqueous concentrate of 5 mg trovafloxacin/mL as alatrofloxacin mesylate intended for dilution prior to intravenous administration of doses of 200 mg or 300 mg of trovafloxacin, respectively. (See HOW SUPPLIED.)

The formulation contains Water for Injection, and may contain sodium hydroxide or hydrochloric acid for pH adjustment.

The pH range for the 5 mg/mL aqueous concentrate is 3.5 to 4.3.

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CLINICAL PHARMACOLOGY

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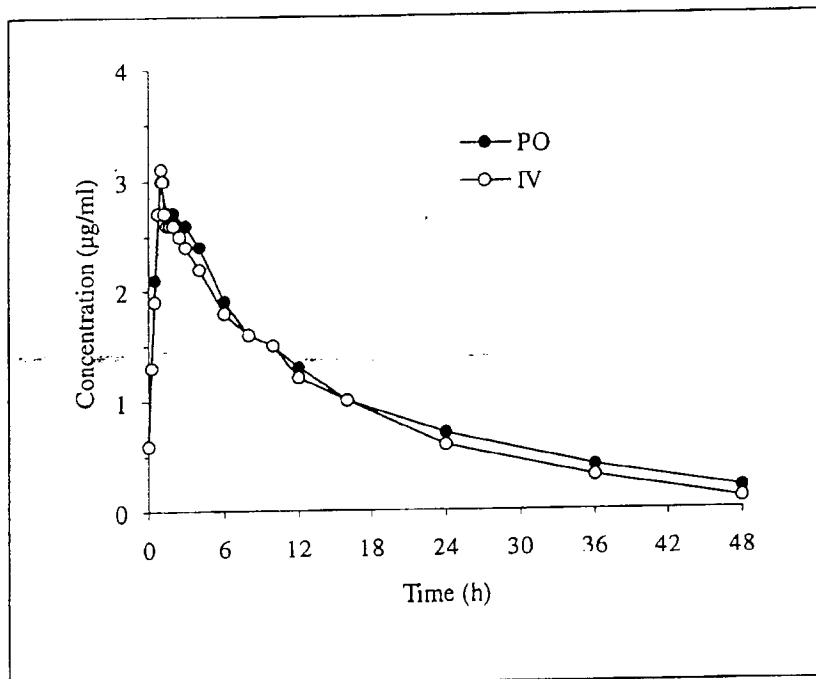
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71

After intravenous administration, alatrofloxacin is rapidly converted to trovafloxacin. Plasma concentrations of alatrofloxacin are below quantifiable levels within 5 to 10 minutes of completion of a one hour infusion.

Absorption

Trovafloxacin is well-absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 88%. For comparable dosages, no dosage adjustment is necessary when switching from parenteral to oral administration (Figure 1). (See DOSAGE AND ADMINISTRATION.)



72 Figure 1. Mean trovafloxacin serum concentrations determined following 1 hour intravenous infusions of
 73 alatrofloxacin at daily doses of 200 mg (trovafloxacin equivalents) to healthy male volunteers and following daily
 74 oral administration of 200 mg trovafloxacin for seven days to six male and six female healthy young volunteers.
 75

76 Pharmacokinetics

77 The mean pharmacokinetic parameters ($\pm$ SD) of trovafloxacin after single and multiple
 78 100 mg and 200 mg oral doses and one hour intravenous infusions of alatrofloxacin in
 79 doses of 200 and 300 mg (trovafloxacin equivalents) appear in the chart below.
 80

	TROVAFLOXACIN PHARMACOKINETIC PARAMETERS						
	C_{max} (μ g/mL)	T_{max} (hrs)	AUC ^{1,2} (μ g·h/mL)	$T_{1/2}$ (hrs)	V_{dss} (L/Kg)	CL (mL/hr/Kg)	CL_r (mL/hr/Kg)
<u>Trovafloxacin 100 mg</u>							
Single dose	1.0 $\pm$ 0.3	0.9 $\pm$ 0.4	11.2 $\pm$ 2.2	9.1	---	---	---
Multiple dose	1.1 $\pm$ 0.2	1.0 $\pm$ 0.5	11.8 $\pm$ 1.8	10.5	---	---	---
<u>Trovafloxacin 200 mg</u>							
Single dose	2.1 $\pm$ 0.5	1.8 $\pm$ 0.9	26.7 $\pm$ 7.5	9.6	---	---	---
Multiple dose	3.1 $\pm$ 1.0	1.2 $\pm$ 0.5	34.4 $\pm$ 5.7	12.2	---	---	---
<u>Alatrofloxacin 200 mg*</u>							
Single dose	2.7 $\pm$ 0.4	1.0 $\pm$ 0.0	28.1 $\pm$ 5.1	9.4	1.2 $\pm$ 0.2	93.0 $\pm$ 17.4	6.5 $\pm$ 3.5
Multiple dose	3.1 $\pm$ 0.6	1.0 $\pm$ 0.0	32.2 $\pm$ 7.3	11.7	1.3 $\pm$ 0.1	81.7 $\pm$ 17.8	8.6 $\pm$ 2.4
<u>Alatrofloxacin 300 mg*</u>							
Single dose	3.6 $\pm$ 0.6	1.3 $\pm$ 0.4	46.1 $\pm$ 5.2	11.2	1.2 $\pm$ 0.1	84.6 $\pm$ 6.0	6.9 $\pm$ 0.5
Multiple dose	4.4 $\pm$ 0.6	1.2 $\pm$ 0.2	46.3 $\pm$ 3.9	12.7	1.4 $\pm$ 0.1	84.5 $\pm$ 11.1	8.4 $\pm$ 1.8

81 *trovafloxacin equivalents

82 ^{1,2} Single dose: AUC(0- ∞), multiple dose: AUC(0-24)

83 C_{max} = Maximum serum concentration; T_{max} =Time to C_{max} ; AUC=Area under concentration vs. time curve.
 84 $T_{1/2}$ =serum half-life; V_{dss} =Volume of distribution; CL=Total clearance; CL_r =Renal clearance

85
 86 Serum concentrations of trovafloxacin are dose-proportional after oral administration of
 87 trovafloxacin in the dose range of 30 to 1000 mg or after intravenous administration of

88 alatrofloxacin in the dose range of 30 to 400 mg (trovafloxacin equivalents). Steady state
89 concentrations are achieved by the third daily oral or intravenous dose of trovafloxacin with
90 an accumulation factor of approximately 1.3 times the single dose concentrations. -

91
92 Oral absorption of trovafloxacin is not altered by concomitant food intake; therefore, it can
93 be administered without regard to food.

94
95 The systemic exposure to trovafloxacin ($AUC_{0-\infty}$) administered as crushed tablets via
96 nasogastric tube into the stomach was identical to that of orally administered intact tablets.
97 Administration of concurrent enteral feeding solutions had no effect on the absorption of
98 trovafloxacin given via nasogastric tube into the stomach. When trovafloxacin was
99 administered as crushed tablets into the duodenum via nasogastric tube, the $AUC_{0-\infty}$ and
100 peak serum concentration (C_{max}) were reduced by 30% relative to the orally administered
101 intact tablets. Time to peak serum level (T_{max}) was also decreased from 1.7 hrs to 1.1
102 hrs..
103

104 **Distribution**

105 The mean plasma protein bound fraction is approximately 76%, and is concentration-
 106 independent. Trovafloxacin is widely distributed throughout the body. Rapid distribution of
 107 trovafloxacin into tissues results in significantly higher trovafloxacin concentrations in most
 108 target tissues than in plasma or serum.

109	<u>Fluid or Tissue</u>	Tissue-Fluid/ Serum Ratio* (Range)
110	<u>Respiratory</u>	
111	bronchial macrophages	
112	(multiple dose)	24.1 (9.6-41.8)
113	lung mucosa	1.1(0.7-1.5)
114	lung epithelial lining fluid	
115	(multiple dose)	5.8 (1.1-17.5)
116	whole lung	2.1 (0.42-5.03)
117		
118	<u>Skin, Musculoskeletal</u>	
119	skin	1.0 (0.20-1.88)
120	subcutaneous tissue	0.4 (0.15-0.68)
121	skin blister fluid	0.7-0.9 (blister/plasma)
122	skeletal muscle	1.5 (0.50-2.90)
123	bone	1.0 (0.55-1.67)
124		
125	<u>Gastrointestinal</u>	
126	colonic tissue	0.7 (0.0-1.47)
127	peritoneal fluid	0.4 (0.0-1.25)
128	bile	15.4 (11.9-21.0)
129		
130	<u>Central Nervous System</u>	
131	cerebrospinal fluid (CSF), adults	0.25 (0.03-0.33)
132	cerebrospinal fluid (CSF), children	0.28**
133		
134	<u>Reproductive</u>	
135	prostatic tissue	1.0 (0.5-1.6)
136	cervix (multiple dose)	0.6 (0.5-0.7)
137	ovary	1.6 (0.3-2.2)
138	fallopian tube	0.7 (0.2-1.1)
139	myometrium (multiple dose)	0.6 (0.4-0.8)
140	uterus	0.6 (0.3-0.8)
141	vaginal fluid (multiple dose)	4.7 (0.8-20.8)
142		
143		
144		

145 * Mean values in adults over 2-29 hours following drug administration, except individual lung tissues, which were
 146 single time points of 6 hours following drug administration

147 ** Ratio of composite AUC(0-24) in CSF/composite AUC(0-24) in serum in 22 pediatric patients aged 1 to 12
 148 years after 1 hour i.v. infusion of single dose alatrofloxacin (equivalent trovafloxacin dose range: 4.5-9.9 mg/kg)
 149

150

Presence in Breast Milk

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Metabolism

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Excretion

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Special Populations

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Geriatric

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Pediatric

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Gender

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Information for Patients).

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195

Chronic Hepatic Disease

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202

Following repeated administration of 100 mg for 7 days to patients with mild cirrhosis (Child-Pugh Class A), the AUC(0-24) for trovafloxacin was increased ~45% compared to matched controls. Repeated administration of 200 mg for 7 days to patients with moderate cirrhosis (Child-Pugh Class B) resulted in an increase of ~50% in AUC(0-24) compared to matched controls. There appeared to be no significant effect on trovafloxacin C_{max} for either group. The oral clearance of trovafloxacin was reduced ~30% in both cirrhosis groups, which corresponded to prolongation of half-life by 2-2.5 hours (25-30% increase) compared to

203 controls. There are no data in patients with severe cirrhosis (Child-Pugh Class C). Dosage
204 adjustment is recommended in patients with mild to moderate cirrhosis. (See **DOSAGE**
205 **AND ADMINISTRATION**)

206
207 **Renal Insufficiency**

208 The pharmacokinetics of trovafloxacin are not affected by renal impairment. Trovafloxacin
209 serum concentrations are not significantly altered in subjects with severe renal insufficiency
210 (creatinine clearance < 20 mL/min), including patients on hemodialysis.

211
212 **Photosensitivity Potential**

213 In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy
214 volunteers (12 per group), the minimum erythematous dose (MED) was measured for
215 ciprofloxacin, lomefloxacin, trovafloxacin and placebo before and after drug administration
216 for 5 days. In this study, trovafloxacin (200 mg q.d.) was shown to have a lower potential
217 for producing delayed photosensitivity skin reactions than ciprofloxacin (500 mg b.i.d.) or
218 lomefloxacin (400 mg q.d.), although greater than placebo. (See **PRECAUTIONS:**

219 **Information for Patients**)

220
221 **Drug-drug Interactions**

222 The systemic availability of trovafloxacin following oral tablet administration is significantly
223 reduced by the concomitant administration of antacids containing aluminum and magnesium
224 salts, sucralfate, vitamins or minerals containing iron, and concomitant intravenous
225 morphine administration.

226
227 Administration of trovafloxacin (300 mg p.o.) 30 minutes after administration of an
228 antacid containing magnesium hydroxide and aluminum hydroxide resulted in reductions
229 in systemic exposure to trovafloxacin (AUC) of 66% and peak serum concentration
230 (C_{max}) of 60%. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND**
231 **ADMINISTRATION**)

232
233 Concomitant sucralfate administration (1g) with trovafloxacin 200 mg p.o. resulted in a
234 70% decrease in trovafloxacin systemic exposure (AUC) and a 77% reduction in peak
235 serum concentration (C_{max}). (See **PRECAUTIONS: Drug Interactions, DOSAGE AND**
236 **ADMINISTRATION**)

237
238 Concomitant administration of ferrous sulfate (120 mg elemental iron) with trovafloxacin
239 200 mg p.o. resulted in a 40% reduction in trovafloxacin systemic exposure (AUC) and a
240 48% decrease in trovafloxacin C_{max}. (See **PRECAUTIONS: Drug Interactions,**
241 **DOSAGE AND ADMINISTRATION**)

242
243 Concomitant administration of intravenous morphine (0.15 mg/kg) with oral trovafloxacin
244 (200 mg) resulted in a 36% reduction in trovafloxacin AUC and a 46% decrease in
245 trovafloxacin C_{max}. Trovafloxacin administration had no effect on the
246 pharmacokinetics of morphine or its pharmacologically active metabolite, morphine-6-β-
247 glucuronide. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND**
248 **ADMINISTRATION**)

249
250 Minor pharmacokinetic interactions that are most likely without clinical significance include
251 calcium carbonate, omeprazole and caffeine.

252
253 Concomitant administration of calcium carbonate (1000 mg) with trovafloxacin 200 mg
254 p.o. resulted in a 20% reduction in trovafloxacin AUC and a 17% reduction in peak
255 serum trovafloxacin concentration (C_{max}).

256 A 40 mg dose of omeprazole given 2 hours prior to trovafloxacin (300 mg p.o.) resulted
257 in a 17% reduction in trovafloxacin AUC and a 17% reduction in trovafloxacin peak
258 serum concentration (C_{max}).
259

260 Administration of trovafloxacin (200 mg) concomitantly with caffeine (200 mg) resulted in
261 a 17% increase in caffeine AUC and a 15% increase in caffeine C_{max}. These changes
262 in caffeine exposure are not considered clinically significant.
263

264 No significant pharmacokinetic interactions include cimetidine, theophylline, digoxin, warfarin
265 and cyclosporine.
266

267 Cimetidine co-administration (400 mg twice daily for 5 days) with trovafloxacin (200 mg
268 p.o. daily for 3 days) resulted in changes in trovafloxacin AUC and C_{max} of less than
269 5%.
270

271 Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with theophylline (300 mg
272 twice daily for 14 days) resulted in no change in theophylline AUC and C_{max}.
273

274 Trovafloxacin (200 mg p.o. daily for 10 days) co-administration with digoxin (0.25 mg
275 daily for 20 days) did not significantly alter systemic exposure (AUC) to digoxin or the
276 renal clearance of digoxin.
277

278 Trovafloxacin (200 mg p.o. daily for 7 days) does not interfere with the pharmacokinetics
279 nor the pharmacodynamics of warfarin (daily for 21 days). Concomitant oral
280 administration of trovafloxacin did not affect the systemic exposure (AUC) or peak
281 plasma concentrations (C_{max}) of the S or R isomers of warfarin, nor did it influence
282 prothrombin times.
283

284 Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with cyclosporine (daily
285 doses from 150-450 mg for 7 days) resulted in decreases of 10% or less in systemic
286 exposure to cyclosporine (AUC) and in the peak blood concentrations of cyclosporine.
287

288 Microbiology

289 Trovafloxacin is a fluoronaphthyridone related to the fluoroquinolones with *in vitro* activity
290 against a wide range of gram-negative and gram-positive aerobic, and anaerobic
291 microorganisms. The bactericidal action of trovafloxacin results from inhibition of DNA
292 gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the
293 replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme
294 known to play a key role in the partitioning of the chromosomal DNA during bacterial cell
295 division. Mechanism of action of fluoroquinolones including trovafloxacin is different from
296 that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines.
297 Therefore, fluoroquinolones may be active against pathogens that are resistant to these
298 antibiotics. There is no cross-resistance between trovafloxacin and the mentioned classes
299 of antibiotics. The overall results obtained from *in vitro* synergy studies, testing
300 combinations of trovafloxacin with beta-lactams and aminoglycosides, indicate that synergy
301 is strain specific and not commonly encountered. This agrees with results obtained
302 previously with other fluoroquinolones. Resistance to trovafloxacin *in vitro* develops slowly
303 via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to
304 trovafloxacin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10} . Although
305 cross-resistance has been observed between trovafloxacin and some other
306 fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be
307 susceptible to trovafloxacin.
308
309

- 310 Trovafloxacin has been shown to be active against most strains of the following
311 microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS
312 AND USAGE section:
313
314 **Aerobic gram-positive microorganisms**
315 *Enterococcus faecalis* (many strains are only moderately susceptible)
316 *Staphylococcus aureus* (methicillin-susceptible strains)
317 *Staphylococcus epidermidis* (methicillin-susceptible strains)
318 *Streptococcus agalactiae*
319 *Streptococcus pneumoniae* (penicillin-susceptible strains)
320 *Streptococcus pyogenes*
321 Viridans group streptococci
322
323 **Aerobic gram-negative microorganisms**
324 *Escherichia coli*
325 *Gardnerella vaginalis*
326 *Haemophilus influenzae*
327 *Haemophilus parainfluenzae*
328 *Klebsiella pneumoniae*
329 *Moraxella catarrhalis*
330 *Neisseria gonorrhoeae*
331 *Proteus mirabilis*
332 *Pseudomonas aeruginosa*
333
334 **Anaerobic microorganisms**
335 *Bacteroides fragilis*
336 *Peptostreptococcus* species
337 *Prevotella* species
338
339 **Other microorganisms**
340 *Chlamydia pneumoniae*
341 *Chlamydia trachomatis*
342 *Legionella pneumophila*
343 *Mycoplasma pneumoniae*
344
345 The following *in vitro* data are available, but their clinical significance is unknown.
346
347 Trovafloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 2 $\mu\text{g/mL}$ against
348 most (90%) strains of the following microorganisms; however, the safety and effectiveness
349 of trovafloxacin in treating clinical infections due to these microorganisms have not been
350 established in adequate and well-controlled clinical trials.
351
352 **Aerobic Gram-positive microorganisms**
353 *Streptococcus pneumoniae* (penicillin-resistant strains)
354
355 **Aerobic Gram-negative microorganisms**
356 *Citrobacter freundii*
357 *Enterobacter aerogenes*
358 *Morganella morganii*
359 *Proteus vulgaris*
360
361 **Anaerobic microorganisms**
362
-

363 *Bacteroides distasonis*
 364 *Bacteroides ovatus*
 365 *Clostridium perfringens*

366
 367 **Other microorganisms**

368 *Mycoplasma hominis*
 369 *Ureaplasma urealyticum*

370
 371 NOTE: *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* complex
 372 organisms are commonly resistant to trovafloxacin.

373 NOTE: The activity of trovafloxacin against *Treponema pallidum* has not been evaluated;
 374 however, other quinolones are not active against *Treponema pallidum*. (See
 375 WARNINGS.)
 376

377 **Susceptibility Tests:**

378
 379 **Dilution techniques:** Quantitative methods are used to determine antimicrobial minimum
 380 inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of
 381 bacteria to antimicrobial compounds. The MICs should be determined using a standardized
 382 procedure. Standardized procedures are based on dilution methods¹ (broth or agar) or
 383 equivalent with standardized inoculum concentrations and standardized concentrations of
 384 trovafloxacin mesylate powder. The MIC values should be interpreted according to the
 385 following criteria:
 386

387 For testing non-fastidious aerobic organisms

388	389 <u>MIC ($\mu\text{g}/\text{mL}$)</u>	389 <u>Interpretation</u>
390	≤ 2.0	Susceptible (S)
391	4.0	Intermediate (I)
392	≥ 8.0	Resistant (R)

393
 394 For testing *Haemophilus* spp.^a:

395	396 <u>MIC ($\mu\text{g}/\text{mL}$)</u>	396 <u>Interpretation^b</u>
397	≤ 1.0	Susceptible (S)

398
 399 ^a These interpretive standards are applicable only to broth microdilution susceptibility
 400 tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)¹

401 ^b The current absence of data on resistant strains precludes defining any results other
 402 than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible"
 403 category should be submitted to a reference laboratory for further testing.
 404

405 For testing *Streptococcus* spp. including *Streptococcus pneumoniae*^c:

406	407 <u>MIC ($\mu\text{g}/\text{mL}$)</u>	407 <u>Interpretation</u>
408	≤ 1.0	Susceptible (S)
409	2.0	Intermediate (I)
410	≥ 4.0	Resistant (R)

411
 412 ^c These interpretive standards are applicable only to broth microdilution susceptibility
 413 tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.
 414

415 For testing *Neisseria gonorrhoeae*^d:

416		
417	<u>MIC (µg/mL)</u>	<u>Interpretation</u>
418	≤ 0.125	Susceptible (S)
419	0.25	Intermediate (I)
420	≥ 0.5	Resistant (R)

421
422 ^d These interpretive standards are applicable to agar dilution tests with GC agar base and
423 1% defined growth supplement¹.

424
425 A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the
426 antimicrobial compound in the blood reaches the concentration usually achievable. A report
427 of "Intermediate" indicates that the result should be considered equivocal, and, if the
428 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should
429 be repeated. This category implies possible clinical applicability in body sites where the
430 drug is physiologically concentrated or in situations where high dosage of drug can be used.
431 This category also provides a buffer zone which prevents small uncontrolled technical
432 factors from causing major discrepancies in interpretation. A report of "Resistant" indicates
433 that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood
434 reaches the concentration usually achievable; other therapy should be selected.
435 Standardized susceptibility test procedures require the use of laboratory control
436 microorganisms to control the technical aspects of the laboratory procedures. Standard
437 trovafloxacin mesylate powder should provide the following MIC values:

438	<u>Microorganism</u>	<u>MIC Range (µg/mL)</u>
439	<i>Escherichia coli</i> ATCC 25922	0.004-0.016
440	<i>Staphylococcus aureus</i> ATCC 29213	0.008-0.03
441	<i>Pseudomonas aeruginosa</i> ATCC 27853	0.25-2.0
442	<i>Enterococcus faecalis</i> ATCC 29212	0.06-0.25
443	<i>Haemophilus influenzae</i> ^e ATCC 49247	0.004-0.016
444	<i>Streptococcus pneumoniae</i> ^f ATCC 49619	0.06-0.25
445	<i>Neisseria gonorrhoeae</i> ^g ATCC 49226	0.004-0.016

446
447
448 ^e This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a
449 microdilution procedure using HTM¹.

450 ^f This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a
451 microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed
452 horse blood.

453 ^g This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an
454 agar dilution procedure using GC agar base with 1% defined growth supplement¹

455
456 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters
457 also provide reproducible estimates of the susceptibility of bacteria to antimicrobial
458 compounds. One such standardized procedure² requires the use of standardized inoculum
459 concentrations. This procedure uses paper disks impregnated with trovafloxacin mesylate
460 equivalent to 10 µg trovafloxacin to test the susceptibility of microorganisms to trovafloxacin.

461
462 Reports from the laboratory providing results of the standard single-disk susceptibility test
463 with a trovafloxacin mesylate disk (equivalent to 10 µg trovafloxacin) should be interpreted
464 according to the following criteria:

465
466 The following zone diameter interpretive criteria should be used for testing non-fastidious
467 aerobic organisms:

468	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
469		

470	≥ 17	Susceptible (S)
471	14-16	Intermediate (I)
472	≤ 13	Resistant (R)

473
474 For testing *Haemophilus* spp.^h:

475	<u>Zone Diameter (mm)</u>	<u>Interpretationⁱ</u>
476	≥ 22	Susceptible (S)

477
478 ^h These zone diameter standards are applicable only to tests with *Haemophilus* spp.
479 using HTM².

480 ⁱ The current absence of data on resistant strains precludes defining any results other
481 than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible"
482 category should be submitted to a reference laboratory for further testing.

483
484 For testing *Streptococcus* spp. including *Streptococcus pneumoniae*^l:

485		
486	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
487	≥ 19	Susceptible (S)
488	18-16	Intermediate (I)
489	≤ 15	Resistant (R)

490
491 ^j These zone diameter standards only apply to tests performed using Mueller-Hinton agar
492 supplemented with 5% sheep blood incubated in 5% CO₂

493
494 For testing *Neisseria gonorrhoeae*^k:

495		
496	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
497	≥ 37	Susceptible (S)
498	34-36	Intermediate (I)
499	≤ 33	Resistant (R)

500
501 ^k These interpretive standards are applicable to disk diffusion tests with GC agar base
502 and 1% defined growth supplement² incubated in 5% CO₂.

503
504 Interpretation should be as stated above for results using dilution techniques. Interpretation
505 involves correlation of the diameter obtained in the disk test with the MIC for trovafloxacin.

506
507 As with standardized dilution techniques, diffusion methods require the use of laboratory
508 control microorganisms that are used to control the technical aspects of the laboratory
509 procedures. For the diffusion technique, the trovafloxacin mesylate equivalent to 10-µg
510 trovafloxacin disk should provide the following zone diameters in these laboratory quality
511 control strains:

512		<u>Zone Diameter Range (mm)</u>
513	<u>Microorganism</u>	
514	<i>Escherichia coli</i> ATCC 25922	29-36
515	<i>Staphylococcus aureus</i> ATCC 25923	29-35
516	<i>Pseudomonas aeruginosa</i> ATCC 27853	21-27
517	<i>Haemophilus influenzae</i> ^l ATCC 49247	32-39
518	<i>Streptococcus pneumoniae</i> ^m ATCC 49619	25-32
519	<i>Neisseria gonorrhoeae</i> ⁿ ATCC 49226	42-55

520
521 ^l This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC
522 49247 using HTM².

- 523 ^m This quality control range is applicable only to tests performed by disk diffusion using
 524 Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.
 525 ⁿ This quality control range is only applicable to tests performed by disk diffusion using
 526 GC agar base and 1% defined growth supplement².

527
 528 **Anaerobic techniques:** For anaerobic bacteria, the susceptibility to trovafloxacin as MICs
 529 can be determined by standardized test methods³. The MIC values obtained should be
 530 interpreted according to the following criteria:

531	<u>MIC (µg/mL)</u>	<u>Interpretation</u>
532	≤ 2.0	Susceptible (S)
533	4.0	Intermediate (I)
534	≥ 8.0	Resistant (R)

535
 536 Interpretation is identical to that stated above for results using dilution techniques.
 537

538
 539 As with other susceptibility techniques, the use of laboratory control microorganisms is
 540 required to control the technical aspects of the laboratory standardized procedures.
 541 Standardized trovafloxacin mesylate powder should provide the following MIC values:

542	<u>Microorganism</u>	<u>MIC^p (µg/mL)</u>
543	<i>Bacteroides fragilis</i> ATCC 25285	0.125-0.5
544	<i>Bacteroides thetaotaomicron</i> ATCC 29741	0.25-1.0
545	<i>Eubacterium lentum</i> ATCC 43055	0.25-1.0

- 546
 547 ^p These quality control ranges were derived from tests performed in the broth formulation
 548 of Wilkins-Chalgren agar.
 549

550
 551

552 INDICATIONS AND USAGE

553
 554 TROVAN is indicated for the treatment of infections caused by susceptible strains of the
 555 designated microorganisms in the conditions listed below. (See **DOSAGE AND**
 556 **ADMINISTRATION**)

557
 558 **Nosocomial pneumonia** caused by *Escherichia coli*, *Pseudomonas aeruginosa*,
 559 *Haemophilus influenzae*, or *Staphylococcus aureus*. As with other antimicrobials, where
 560 *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy
 561 with either an aminoglycoside or aztreonam may be clinically indicated.

562
 563 **Community acquired pneumonia** caused by *Streptococcus pneumoniae*, *Haemophilus*
 564 *influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*,
 565 *Moraxella catarrhalis*, *Legionella pneumophila* or *Chlamydia pneumoniae*.

566
 567 **Acute bacterial exacerbation of chronic bronchitis** caused by *Haemophilus influenzae*,
 568 *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Haemophilus*
 569 *parainfluenzae*.

570
 571 **Acute sinusitis** caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus*
 572 *pneumoniae*.
 573

574 **Complicated intra-abdominal infections, including post-surgical infections** caused by
 575 *Escherichia coli*, *Bacteroides fragilis*, viridans group streptococci, *Pseudomonas aeruginosa*,
 576 *Klebsiella pneumoniae*, *Peptostreptococcus* species or *Prevotella* species.

577

578 **Gynecologic and pelvic infections including endomyometritis, parametritis, septic**
 579 **abortion and post-partum infections** caused by *Escherichia coli*, *Bacteroides fragilis*,
 580 viridans group streptococci, *Enterococcus faecalis*, *Streptococcus agalactiae*,
 581 *Peptostreptococcus* species, *Prevotella* species or *Gardnerella vaginalis*.

582

583 **Prophylaxis of infection associated with elective colorectal surgery, vaginal and**
 584 **abdominal hysterectomy.**

585

586 **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus*,
 587 *Streptococcus pyogenes* or *Streptococcus agalactiae*.

588

589 **Complicated skin and skin structure infections, including diabetic foot infections,**
 590 **caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*,**
 591 ***Enterococcus faecalis*, *Escherichia coli*, or *Proteus mirabilis*. NOTE: TROVAN has not been**
 592 **studied in the treatment of osteomyelitis. The safety and efficacy of TROVAN given for >4**
 593 **weeks have not been studied. (See PRECAUTIONS: General)**

594

595 **Uncomplicated urinary tract infections (cystitis)** caused by *Escherichia coli*.

596

597 **Chronic bacterial prostatitis** caused by *Escherichia coli*, *Enterococcus faecalis* or
 598 *Staphylococcus epidermidis*.

599

600 **Uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in**
 601 **females** caused by *Neisseria gonorrhoeae*. (See WARNINGS.)

602

603 **Cervicitis due to *Chlamydia trachomatis*. NOTE: In males with nongonococcal urethritis**
 604 **TROVAN was somewhat less effective than doxycycline.**

605

606 **Pelvic inflammatory disease (mild to moderate)** caused by *Neisseria gonorrhoeae* or
 607 *Chlamydia trachomatis*.

608

608 **CONTRAINDICATIONS**

609 TROVAN is contraindicated in persons with a history of hypersensitivity to trovafloxacin,
 610 alatrofloxacin, quinolone antimicrobial agents or any other components of these products.

611

612 **WARNINGS**

613 **THE SAFETY AND EFFECTIVENESS OF TROVAFLOXACIN IN PEDIATRIC**
 614 **POPULATIONS LESS THAN 18 YEARS OF AGE, PREGNANT WOMEN, AND NURSING**
 615 **WOMEN HAVE NOT BEEN ESTABLISHED.** (See PRECAUTIONS: Pediatric Use,
 616 **Pregnancy, and Nursing Mothers subsections.)**

617

618 As with other members of the quinolone class, trovafloxacin has caused arthropathy and/or
 619 chondrodysplasia in immature rats and dogs. The significance of these findings to humans
 620 is unknown. (See ANIMAL PHARMACOLOGY.)

621

622 Convulsions, increased intracranial pressure and psychosis have been reported in patients
 623 receiving quinolones. Quinolones may also cause central nervous system stimulation which
 624 may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia,

625 depression, nightmares and insomnia. These reactions may occur following the first dose.
626 If these reactions occur in patients receiving trovafloxacin or alatrofloxacin, the drug should
627 be discontinued and appropriate measures instituted. (See PRECAUTIONS: General
628 Information for Patients, Drug Interactions and ADVERSE REACTIONS.)

629
630 As with other quinolones, TROVAN should be used with caution in patients with known or
631 suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other
632 factors that predispose to seizures. (See ADVERSE REACTIONS.)

633
634 Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been
635 reported in patients receiving therapy with quinolones. These reactions may occur following
636 the first dose. Some reactions have been accompanied by cardiovascular collapse,
637 hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue,
638 laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm,
639 shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other
640 serious skin reactions.

641
642 TROVAN should be discontinued at the first appearance of a skin rash or any other sign of
643 hypersensitivity. Serious acute hypersensitivity reactions may require treatment with
644 epinephrine and other resuscitative measures, including oxygen, intravenous fluids,
645 antihistamines, corticosteroids, pressor amines and airway management, as clinically
646 indicated. (See PRECAUTIONS and ADVERSE REACTIONS.)

647
648 Serious and sometimes fatal events, some due to hypersensitivity, and some due to
649 uncertain etiology have been reported in patients receiving therapy with all antibiotics.
650 These events may be severe and generally occur following the administration of multiple
651 doses. Clinical manifestations may include one or more of the following: fever, rash or
652 severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson
653 Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial
654 nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or
655 failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic
656 thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other
657 hematologic abnormalities.

658
659 Pseudomembranous colitis has been reported with nearly all antibacterial agents, including
660 TROVAN, and may range in severity from mild to life-threatening. Therefore, it is important
661 to consider this diagnosis in patients who present with diarrhea subsequent to the
662 administration of any antibacterial agent.

663
664 Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth
665 of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary
666 cause of "antibiotic-associated colitis."

667
668 After the diagnosis of pseudomembranous colitis has been established, therapeutic
669 measures should be initiated. Mild cases of pseudomembranous colitis usually respond to
670 drug discontinuation alone. In moderate to severe cases, consideration should be given to
671 management with fluids and electrolytes, protein supplementation, and treatment with an
672 antibacterial drug clinically effective against *C. difficile* colitis. (See ADVERSE
673 REACTIONS.)

674
675 Although not seen in TROVAN clinical trials, ruptures of the shoulder, hand, and Achilles
676 tendons that required surgical repair or resulted in prolonged disability have been reported in
677 patients receiving quinolones. TROVAN should be discontinued if the patient experiences
678 pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise

679 until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon
680 rupture can occur during or after therapy with quinolones.

681
682 Trovafloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial
683 agents used in high doses for short periods of time to treat gonorrhea may mask or delay
684 the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test
685 for syphilis at the time of diagnosis.

686
687 **PRECAUTIONS**

688
689 **General:**

690 Because TROVAN can cause elevations of liver function tests during or soon after
691 prolonged therapy (i.e., ≥ 21 days), periodic assessment of hepatic function is advisable. The
692 safety and efficacy of TROVAN given for >4 weeks have not been studied. (See **ADVERSE**
693 **REACTIONS**)

694 Moderate to severe phototoxicity reactions have been observed in patients who are exposed
695 to direct sunlight while receiving some drugs in this class. Therapy should be discontinued if
696 phototoxicity (e.g., a skin eruption, etc.) occurs.

697
698 The safety and efficacy of TROVAN in patients with severe cirrhosis (Child-Pugh Class C)
699 have not been studied.
700

701 **Information for Patients:**

702

703

Patients should be advised:

704

705

- that TROVAN Tablets may be taken without regard to meals;

706

707

708

709

710

- that vitamins or minerals containing iron, aluminum-, or magnesium- base antacids, antacids containing citric acid buffered with sodium citrate, or sucralfate should be taken at least two hours before or two hours after taking TROVAN Tablets. (See **Drug Interactions.**);

711

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714

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719

- that TROVAN may cause lightheadedness and/or dizziness. Dizziness and/or lightheadedness was the most common adverse reaction reported, and for females under 45 years, it was reported significantly more frequently than in other groups. The incidence of dizziness may be substantially reduced if TROVAN Tablets are taken at bedtime or with food. Patients should know how they react to trovafloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination. (See **WARNINGS and ADVERSE REACTIONS**);

720

721

722

- to discontinue treatment and inform their physician if they experience pain, inflammation or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;

723

724

725

726

727

728

729

- that TROVAN may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema, (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS and ADVERSE REACTIONS**);

730

731

732

733

- to avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds) while taking TROVAN and to discontinue therapy if phototoxicity (e.g., sunburn-like reaction or skin eruption) occurs.

734

735

736

Drug Interactions:

737

738

739

No significant interactions with theophylline, cimetidine, digoxin, warfarin or cyclosporine have been observed with TROVAN Tablets (see **CLINICAL PHARMACOLOGY**).

740

741

742

Minor pharmacokinetic interactions without clinical significance have been observed with co-administration of TROVAN Tablets with caffeine, omeprazole and calcium carbonate (see **CLINICAL PHARMACOLOGY**).

743

744

745

746

747

748

Antacids, Sucralfate, and Iron: The absorption of oral trovafloxacin is significantly reduced by the concomitant administration of some antacids containing magnesium or aluminum, citric acid/sodium citrate (Bicitra[®]), as well as sucralfate and iron (as ferrous ions). The above oral agents should be taken at least two hours before or two hours after oral trovafloxacin administration (see **CLINICAL PHARMACOLOGY**).

749

750

751

752

Morphine: Co-administration of intravenous morphine significantly reduces the absorption of oral trovafloxacin. Intravenous morphine should be administered at least 2 hours after oral TROVAN dosing in the fasted state and at least 4 hours after oral TROVAN is taken with

753 food. Trovafloxacin administration had no effect on the pharmacokinetics of morphine or its
754 metabolite, morphine-6- β -glucuronide. (See **CLINICAL PHARMACOLOGY**).

755

756 Alatrofloxacin should not be co-administered with any solution containing multivalent
757 cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND**
758 **ADMINISTRATION**)

759

760 **Laboratory Test Interactions:** There are no reported laboratory test interactions.

761

762 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

763

764 Long term studies in animals to determine the carcinogenic potential of trovafloxacin or
765 alatrofloxacin have not been conducted.

766

767 Trovafloxacin was not mutagenic in the Ames Salmonella reversion assay
768 or CHO/HGPRT mammalian cell gene mutation assay and it was not clastogenic in
769 mitogen-stimulated human lymphocytes or mouse bone marrow cells. A mouse
770 micronucleus test conducted with alatrofloxacin was also negative. The positive response
771 observed in the *E. coli* bacterial mutagenicity assay may be due to the inhibition of DNA
772 gyrase by trovafloxacin.

773

774 Trovafloxacin and alatrofloxacin did not affect the fertility of male or female rats at oral and
775 IV doses of 75 mg/kg/day and 50 mg/kg/day, respectively. These doses are 15 and 10
776 times the recommended maximum human dose based on mg/kg or approximately 2 times
777 based on mg/m². However, oral doses of trovafloxacin at 200 mg/kg/day (40 times the
778 recommended maximum human dose based on mg/kg or about 6 times based on mg/m²)
779 were associated with increased preimplantation loss in rats.

780

781 **Pregnancy: Teratogenic Effects. Pregnancy Category C:**

782

783 An increase in skeletal variations was observed in rat fetuses after daily oral 75 mg/kg
784 maternal doses of trovafloxacin (approximately 15 times the highest recommended human
785 dose based on mg/kg or twice the based upon body surface area) were administered during
786 organogenesis. However, fetal skeletal variations were not observed in rats dosed orally with
787 15 mg/kg trovafloxacin. Evidence of fetotoxicity (increased perinatal mortality and decreased
788 body weights) was also observed in rats at 75 mg/kg. Daily oral doses of trovafloxacin at 45
789 mg/kg (approximately 9 times the highest recommended human dose based on mg/kg or
790 2.7 times based upon body surface area) in the rabbit were not associated with an increased
791 incidence of fetal skeletal variations or malformations.

792

793 An increase in skeletal variations and malformations was observed in rat fetuses after daily
794 intravenous doses of alatrofloxacin at ≥ 20 mg/kg/day (approximately 4 times the highest
795 recommended human dose based on mg/kg or 0.6 times based upon body surface area)
796 were administered to dams during organogenesis. In the rabbit, an increase in fetal skeletal
797 malformations was also observed when 20 mg/kg/day (approximately equal to the highest
798 recommended human dose based upon body surface area) of alatrofloxacin was given
799 intravenously during the period of organogenesis. Intravenous dosing of alatrofloxacin at
800 6.5 mg/kg in the rat or rabbit was not associated with an increased incidence of skeletal
801 variations or malformations. Fetotoxicity and fetal skeletal malformations have been
802 associated with other quinolones.

803

804 Oral doses of trovafloxacin >5 mg/kg were associated with an increased
805 gestation time in rats and several dams at 75 mg/kg experienced uterine dystocia.

806

807 There are no adequate and well-controlled studies in pregnant women. TROVAN should be
 808 used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
 809 (See **WARNINGS**)

810
 811 **Nursing Mothers:**

812 Trovafloxacin is excreted in human milk and was found in measurable concentrations in the
 813 breast milk of lactating subjects (See **CLINICAL PHARMACOLOGY, Distribution**).

814 Because of the potential for unknown effects from trovafloxacin in nursing infants from
 815 mothers taking trovafloxacin, a decision should be made either to discontinue nursing or to
 816 discontinue the drug, taking into account the importance of the drug to the mother.
 817

818
 819 **Pediatric Use:**

820 The safety and effectiveness of trovafloxacin in pediatric populations less than 18 years of
 821 age have not been established. Quinolones, including trovafloxacin, cause arthropathy and
 822 osteochondrosis in juvenile animals of several species. (See **WARNINGS**)

823
 824 **Geriatric Use:**

825 In multiple-dose clinical trials of trovafloxacin, 27% of patients were $\geq$ 65 years of age and
 826 12% of patients were $\geq$ 75 years of age. The overall incidence of drug-related adverse
 827 reactions, including central nervous system and gastrointestinal side effects, was less in the
 828 $\geq$ 65 year group than the other age groups.
 829

830 **ADVERSE REACTIONS**

831 Over 6000 patients have been treated with TROVAN in multidose clinical efficacy trials
 832 worldwide.

833 In TROVAN studies the majority of adverse reactions were described as mild in nature (over
 834 90% were described as mild or moderate). TROVAN was discontinued for adverse events
 835 thought related to drug in 5% of patients (dizziness 2.4%, nausea 1.9%, headache 1.1%,
 836 and vomiting 1.0%).
 837
 838
 839

Trovon® Drug-Related Adverse Reactions (frequency $\geq$ 1%) in Multiple-Dose Clinical Trials				
	100 mg oral qd (N=1536)	200 mg oral qd (N=3259)	200 mg IV→ 200 mg oral qd (N=634)	300 mg IV→ 200 mg oral qd (N=623)
Dizziness	3%	11%	2%	2%
Lightheadedness	2%	4%	2%	<1%
Nausea	4%	8%	5%	4%
Headache	4%	5%	5%	1%
Vomiting	<1%	3%	1%	3%
Diarrhea	2%	2%	2%	2%
Abdominal pain	<1%	1%	1%	0%
Application/ injection/ insertion site reaction	n/a	n/a	5%	2%
Vaginitis	1%	1%	<1%	<1%

Pruritus	<1%	<1%	2%	2%
Rash	<1%	<1%	2%	2%

- 840
841 Dizziness/lightheadedness on TROVAN is generally mild, lasts for a few hours following a
842 dose, and in most cases, resolves with continued dosing. The incidence of dizziness and
843 lightheadedness in TROVAN patients over 65 years is 3.1% and 0.6%, respectively. (See
844 **PRECAUTIONS: Information for Patients**)
- 845
846 TROVAN appears to have a low potential for phototoxicity. In clinical trials with TROVAN,
847 only mild, treatment-related phototoxicity was observed in less than 0.03% (2/7096) of
848 patients.
- 849
850 Additional reported drug-related events in clinical trials (remotely, possibly, probably or
851 unknown) that occurred in <1% of TROVAN-treated patients are:
- 852
853 **APPLICATION/INJECTION/INCISION/INSERTION SITE:**
854 Application/incision/injection/insertion site device complications, inflammation, pain, edema
- 855
856 **AUTONOMIC NERVOUS:** flushing, increased sweating, dry mouth, cold clammy skin,
857 increased saliva
- 858
859 **CARDIOVASCULAR:** peripheral edema, chest pain, thrombophlebitis, hypotension,
860 palpitation, periorbital edema, hypertension, syncope, tachycardia, angina pectoris,
861 bradycardia, peripheral ischemia, edema, dizziness postural
- 862
863 **CENTRAL & PERIPHERAL NERVOUS SYSTEM:** confusion, paresthesia, vertigo,
864 hypoesthesia, ataxia, convulsions, dysphonia, hypertonia, migraine, involuntary muscle
865 contractions, speech disorder, encephalopathy, abnormal gait, hyperkinesia, hypokinesia,
866 tongue paralysis, abnormal coordination, tremor, dyskinesia
- 867
868 **GASTROINTESTINAL:** abdominal pain, altered bowel habit, constipation, diarrhea-
869 *Clostridium difficile*, dyspepsia, flatulence, loose stools, gastritis, dysphagia, increased
870 appetite, gastroenteritis, rectal disorder, colitis, pseudomembranous colitis, enteritis,
871 eructation, gastrointestinal disorder, melena, hiccup
- 872
873 **ORAL CAVITY:** gingivitis, stomatitis, altered saliva, tongue disorder, tongue edema, tooth
874 disorder, cheilitis, halitosis
- 875
876 **GENERAL/OTHER:** fever, fatigue, pain, asthenia, moniliasis, hot flushes, back pain, chills,
877 infection(bacterial, fungal), malaise, sepsis, alcohol intolerance, allergic reaction,
878 anaphylactoid reaction, drug(other) toxicity/reaction, weight increase, weight decrease
- 879
880 **HEMATOPOIETIC:** anemia, granulocytopenia, hemorrhage unspecified, leukopenia,
881 prothrombin decreased, thrombocytopenia, thrombocytopenia
- 882
883 **LIVER/BILIARY:** increased hepatic enzymes, hepatic function abnormal, bilirubinemia,
884 discolored feces, jaundice
- 885
886 **METABOLIC/NUTRITIONAL:** hyperglycemia, thirst
- 887
888 **MUSCULOSKELETAL:** arthralgia, muscle cramps, myalgia, muscle weakness, skeletal
889 pain, tendinitis, arthropathy
890

891 **PSYCHIATRIC:** anxiety, anorexia, agitation, nervousness, somnolence, insomnia,
892 depression, amnesia, concentration impaired, depersonalization, dreaming abnormal,
893 emotional lability, euphoria, hallucination, impotence, libido decreased-male, paroniria,
894 thinking abnormal

895
896 **REPRODUCTIVE:** Female: leukorrhea, menstrual disorder;
897 Male: balanoposthitis

898
899 **RESPIRATORY:** dyspnea, rhinitis, sinusitis, bronchospasm, coughing, epistaxis, respiratory
900 insufficiency, upper respiratory tract infection, respiratory disorder, asthma, hemoptysis,
901 hypoxia, stridor

902
903 **SKIN/APPENDAGES:** pruritus, pruritus ani, skin disorder, skin ulceration, angioedema,
904 dermatitis, dermatitis fungal, photosensitivity skin reaction, seborrhea, skin exfoliation,
905 urticaria

906
907 **SPECIAL SENSES:** taste perversion, eye pain, abnormal vision, conjunctivitis, photophobia,
908 conjunctival hemorrhage, hyperacusis, scotoma, tinnitus, visual field defect, diplopia,
909 xerophthalmia

910
911 **URINARY SYSTEM:** dysuria, face edema, micturition frequency, nephritis interstitial, renal
912 failure acute, renal function abnormal, urinary incontinence

913
914 **LABORATORY CHANGES:** Changes in laboratory parameters, without regard to drug
915 relationship, occurring in $\geq 1\%$ of TROVAN treated patients were: Decreased hemoglobin
916 and hematocrit; increased platelets; decreased and increased WBC; eosinophilia; increased
917 ALT (SGPT), AST (SGOT), and alkaline phosphatase; decreased protein and albumin;
918 increased BUN and creatinine; decreased sodium; and bicarbonate. It is not known whether
919 these abnormalities were caused by the drug or the underlying condition being treated.

920
921 The incidence and magnitude of liver function abnormalities with TROVAN were the same
922 as comparator agents except in the only study in which oral TROVAN was administered for
923 28 days. In this study (chronic bacterial prostatitis) nine percent (13/140) of TROVAN-treated
924 patients experienced elevations of serum transaminases (AST and/or ALT) of ≥ 3 times the upper
925 limit of normal. These liver function test abnormalities generally developed at the end of, or following
926 completion of, the planned 28-day course of therapy, but were not associated with concurrent
927 elevations of related laboratory measures of hepatic function (such as serum bilirubin, alkaline
928 phosphatase, or lactate dehydrogenase). Patients were asymptomatic with these abnormalities,
929 which generally returned to normal within 1-2 months after discontinuation of therapy. (See
930 **PRECAUTIONS - General.**)

931
932 **OVERDOSAGE**

933
934 Trovafloxacin has a low order of acute toxicity. The minimum lethal oral dose in mice and
935 rats was 2000 mg/kg or greater. The minimum lethal i.v. dose for the prodrug, alatrofloxacin,
936 was 50-125 mg/kg for mice and greater than 75 mg/kg for rats. Clinical signs observed
937 included decreased activity and respiration, ataxia, ptosis, tremors and convulsions.

938
939 In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting
940 or by gastric lavage. The patient should be carefully observed and given symptomatic and
941 supportive treatment. Adequate hydration should be maintained. Trovafloxacin is not
942 efficiently removed from the body by hemodialysis.

943
944

945 **DOSAGE AND ADMINISTRATION**

946
947 The recommended dosage for TROVAN Tablets or TROVAN I.V. for the treatment of
948 infections is described in the table below. Doses of TROVAN are administered once every
949 24 hours.

950
951 Oral doses should be administered at least two hours before or two hours after antacids containing
952 magnesium or aluminum, as well as sucralfate, citric acid buffered with sodium citrate (e.g., Bicitra[®])
953 and metal cations (e.g., ferrous sulfate).

954
955 Intravenous morphine should be administered at least 2 hours after oral TROVAN dosing in
956 the fasted state and at least 4 hours after oral TROVAN is taken with food.

957
958 When switching from intravenous to oral dosage administration, for comparable dosages,
959 no adjustment is necessary. Patients whose therapy is started with TROVAN I.V. may be
960 switched to TROVAN Tablets when clinically indicated at the discretion of the physician.

961
962 TROVAN I.V. (atrofloxacin mesylate injection) should only be administered by
963 INTRAVENOUS infusion. It is not for intramuscular, intrathecal, intraperitoneal, or
964 subcutaneous administration.

965
966 Single-use vials require dilution prior to administration. (See **PREPARATION FOR**
967 **ADMINISTRATION.**)

968
969

DOSAGE GUIDELINES		
INFECTION*/LOCATION AND TYPE	DAILY UNIT DOSE AND ROUTE OF ADMINISTRATION	TOTAL DURATION
Nosocomial Pneumonia (See NOTE 1 below.)	300 mg I.V. followed by 200 mg oral	10-14 days
Community Acquired Pneumonia	200 mg oral or 200 mg I.V. followed by 200 mg oral	7-14 days
Acute Bacterial Exacerbation of Chronic Bronchitis	100 mg oral	7-10 days
Acute Sinusitis	200 mg oral	10 days
Complicated Intra-Abdominal Infections, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Gynecologic and Pelvic Infections	300 mg I.V. followed by 200 mg oral	7-14 days
Surgical Prophylaxis - Elective Colorectal Surgery (See NOTE 2 below.)	200 mg I.V. or oral	Single intravenous or oral dose within 30 min. to 4 hours before surgery
Surgical Prophylaxis - Elective Abdominal and Vaginal Hysterectomy (See NOTE 2 below.)	200 mg I.V. or oral	Single intravenous or oral dose within 30 min. to 4 hours before surgery
Skin and Skin Structure Infections, Uncomplicated	100 mg Oral	7-10 days
Skin and Skin Structure Infections, Complicated, including diabetic foot infections	200 mg oral or 200 mg I.V. followed by 200 mg oral	10-14 days
Uncomplicated Urinary Tract Infections (cystitis)	100 mg oral	3 days
Chronic Bacterial Prostatitis	200 mg oral	28 days
Uncomplicated Urethral Gonorrhea Males; Endocervical and Rectal Gonorrhea in Females	100 mg oral	Single Dose
Cervicitis due to <i>Chlamydia trachomatis</i>	200 mg oral	5 days
Pelvic Inflammatory Disease (mild to moderate)	200 mg oral	14 days

* due to the designated pathogens (See INDICATIONS AND USAGE)

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NOTE 1: As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

NOTE 2: In patients where surgical prophylaxis with oral TROVAN is indicated, Bicitra[®] should not be given within 2 hours. (See PRECAUTIONS: Drug Interactions)

The safety and efficacy of TROVAN use for >4 weeks have not been studied. (See PRECAUTIONS.)

IMPAIRED RENAL FUNCTION: No adjustment in the dosage of TROVAN is necessary in patients with impaired renal function. Trovafloxacin is eliminated primarily by biliary excretion. Trovafloxacin is not efficiently removed from the body by hemodialysis.

987 **CHRONIC HEPATIC DISEASE (cirrhosis):** The following table provides dosing guidelines
988 for patients with mild or moderate cirrhosis (Child-Pugh Class A and B). There are no data in
989 patients with severe cirrhosis (Child-Pugh Class C).
990

INDICATED DOSE (Normal hepatic function)	CHRONIC HEPATIC DISEASE DOSE
300 mg i.v.	200 mg i.v.
200 mg i.v. or oral	100 mg i.v. or oral.
100 mg oral	100 mg oral

991 **INTRAVENOUS ADMINISTRATION**
992 AFTER DILUTION WITH AN APPROPRIATE DILUENT TROVAN I.V. SHOULD BE
993 ADMINISTERED BY INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES.
994 CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION SHOULD BE AVOIDED.
995

996 TROVAN I.V. is supplied in single-use vials containing a concentrated solution of
 997 alatrofloxacin mesylate in Water for Injection (equivalent of 200 mg or 300 mg as
 998 trovafloxacin). Each mL contains alatrofloxacin mesylate equivalent to 5 mg trovafloxacin.
 999 (See **HOW SUPPLIED** for container sizes.) THESE TROVAN I.V. SINGLE-USE VIALS
 1000 MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO
 1001 INTRAVENOUS ADMINISTRATION. This parenteral drug product should be inspected
 1002 visually for discoloration and particulate matter prior to dilution and administration. Since no
 1003 preservative or bacteriostatic agent is present in this product, aseptic technique must be
 1004 used in preparation of the final parenteral solution.

1005
 1006 PREPARATION OF ALATROFLOXACIN MESYLATE INJECTION FOR ADMINISTRATION
 1007 The intravenous dose should be prepared by aseptically withdrawing the appropriate
 1008 volume of concentrate from the vials of TROVAN I.V. This should be diluted with a suitable
 1009 intravenous solution to a final concentration of 1-2 mg/mL. (See **Compatible Intravenous**
 1010 **Solutions.**) The resulting solution should be infused over a period of
 1011 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already
 1012 be in place.

1013
 1014 Since the vials are for single-use only, any unused portion should be discarded.

1015
 1016 Since only limited data are available on the compatibility of alatrofloxacin intravenous
 1017 injection with other intravenous substances, additives or other medications should not be
 1018 added to TROVAN I.V. in single-use vials or infused simultaneously through the same
 1019 intravenous line.

1020
 1021 If the same intravenous line is used for sequential infusion of several different drugs, the line
 1022 should be flushed before and after infusion of TROVAN I.V. with an infusion solution
 1023 compatible with TROVAN I.V. and with any other drug(s) administered via this common line.

1024
 1025 If TROVAN I.V. is to be given concomitantly with another drug, each drug should be given
 1026 separately in accordance with the recommended dosage and route of administration for
 1027 each drug.

1028
 1029 The desired dosage of TROVAN I.V. may be prepared according to the following chart:

1030

DOSAGE STRENGTH (mg) (trovafloxacin equivalent)	VOLUME TO WITHDRAW (mL)	DILUENT VOLUME (mL)	TOTAL VOLUME (mL)	INFUSION CONC (mg/mL)
100 mg	20	30	50	2
100 mg	20	80	100	1
200 mg	40	60	100	2
200 mg	40	160	200	1
300 mg	60	90	150	2
300 mg	60	240	300	1

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For example, to prepare a 200 mg dose at an infusion concentration of 2 mg/mL (as trovafloxacin), 40 mL of TROVAN I.V. is withdrawn from a vial and diluted with 60 mL of a compatible intravenous fluid to produce a total infusion solution volume of 100 mL.

Compatible Intravenous Solutions:

5% Dextrose Injection, USP

0.45% Sodium Chloride Injection, USP

5% Dextrose and 0.45% Sodium Chloride Injection, USP

5% Dextrose and 0.2% Sodium Chloride Injection, USP

Lactated Ringer's and 5% Dextrose Injection, USP

- 1042 Stability of TROVAN I.V. as supplied:
1043 When stored under recommended conditions, TROVAN I.V., as supplied in (20 mL) 40 mL
1044 or 60 mL vials, is stable through the expiration date printed on the label. -
1045
1046 **Stability of TROVAN I.V. Following Dilution:**
1047 TROVAN I.V., when diluted with the following intravenous solutions to concentrations of
1048 0.5 to 2.0 mg/mL (as trovafloxacin), is physically and chemically stable for up to 7 days
1049 when refrigerated or up to 3 days at room temperature stored in glass bottles or plastic
1050 (PVC type) intravenous containers.
1051
1052 **HOW SUPPLIED**
1053 **Tablets**
1054 TROVAN (trovafloxacin mesylate) Tablets are available as blue, film-coated tablets. The
1055 100 mg tablets are round and contain trovafloxacin mesylate equivalent to 100 mg
1056 trovafloxacin. The 200 mg tablets are modified oval-shaped and contain trovafloxacin
1057 mesylate equivalent to 200 mg trovafloxacin.
1058
1059 TROVAN Tablets are packaged and in unit dose blister strips in the following configurations:
1060
1061 100-mg tablets: color: blue; shape: round
1062 debossing: "PFIZER" on side 1 and "378" on side 2
1063 Bottles of 30 (NDC 0049-3780-30)
1064 Unit Dose/ 40 tablets (NDC 0049-3780-43)
1065
1066 200-mg tablets: color: blue; shape: modified oval
1067 debossing: "PFIZER" on side 1 and "379" on side 2
1068 Bottles of 30 (NDC 0049-3790-30)
1069 Unit Dose/ 40 tablets (NDC 0049-3790-43)
1070
1071 **Storage**
1072 TROVAN Tablets should be stored at 15 °C to 30 °C (59 °F to 86 °F) in well-closed
1073 containers.
1074
1075 **Injection**
1076 TROVAN is also available for intravenous administration as the prodrug, TROVAN I.V.
1077 (alatrofloxacin mesylate injection), in the following configurations:
1078 Single-use vials containing a clear, colorless to pale-yellow concentrated solution of
1079 alatrofloxacin mesylate equivalent to 5 mg trovafloxacin/mL.
1080
1081 5 mg/mL, 40 mL, 200 mg
1082 Unit dose package (NDC 0049-3890-28)
1083
1084 5 mg/mL, 60 mL, 300 mg
1085 Unit dose package (NDC 0049-3900-28)
1086
1087 **Storage**
1088 TROVAN I.V. should be stored at 15 °C to 30 °C (59 °F to 86 °F). Protect From Light. Do
1089 Not Freeze.
1090
1091 **ANIMAL PHARMACOLOGY:**
1092
1093 Quinolones have been shown to cause arthropathy in immature animals.
1094

1095 Arthropathy and chondrodysplasia were observed in immature animals given trovafloxacin
 1096 (See **WARNINGS**).
 1097
 1098 At doses from 10 to 15 times the human dose based on a mg/kg or approximately 3 to
 1099 5 times based on mg/m², trovafloxacin has been shown to cause arthropathy in immature
 1100 rats and dogs. In addition, these drugs are associated with an increased incidence of
 1101 chondrodysplasia in rats compared to controls. There is no evidence of arthropathies in fully
 1102 mature rats and dogs at doses from 40 or 10 times the human dose based on mg/kg or
 1103 approximately 5 times based on mg/m² for a 6 month exposure period.
 1104
 1105 Unlike some other members of the quinolone class, crystalluria and ocular toxicity were not
 1106 observed in chronic safety studies with rats or dogs with either trovafloxacin or its prodrug,
 1107 alatrofloxacin.
 1108

1109 Quinolones have been reported to have proconvulsant activity that is exacerbated with
 1110 concomitant use of non-steroidal antiinflammatory drugs (NSAIDS). Neither trovafloxacin
 1111 administered orally at 500 mg/kg, nor alatrofloxacin administered intravenously at 75 mg/kg,
 1112 showed an increase in measures of seizure activity in mice at doses when used in
 1113 combination with the active metabolite of the NSAID, fenbufen.
 1114

1115 As with other members of the quinolone class, trovafloxacin at doses 5 to 10 times the
 1116 human dose based on mg/kg or 1 to 5 times the human dose based on mg/m² produces
 1117 testicular degeneration in rats and dogs dosed for 6 months.
 1118

1119 At a dose of trovafloxacin 10 times the highest human dose based on mg/kg or
 1120 approximately 5 times based on mg/m², elevated liver enzyme levels which correlated with
 1121 centrilobar hepatocellular vacuolar degeneration and necrosis were observed in dogs in a
 1122 6 month study. A subsequent study demonstrated reversibility of these effects when
 1123 trovafloxacin was discontinued.
 1124

1125 CLINICAL STUDIES

1127 Acute Bacterial Exacerbation of Chronic Bronchitis

1128 Patients with clinically documented acute bacterial exacerbation of chronic bronchitis
 1129 participated in a randomized, double blind, multicenter trial comparing oral trovafloxacin
 1130 (100mg once daily) with oral clarithromycin (500mg twice daily) for 7 days. The clinical
 1131 success rate (cure + improvement, with no need for further antibiotic therapy) at the End of
 1132 Treatment was 89% (181/203) and 85% (160/188) for trovafloxacin and clarithromycin
 1133 respectively. The clinical success rate at the End of Study (Day 28) was 80% (158/197) and
 1134 74% (131/178) for trovafloxacin and clarithromycin respectively.
 1135

1136 The following are the clinical success rates for the clinically evaluable groups by pathogen:
 1137

Pathogen	End of Treatment		End of Study	
	Trovafloxacin 100 mg	Clarithromycin 500 mg BID	Trovafloxacin 100 mg	Clarithromycin 500 mg BID
<i>H. influenzae</i>	92% (24/26)	89% (16/18)	92% (24/26)	44% (7/16)*
<i>M. catarrhalis</i>	78% (14/18)	80% (16/20)	71% (12/17)	74% (14/19)
<i>S. pneumoniae</i>	100% (7/7)	91% (10/11)	86% (6/7)	91% (10/11)
<i>H. parainfluenzae</i>	100% (6/6)	86% (6/7)	100% (6/6)	86% (6/7)
<i>S. aureus</i>	93% (13/14)	83% (10/12)	85% (11/13)	75% (9/12)

1138 *p= 0.001

1139

1140 Of the above patients with clinical failure at end of treatment or study, no trovafloxacin and 2
1141 clarithromycin patients (both *H. influenzae*) had positive post treatment cultures for the
1142 baseline pathogen. There was no emergence of resistance in either treatment group.
1143 Fewer patients required hospitalization during study (Day 1-35) in the trovafloxacin group
1144 (3/210) than in the clarithromycin group (10/200), p=0.039.

1145

1146 Hospitalized Community Acquired Pneumonia

1147 Adult patients with clinically and radiologically documented community acquired pneumonia,
1148 requiring hospitalization and initial intravenous therapy, participated in two randomized,
1149 multicenter, double-blind, double-dummy trials. The first trial compared intravenous
1150 alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once
1151 daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg BID) plus
1152 ampicillin (500mg QID) for 2 to 7 days followed by oral ciprofloxacin (500mg BID) plus
1153 amoxicillin (500mg TID) for a total of 7 to 14 days of therapy. The second study compared
1154 intravenous alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin
1155 (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ceftriaxone (1000mg
1156 once daily for 2 to 7 days) followed by oral cefpodoxime (400mg BID) for 7 to 14 days of
1157 total therapy with optional blinded erythromycin added to the ceftriaxone/cefpodoxime arm if
1158 an atypical pneumonia was suspected.

1159

1160 The clinical success rate (cure + improvement with no need for further antibiotic therapy) at
1161 the End of Treatment was 90% (311/346) and 90% (325/363) for TROVAN and the
1162 comparator agents respectively. The clinical success rate at the End of Study (Day 30) was
1163 86% (256/299) and 85% (283/334) for TROVAN and the comparator agents respectively.
1164 All cause mortality (Day 1-35) was 2.45% (10/408) on TROVAN and 5.45% (23/422) on the
1165 comparator agents.

1166

1167 The following outcomes are the clinical success rates for the clinically evaluable patient
1168 groups by pathogen in these two studies:

1169

Pathogen	End of Treatment		End of Study	
	TROVAN	Comparators	TROVAN	Comparators
<i>S. pneumoniae</i>	89% (63/71)	95% (62/65)	87% (55/63)	91% (50/55)
<i>H. influenzae</i>	97% (35/36)	94% (46/49)	90% (28/31)	94% (44/47)
<i>M. catarrhalis</i>	100% (8/8)	100% (4/4)	100% (6/6)	100% (4/4)
<i>S. aureus</i>	100% (8/8)	93% (13/14)	100% (6/6)	91% (10/11)
<i>K. pneumoniae</i>	100% (3/3)	89% (8/9)	100% (3/3)	86% (6/7)
<i>L. pneumophila</i>	77% (10/13)	86% (12/14)	75% (9/12)	86% (12/14)
<i>M. pneumoniae</i>	100% (20/20)	87% (13/15)	94% (17/18)	79% (11/14)
<i>C. pneumoniae</i>	75% (6/8)	100% (18/18)	67% (4/6)	94% (16/17)

1170

1171 Of the above patients with clinical failure at end of treatment or study, only one alatrofloxacin
1172 patient (*H. influenzae* + *S. pneumoniae*) and one ceftriaxone + erythromycin patient
1173 (*Legionella*) had a microbiologically confirmed persistent pathogen at the time of failure with
1174 no emergence of resistance in either study.

1175

1176 Nosocomial Pneumonia

1177 Adult patients with clinically and radiologically documented nosocomial pneumonia,
 1178 participated in a randomized, multicenter, double-blind, double-dummy trial comparing
 1179 intravenous alatrofloxacin (300mg once daily for 2 to 7 days) followed by oral trovafloxacin
 1180 (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg
 1181 BID) for 2 to 7 days followed by oral ciprofloxacin (750mg BID) for a total of 7 to 14 days of
 1182 therapy with optional blinded clindamycin or metronidazole added to the ciprofloxacin arm if
 1183 an anaerobic pneumonia was suspected. In subjects with documented *Pseudomonas*
 1184 infection or methicillin-resistant *S. aureus*, aztreonam or vancomycin, respectively, could
 1185 have been added to either treatment regimen.

1186
 1187 The clinical success rate (cure + improvement with no need for further antibiotic therapy) at
 1188 the End of Treatment was 77% (68/88) and 78% (79/101) for TROVAN and ciprofloxacin
 1189 respectively. The clinical success rate at the End of Study (Day 30) was 69% (50/72) and
 1190 68% (54/79) for TROVAN and ciprofloxacin respectively.

1191
 1192 The following outcomes are the clinical success rates for the clinically evaluable patient
 1193 groups by pathogen:
 1194

Pathogen	End of Treatment		End of Study	
	TROVAN	Ciprofloxacin	TROVAN	Ciprofloxacin
<i>P. aeruginosa</i>	67% (10/15)	55% (6/11)	62% (8/13)	25% (2/8)
<i>H. influenzae</i>	88% (7/8)	89% (8/9)	83% (5/6)	86% (6/7)
<i>E. coli</i>	71% (5/7)	80% (4/5)	50% (3/6)	80% (4/5)
<i>S. aureus</i>	64% (7/11)	80% (8/10)	50% (4/8)	67% (4/6)

1195
 1196 Of the above patients with clinical failure at end of treatment or study, two alatrofloxacin
 1197 patients (*S.aureus*, *P.aeruginosa*) and 4 ciprofloxacin patients (all *P.aeruginosa*) had a
 1198 microbiologically confirmed persistent pathogen at the time of failure. Three of the 4
 1199 ciprofloxacin patients with clinical failure and persistence had emergence of resistance with
 1200 none on alatrofloxacin.

1201 1202 Complicated Intra-Abdominal Infections

1203 Patients hospitalized with clinically-documented, complicated intra-abdominal infections,
 1204 including post-surgical infections participated in a randomized, double-blind, multicenter trial
 1205 comparing intravenous alatrofloxacin (300 mg once daily) followed by oral trovafloxacin (200
 1206 mg once daily) to intravenous imipenem/cilastatin (1g q8h) followed by oral
 1207 amoxicillin/clavulanic acid (500 mg TID) for a maximum of 14 days of therapy. The clinical
 1208 success rate (cure + improvement) at the End of Treatment was 88% (136/155) and 86%
 1209 (122/142) for alatrofloxacin→trovafloxacin and imipenem/cilastatin→amoxicillin/clavulanic
 1210 acid, respectively. The clinical success rate at the End of Study (Day 30) was 83%
 1211 (129/156) and 84% (127/152) for alatrofloxacin→trovafloxacin and
 1212 imipenem/cilastatin→amoxicillin/clavulanic acid respectively.

1213
 1214 The following are the clinical success rates for the clinically-evaluable patient groups by
 1215 pathogen:
 1216

Pathogen	End of Treatment		End of Study	
	TROVAN	Imipenem/Cila Amox/Clav	TROVAN	Imipenem/Cila Amox/Clav
<i>E. coli</i>	94% (72/77)	90% (52/58)	86% (66/77)	86% (51/59)

<i>Bacteroides fragilis</i>	97% (30/31)	82% (28/34)	84% (26/31)	75% (27/36)
viridans group streptococci	90% (18/20)	83% (19/23)	90% (18/20)	78% (18/23)
<i>Pseudomonas aeruginosa</i>	94% (15/16)	82% (14/17)	88% (14/16)	83% (15/18)
<i>Klebsiella pneumoniae</i>	80% (12/15)	71% (10/14)	67% (10/15)	71% (10/14)
<i>Peptostreptococcus</i> spp.	86% (12/14)	88% (7/8)	79% (11/14)	75% (6/8)
<i>Prevotella</i> spp.	77% (10/13)	50% (2/4)	77% (10/13)	60% (3/5)

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Of patients with a baseline pathogen and a clinical response of failure at the End of Study, 9 of 26 on TROVAN and 10 of 21 on imipenem/cilastatin had microbiologically-confirmed persistence of the baseline pathogen with no emergence of resistance in either group.

CAUTION: FEDERAL (USA) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

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Roerig
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1242

<i>Bacteroides fragilis</i>	97% (30/31)	82% (28/34)	84% (26/31)	75% (27/36)
viridans group streptococci	90% (18/20)	83% (19/23)	90% (18/20)	78% (18/23)
<i>Pseudomonas aeruginosa</i>	94% (15/16)	82% (14/17)	88% (14/16)	83% (15/18)
<i>Klebsiella pneumoniae</i>	80% (12/15)	71% (10/14)	67% (10/15)	71% (10/14)
<i>Peptostreptococcus</i> spp.	86% (12/14)	88% (7/8)	79% (11/14)	75% (6/8)
<i>Prevotella</i> spp.	77% (10/13)	50% (2/4)	77% (10/13)	60% (3/5)

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Of patients with a baseline pathogen and a clinical response of failure at the End of Study, 9 of 26 on TROVAN and 10 of 21 on imipenem/cilastatin had microbiologically-confirmed persistence of the baseline pathogen with no emergence of resistance in either group.

CAUTION: FEDERAL (USA) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

REFERENCES:

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fourth Edition; Approved Standard, NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Villanova, PA, January, 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Sixth Edition; Approved Standard, NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Villanova, PA, January 1997.
3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria--Third Edition; Approved Standard, NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA, December, 1993.

TROVAN is manufactured and distributed by:

Roerig
Division of Pfizer Inc., NY, NY 10017

U.S. Patent No. 5,164,402
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1242

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 020759/020760

MEDICAL REVIEW(S)

Medical Officer Review of Sinusitis indication

1. Overview of requested labeling and organisms.

The proposed consolidated labeling for NDAs 20-759 and 20-760 includes the following:

- ◆ Under INDICATIONS AND USAGE: “**ACUTE SINUSITIS** caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Streptococcus pneumoniae*.”
- ◆ Under DOSAGE AND ADMINISTRATION: the table entitled “Dosage Guidelines” calls for the Acute Sinusitis indication to be treated with a 10 day course of trovafloxacin at a dose of 200 mg per day.

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2. Comments on IDSA guidelines for the sinusitis indication.

The sinusitis section of the IDSA guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections (Clin Infect Dis 15 [Suppl 1]: S62-88, 1992) makes specific recommendations for the design and conduct of clinical trials in support of a sinusitis indication. This includes the following recommendations:

- a small (~ 100 patient) phase 2 trial in which sinus puncture and culture is performed for all patients, with at least 20 cases of each of the three major bacterial pathogens implicated (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*). In this phase 2 study, an ‘open’ study design is acceptable.
- assuming a favorable result from this phase 2 study (i.e., a clinical and presumed microbiological response rate of $\geq 70\%$), a larger comparative phase 3 study should be conducted using an active control arm. Sinus puncture and pre-treatment radiography are desirable but not required in this study.
- assessment during course of therapy in these trials should include clinical evaluation at 2-3 and 5-7 days after initiation of antimicrobial therapy, and weekly or biweekly thereafter until resolution of all symptoms and signs. Patients should be followed clinically for at least 2 weeks after completion of antimicrobial therapy to assess relapse or recurrence, clinical complications, and adverse effects of the antimicrobial regimen.

Thus, the IDSA guidelines recommend two studies, only one of which must have a microbiologic component for study entry.

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3. Points To Consider document regarding sinusitis.

The divisional Points to Consider document addresses the acute sinusitis indication as follows:

“One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this trial, rigorous case definitions with specific clinical and either radiographic or ultrasonic entry criteria and endpoints as the primary effectiveness parameters should be used. No sinus aspiration should be required in this study, although sinus aspiration of patients judged to be therapeutic failures should be strongly encouraged to document any bacterial pathogen(s) not adequately treated in the trial. This trial should preferably be performed in the United States for purposes of US product registration.

Also suggested would be one open study utilizing sinus aspiration. This trial should establish successful microbial, clinical, and radiographic or ultrasonic outcome in at least 90 patients. This trial should be performed by at least two investigators in geographically diverse regions, and no one center should contribute more than 55% of the evaluable patients.

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4. Structure of claim

The applicant has submitted three studies in support of this indication. Overall, these studies appear to conform with the recommendations of both the IDSA document and the Divisional PTC document.

- a. study 154-114: a noncomparative, open-label, phase 2 study. Consent to undergo direct aspiration of the maxillary sinus was required for study entry. At the initiation of the study, at least 150 subjects were to be enrolled, with at least 15 investigators enrolling at least 10 subjects each. The completed study included 255 subjects, who were treated with 200 mg of trovafloxacin daily for 10 days. The investigator who enrolled the largest number of patients in this study was located in Costa Rica; other investigators were located in the UK, Finland, and the US.
- b. study 154-115: a double-blinded, prospective, comparative trial which randomized subjects to either trovafloxacin (200 mg QD x 10 days) or clarithromycin (500 mg BID for 14 days). The completed study enrolled 206 patients in the trovafloxacin arm and 214 in the clarithromycin arm. Although this protocol 'encouraged' collection of pre-therapy microbiology specimens, this was not a requirement for study entry. Thus, there are no microbiology data included in this study. It was conducted entirely in the US.
- c. study 154-138: an open label, comparative study which randomized subjects to either trovafloxacin (200 mg BID for 10 days) or amoxicillin/clavulanate (500/125 mg TID for 10 days). This study randomized 207 patients to the trovafloxacin arm and 211 to the amox/clav arm. It was conducted entirely in Europe (UK, France, Holland, Germany, Belgium, and Finland). As in study 115, pre-randomization microbiology specimen collection was encouraged but not required; unlike study 115, there were actually 16 trovafloxacin and 14 amox/clav patients who agreed to trans-antral sinus puncture.

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5. Medical officer comments:

- a. Issue of endoscopically obtained microbiology specimens. Since all microbiology specimens submitted in this portion of the NDA were obtained in the standard fashion (i.e., by trans-antral puncture and aspiration of the maxillary sinus), there is no concern over the applicability of endoscopically-obtained microbiology specimens.
- b. Comments on pharmacokinetics applicable to indication. The sponsor has not performed any clinical pharmacokinetic studies which specifically examine the penetration of trovafloxacin into sinus mucosal tissue. However, Study 154-020 examined the penetration of trovafloxacin into bronchial epithelium at various time points (6, 12, and 24 hours) following a single 200 mg dose, as well as 6 hours following a multiple dose (200 mg qd x 4 days) regimen. In the 9 patients studied in the multiple-dose regimen, there was a serum: epithelial tissue concentration

ratio of 1.1, indicating a slight degree of concentration of trovafloxacin in bronchial respiratory epithelium.

c. *In vitro* MIC data for important pathogens. The proposed susceptibility breakpoints for trovafloxacin as presented in the draft labeling interpret 'susceptible' as an MIC of ≤ 2 $\mu\text{g/mL}$. The reported MIC₉₀ for the major pathogens of concern in sinusitis (as cited in the trovafloxacin investigator's brochure) are as follows: *Haemophilus influenzae* 0.008-0.03 $\mu\text{g/mL}$; *Streptococcus pneumoniae* 0.06-0.25 $\mu\text{g/mL}$; *Moraxella catarrhalis* 0.015-0.06 $\mu\text{g/mL}$; and *Staphylococcus aureus* 0.03-0.12 $\mu\text{g/mL}$ (for methicillin and ciprofloxacin-susceptible strains) to 1.0-8.0 $\mu\text{g/mL}$ (for methicillin and ciprofloxacin-resistant strains). From these data, trovafloxacin might be anticipated to show acceptable activity against the pathogens most commonly implicated in this clinical scenario.

d. Use of approved comparators. The choice of comparators for the two comparative studies appears to be acceptable. Amoxicillin/clavulanate (Augmentin®, SmithKline Beecham) is labeled for the treatment of sinusitis due to beta-lactamase-producing strains of *Moraxella catarrhalis* and *Haemophilus influenzae* at a dose of either 250 mg or 500 mg (of the amoxicillin component) TID (the duration of therapy is not specified in the package insert). Clarithromycin (Biaxin®, Abbot) is labeled for the treatment of acute maxillary sinusitis due to *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* at a dose of 500 mg BID for 14 days.

e. Domestic vs international microbiology data. The microbiology data included in this proposed indication essentially comes from one study (114), which was conducted in both the US and elsewhere. Enrollment was predominantly (194 vs. 65) domestic, and therefore the microbiology derived from this study is generally representative of domestic resistance patterns.

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Medical officer review of Sinusitis Study 154-114**APPEARS THIS WAY
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1. Per applicant

The synopsis of the applicant's final study report for study 114 is presented below; for a more complete discussion of these results, the reader is referred to the appropriate section of the NDA.

NOTE: Medical officer text will appear as Times New Roman; applicant (aka sponsor) text will appear as **ARIAL**:

AN OPEN NONCOMPARATIVE, MULTI-CENTER TRIAL DESIGNED TO ASSESS THE EFFICACY AND SAFETY OF 10 DAYS ORAL THERAPY WITH TROVAFLOXACIN (CP-99,219) (200 MG ONCE DAILY) FOR THE TREATMENT OF ACUTE SINUSITIS.

FINAL STUDY REPORT: PROTOCOL 154-114**REPORT DATE: 12 December, 1996 (Final)**

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5041	Robert Fiddes, M.D.
	5137	Richard Sterling, M.D.
	5195	Robert Ziering, M.D.
	5196	Richard Perrotta, M.D.
	5197	Trevor Goldberg, M.D.
	5198	C. Lawrence Neal, M.D.
	5218	Patrick Bianchi, M.D.
	5219	Thomas Sydnor Jr, M.D.
	5485	Peter Johnson, M.D.
	United Kingdom	5105
Finland	5388	Henrik Malmberg, M.D.
	5389	Matti Pietola, M.D.
	5391	Juhani Pukander, M.D.
	5392	Seppo Savolainen, M.D.
Costa Rica	5393	Heikki Kiukaanniemi, M.D.
	5484	Luis Arce Rodriguez, M.D.

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Study Publication: Not Applicable

Study Dates: 15 November, 1994 - 3 August, 1995

Study Objectives: The objective of this study was to evaluate the safety and efficacy of trovafloxacin administered as a 200 mg oral dose for 10 days for the treatment of subjects with acute sinusitis.

Study Design: Study 154-114 was an open, noncomparative, multicenter trial.

Evaluation Groups:	Trovafloxacin (200 mg/day)	
Entered Study ^a	255	(100%)
All Treated	254	(>99%)
Completed Treatment	243	(96%)
Completed Study	242	(95%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	251	(98%)
Clinically Evaluable ^b	235	(92%)
Bacteriological Intent-to-Treat	131	(51%)
Bacteriological Evaluable ^b	125	(49%)
Assessed for Safety		
Adverse Events	254	(100%)
Laboratory Tests	247	(97%)

a Subjects who were enrolled; Percentages for efficacy based on enrolled subjects as the denominator and percentages for safety based on all treated subjects.

b Based on End of Treatment assessment.

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Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 16 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray.

Drug Administration: Study drug was in the form of tablets and was packaged in blister packs.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection) and bacteriologic response (based on eradication or presumptive eradication of causative organisms isolated from trans-antral aspirations at baseline). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Both intent-to-treat and evaluable subjects were analyzed in this study. For clinical efficacy (clinical success rate) and bacteriological efficacy (pathogen eradication rate), confidence intervals (95%) were calculated using the normal approximation method for success rates. No inferential statistics were presented if fewer than 15 subjects had a particular baseline pathogen for the by-pathogen analysis. Safety results including adverse events, laboratory abnormalities and vital signs were analyzed using descriptive statistics.

Efficacy Results: Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects and pathogen eradication rates for bacteriologically evaluable and intent-to-treat subjects are presented in the following table.

APPENDIX
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Summary of the Sponsor's-Assessment of Clinical Response (Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=235)		Trovafloxacin 200 mg (N=227)	
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	235	(100%)	227	(100%)
Success (Cure + improvement)	213	(91%)	199	(88%)
Distribution of Clinical Response:				
Cure	110	(47%)	174	(77%)
Improvement	103	(44%)	25	(11%)
Failure	22	(9%)	22	(10%)
Relapse	NA	NA	6	(3%)
(Clinically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=251)		Trovafloxacin 200 mg (N=251)	
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	251	(100%)	251	(100%)
Success (Cure + improvement)	222	(88%)	215	(86%)
Distribution of Clinical Response:				
Cure	113	(45%)	182	(73%)
Improvement	109	(43%)	33	(13%)
Failure	29	(12%)	29	(12%)
Relapse	NA	NA	7	(3%)
Summary of Sponsor-Defined Pathogen Eradication Rates ^a (Bacteriologically Evaluable Subjects)				
	Trovafloxacin 200 mg (N=125)		Trovafloxacin 200 mg (N=121)	
Number of Pathogens				
Pathogen ^b	End of Treatment		End of Study	
<i>S. pneumoniae</i>	24/25	(96%)	24/25	(96%)
<i>H. influenzae</i>	44/45	(98%)	43/45	(96%)
<i>S. aureus</i>	18/18	(100%)	16/16	(100%)
<i>M. catarrhalis</i>	22/23	(96%)	19/21	(90%)
(Bacteriologically Intent-to-Treat Subjects)				
	Trovafloxacin 200 mg (N=131)		Trovafloxacin 200 mg (N=131)	
Number of Pathogens				
Pathogen ^b	End of Treatment		End of Study	
<i>S. pneumoniae</i>	25/26	(96%)	25/26	(96%)
<i>H. influenzae</i>	47/48	(98%)	44/46	(96%)
<i>S. aureus</i>	19/19	(100%)	17/17	(100%)
<i>M. catarrhalis</i>	22/23	(96%)	19/21	(90%)
a Includes subjects with presumptive eradication (subjects clinically improved or cured who did not undergo post-treatment transantral aspiration of the sinus). b ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline NA=Not applicable Ref.: Tables 5.1.1, 5.1.2, 5.4.1, and 5.4.2				

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg	
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	137/254	(54%)
Treatment-Related Adverse Events	87/254	(34%)
Discontinuations Due to an Adverse Event ^a	5/254	(2%)
Clinically Significant Laboratory Abnormalities	34/247	(14%)

a With the exception of one subject who was discontinued due to unrelated adverse events, all subjects were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related.
 Ref.: Tables 1.2, 6.1, 6.2, 6.3, and 7.1

Two subjects experienced serious adverse events unrelated to study drug. There were no subject deaths during the study.

Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was safe and effective in the treatment of acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 2%. The overall percentage of subjects reporting adverse events was 54%; treatment-related adverse events were reported in 34% of subjects. The most commonly reported adverse events were dizziness and headache. No subjects were discontinued due to laboratory abnormalities.

2. Per medical officer

- a. Comments on study design. This open label phase 2 study was designed and conducted to comply with the divisional Points to Consider document. As such, the medical officer has no specific criticisms of this study. The inclusion and exclusion criteria were as follows:

Inclusion Criteria

1. Age ≥16 years at baseline.
2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or ≤1 year post-menopausal) were to have had a negative urine gonadotropin pregnancy test immediately prior to entry in the study and were to have used adequate contraception both during the study and for one month after the end of the study.
3. Clinically and radiologically documented acute sinusitis as defined in Section 3.1.

4. Subjects who would submit to direct aspiration of the sinus cavity.
5. Written informed consent was to be obtained. For subjects <18 years, written informed consent from the subject's parent or legal guardian was also to be obtained.

Exclusion Criteria

1. Treatment with any other systemic antibiotic for 24 hours or longer within 2 weeks prior to the baseline assessment; or subjects with infections that may have required treatment with an antibiotic other than the study drugs.
2. Subjects with a history of chronic sinusitis (three or more episodes of sinusitis within the last 6 months).
3. Subjects with evidence or history of significant gastrointestinal, hematological, renal or cardiovascular disease or immunologic compromise (i.e., neutropenia, ARC/AIDS, non-skin cancers, or malignant melanoma).

Complete details for all inclusion/exclusion criteria can be found in the Protocol (Section 5).

Criteria for the clinical diagnosis of sinusitis were as follows:

1. Post nasal purulent discharge, nasal congestion, facial pain over affected sinus, hyposmia, and jaw pain with mastication were each to be assessed at baseline (Day 1) and at every clinic visit thereafter by the investigator and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.
2. A sinus x-ray (Water's view) was to be obtained at baseline (Visit 1, Day 1) and the end of therapy (Visit 3, Day 11) and at any other time point deemed necessary by the investigator. In addition, Caldwell's and lateral views were to be performed if the Water's view was inconclusive. The radiographs were to be compared to baseline using the following categories:
 - worse than at baseline;
 - same as baseline;
 - better than baseline;
 - complete resolution.

The evaluation timepoints were baseline (Day 1), during therapy (Day 4), end of therapy or EOT (Day 11), and end of study or EOS (Day 24). These timepoints are acceptable, with the caveat that the EOS evaluation should not be any sooner than day 24 but evaluations that come later than this will be considered acceptable.

The recruitment into the study was dominated by a small number of investigators. The total recruited into this study, by investigator in descending order, is as follows:

<u>Investigator</u>	<u>site</u>	<u>N</u>
Sydnor 5219	VA	71
Fiddes 5041	CA	32
Johnson 5485	VA	26
Savolainen 5392	Finland	21
Sterling 5137	SC	19
Rodriguez 5484	Costa Rica	16
Bianchi 5218	AL	15
Kiukaanniemi 5393	Finland	13
Goldberg 5197	NC	10
Neal 5198	LA	9
Zeiring 5195	CA	8
Pietola 5389	Finland	8
Malmberg 5388	Finland	7

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Thus it can be seen that the initial goal of the study, which was to have at least 15 investigators enrolling 10 or more subjects, was not met. There were only 9 investigators who enrolled 10 or more subjects into this study.

In order to verify the results presented by the applicant above, the medical officer undertook an audit of the primary patient data as presented in the ClinView portion of the electronic submission. The data compiled on the CRFs was checked to verify that the same information was present for each patient in the electronic portion of the database, both as presented in the 'Patient Profiles' as well as the data as present in SAS-PH Clinical.

A random sample of 10% of the enrolled subjects was identified by Patient Identification Number. This randomized list was provided by the biostatistical reviewer, Dr. Silliman. These were individually reviewed in order to verify that the data as generated by the investigator had been accurately entered into the electronic database, from which all the applicant's summary tables were generated.

The following patient profiles were examined and compared to the corresponding CRF:

<u>Patient ID number (PID)</u>	<u>Investigator</u>	<u>location</u>	<u>OK?</u>	<u>comments</u>
11450410117	Fiddes	California, USA	✓	
11450410119	" "		✓	
11450410121	" "		✓	
11450410234	" "		✓	
11451370056	Sterling	S. Carolina, USA	✓	
11451370058	" "		✓	
11451370149	" "		✓	
11452180152	Bianchi	Alabama, USA	✓	
11452190089	Sydnor	Virginia, USA	✓	
11452190140	" "		✓	

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Patient ID number (PID)	Investigator	location	OK?	comments
11452190168	Sydnor		✓	1+ nasal congestion, 3+ hyposmia at EOS; called 'cure'
11452190184	" "		●	reported as clinical 'improvement' yet had EOS re-aspilation and culture + for <i>Strep pneumo</i>
11452190198	" "		✓	
11452190224	" "		✓	
11452190227	" "		✓	
11452190228	" "			
11453880006	Malmberg	Finland	✓	
11453890005	Pietola	Finland	✓	baseline x-ray on profile states 'opacification absent', but CRF calls "Right max. sinus completely shadowed"
11453890006	" "		✓	
11453920003	Savolainen	Finland	✓	
11453920005	" "		✓	
11453920011	" "		✓	
11453920012	" "		✓	
11454840002	Rodriguez	Costa Rica	✓	
11454850175	Johnson	Virginia, USA	✓	
11454850177	" "		✓	

Medical officer conclusions regarding 10% CRF audit:

In general, the data found in the Patient Profiles and that upon which the applicant's tabular results are based was found to be consistent with the information that had been collected by the investigator during the study's conduct. The only exception was the case noted above, wherein the investigator called the subject an 'improvement' even though a repeat sinus tap was performed (in which, following a negative culture at entry, was positive for *Strep pneumo*).

Medical officer comments:

1. During the course of this NDA review, the Division of Scientific Investigations notified the review division that there was reason to be concerned about the integrity of one of the investigators in this study. Investigator #5041, Dr. Fiddes, was the second-highest enrolling investigator in this study. Since this study was noncomparative, the invalidation of this portion of the data will not cause the study to

become statistically underpowered; it does, however, have the potential to decrease the numbers of pathogens to a point where their inclusion in the labeling may become problematic. The two large phase 3 studies (reviewed below) did not collect any microbiology information. (Actually, study 138 did collect microbiology data from a small proportion of the enrolled patients, but the sponsor did not present these data in the final study report. A brief glimpse of these data reveals a total of 5 subjects in study 138 who had cultures positive for *Moraxella catarrhalis*.)

Thus, the micro section of this indication is based entirely on the results of study 114.

Dr. Fiddes enrolled a total of 32 patients into this study. These 32 included 6 patients with no growth following culture of transantral sinus puncture fluid; 3 with *Strep pneumo*; 1 with *Strep pyogenes*; 1 with *Staph aureus*; 9 with *Haemophilus influenzae*; and 12 with *Moraxella catarrhalis*. If the table presented by the sponsor in the above summary, entitled "Summary of the Sponsor's Assessment of Clinical Response", is examined, the following changes would need to be made if all of investigator 5041's patients were to be considered invalid:

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Summary of Sponsor-Defined Pathogen Eradication Rates
(Bacteriologically Intent-to-Treat Subjects)
Study 114

Pathogen	End of treatment (N = 125) per Sponsor	End of treatment minus investigator 5041
<i>S. pneumoniae</i>	25/26 (96%)	22/23 (96%)
<i>H. influenzae</i>	47/48 (98%)	38/39 (97%)
<i>S. aureus</i>	19/19 (100%)	18/18 (100%)
 <i>M. catarrhalis</i>	 22/23 (96%)	 10/11 (91%)

Thus it can be seen that the number of bacteriologically evaluable (by intent-to-treat analysis) subjects is rather small. It should also be kept in mind that these data are taken from the end-of-treatment timepoint; if the end-of-study timepoint is used, there are two fewer *M. catarrhalis* subjects.

With regard to the adequacy of these numbers, the Points to Consider document states the following:

Also suggested would be one open study utilizing sinus aspiration. This trial should establish successful microbial, clinical, and radiographic or ultrasonic outcome in at least 100 patients. This study should establish acceptable microbial and clinical outcome in at least 25 patients with H. influenzae, in at least 25 patients with S. pneumoniae, and in at least 15 patients with M. catarrhalis. Post-therapy sinus aspiration is strongly encouraged in those patients judged to be therapeutic failures so that bacterial persistence or superinfection could be determined. In this trial, outcomes on all patients enrolled should be reported, not just those patients with the bacterial pathogens mentioned previously in this paragraph. This trial should be performed by at least two investigators in geographically diverse regions, and no one center should contribute more than 55% of the evaluable patients.

When the Fiddes subjects are removed from the analysis, the numbers of *M. catarrhalis* subjects drops to a point where this organism cannot be approved for inclusion in the labeling. As noted, there were some patients in Study 138 who had microbiology data collected; however, of the 5 who had cultures positive for *M. catarrhalis*, only three randomized to the trovafloxacin arm. (One of these three isolates did not have any susceptibilities reported, but all three were assessed as 'cure' by both the investigator and sponsor at the end-of-study [EOS] timepoint.) Thus, even if these subjects are added to the totals for Study 114 (minus Fiddes), the total number of *M. catarrhalis* patients is 14.

Study 138 also contributes five trovafloxacin-treated subjects with cultures positive for *S. pneumoniae*. As can be seen above, the organism-specific results for study 114 (minus Fiddes) show a total of 23 such patients, which again does not meet the PTC criteria. Of these five patients derived from study 138, four (56950439, 57240271, 57240355, 57250205) are considered to be clinically evaluable; three of the 4 were assessed as 'cure' and one was assessed as 'improvement' at the EOS visit. If these subjects are permitted to be grouped with those of study 114, the result is a total of 25/27 *S. pneumoniae* subjects who had satisfactory outcomes.

These numbers do not preclude approval of this indication for all three of the major pathogens; they do, however, indicate that the results of the AECB and CAP studies, additional indications in which these same three pathogens play important roles, will be looked at for confirmation of trovafloxacin's efficacy in infections caused by these organisms.

2. Listing of *Staphylococcus aureus* as a pathogen in sinusitis.

The sponsor has requested that *S. aureus* be granted as a pathogen in this indication. The precise role of this organism in the pathogenesis of this disease is somewhat controversial, in large part due to the fact that anywhere from _____ of normal healthy adults will harbor *S. aureus* in their nasal cavities.

On 6 September 1997, the following electronic communication was sent by this reviewer to the sponsor:

"I have a request for some further data synthesis regarding the sinusitis indication, specifically regarding the inclusion of *Staph aureus* in the listed organisms.

As you may know, the Division has not to this date approved the acute sinusitis indication for *Staph aureus*. The role of this organism in this disease has been of some controversy, mainly because this bug is considered to be part of the normal nasal flora in some _____ proportion of the population. As stated in the IDSA Guidelines, "*S. aureus* is a common nasal contaminant and an infrequent cause of acute sinusitis." It is necessary to differentiate between persons with nasal carriage with *S. aureus* and persons who truly have an infected maxillary sinus with this bug.

To be an evaluable *Staphylococcus aureus* subject in an acute sinusitis study, the following criteria have all been used in the review of other sinusitis applications:

1. A specimen obtained by antral puncture and NOT by endoscopic cannulation and irrigation. (Not an issue with study 114.)
2. A Gram's stain of the aspirated material that shows Gram positive cocci in clusters.
3. A culture which is ONLY *Staph aureus*, not polymicrobial.
4. A quantitative culture result showing greater than 10^4 organisms in the cultured material.

Although no information of this nature was presented in tabular form (or otherwise) in the study report of study 114, the Case Record Forms appear to include such information. Would it be possible to tabulate these results so that I can efficiently review the information?"

The following information was compiled by the sponsor:

A total of 19 subjects in study 114 had *Staph aureus* in cultures of trans-antral aspirates. All of these reports were from the local, rather than the centralized (Scicor) laboratory. These 19 cases can be sorted as follows:

Of the 19, 7 were mixed cultures with other pathogens:

<i>Staph aureus</i> and <i>Haemophilus influenzae</i>	3
<i>Staph aureus</i> and <i>Enterobacter cloacae</i>	1
<i>Staph aureus</i> and <i>Escherichia coli</i>	1
<i>Staph aureus</i> and <i>Strep pneumoniae</i>	1
<i>Staph aureus</i> , <i>Serratia marcescens</i> , and <i>Pseudomonas aeruginosa</i>	1

Of the 12 remaining, 6 had no Gram stain reported.

Of the 6 with Gram stains, 3 showed Gram positive cocci.

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Of these 3, only one had quantification of the growth in culture (expressed as "Many, Profuse").

Medical officer conclusions regarding study 114:

1. This open, bacteriologically-driven study appears to demonstrate the clinical and bacteriologic efficacy of trovafloxacin in the treatment of acute bacterial maxillary sinusitis due to *Streptococcus pneumoniae* and *Haemophilus influenzae*.
2. Because of concerns over the integrity of one of the major contributing investigators in this study, the number of evaluable subjects with culture-confirmed *Moraxella catarrhalis* sinusitis is less than the number recommended by the divisional Points To Consider document.
3. The eventual recommendation regarding inclusion of *M. catarrhalis* in the product labeling will hinge upon the efficacy of trovafloxacin in other respiratory infections in which this organism plays an acknowledged role. If the drug appears efficacious in these settings, in adequate numbers to warrant inclusion of *M. catarrhalis* as a listed pathogen, then it would seem reasonable to include this organism in the labeling for acute bacterial sinusitis.
4. The data presented in this study are inadequate to support the inclusion of *Staphylococcus aureus* as a pathogen for this indication.

Medical officer review of Study 154-115

1. Introduction

The applicant conducted two phase 3 studies following the completion of study 114 (reviewed above). Both of these were prospective, randomized, studies using FDA-approved active comparators.

Study 115 was a double-blinded, double-dummy, multicenter study conducted exclusively in the US, using clarithromycin as the comparator agent. The choice of this agent and the dosage used (500 mg BID for 14 days) constitute an FDA-approved regimen for the treatment of acute sinusitis.

2. Results per applicant

The applicant's synopsis of study 115 follows:

PROTOCOL 154-115: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (CP-99,219) (200 MG DAILY) AND 14 DAYS OF ORAL CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE SINUSITIS.

Principal Investigators:

George Bensch, M.D.	Wayne Beauford, M.D.	James Allen, M.D.	James Carrabre, M.D.
Milan Brandon, M.D.	Jay Grossman, M.D.	Wade Bateman, M.D.	Jason Chu, M.D.
Timothy Bruya, M.D.	Guy Handley, M.D.	Jimmy Durden, M.D.	Kelly Stoker, M.D.
Jacques Caldwell, M.D.	Joseph Hill, M.D.	Kirk Jacobson, M.D.	
C. Andrew De Abate, M.D.	Lance Rudolph, M.D.	Stephen Kraus, M.D.	
W. Travis Ellison, M.D.	Harry Serfer, D.O.	Richard Nielsen, M.D.	
Frank Garamy, Jr., M.D.	Thomas Wolff, M.D.	Alex Pareigis, M.D.	
Robert Jones, M.D.	Kent Anthony, M.D.	Stan Parman, M.D.	
Alan Wanderer, M.D.	Michael McAdoo, M.D.	Gary Ruoff, M.D.	
W. Murray Yarbrough, M.D.	David Miller, D.O.	Irwin Spirn, M.D.	
William Ziering, M.D.	Michael Nelson, M.D.	Keith Vanzandt, M.D.	
Jeffrey Adelglass, M.D.	Randall Stoltz, M.D.	B. Thomas Bock, D.O.	

Study Publication: Not Applicable

Study Dates: 28 November 1994 - 20 March 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to clarithromycin in the treatment of subjects with acute sinusitis.

Study Design: Study 154-115 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg daily as a single dose) administered orally for 10 days versus clarithromycin (1000 mg daily as 500 mg twice daily), administered orally for 14 days for the treatment of acute sinusitis.

Evaluation Groups:

	Trovafloxacin (200 mg/day)	Clarithromycin (500 mg BID)
Entered Study ^a	206	214
All Treated	203 (100%) ^b	214 (100%) ^b
Completed Study	186 (92%)	200 (93%)
Completed Treatment	158 (78%)	181 (85%)
Evaluated for Efficacy		
Intent-to-treat	193 (94%)	203 (95%)
Evaluable ^c	162 (79%)	188 (88%)
Assessed for Safety		
Adverse Events	203 (100%)	214 (100%)
Laboratory Tests	197 (97%)	211 (99%)

a Subjects who were randomized.

b Percentages based on treated subjects as the denominator

c Based on End of Treatment assessment.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 16 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray.

Drug Administration: Study drug was in the form of tablets and was packaged in blister cards, using a double-dummy technique to maintain blinding.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Both intent-to-treat and evaluable subjects were analyzed in this study. For clinical efficacy, confidence intervals (95%) for each pairwise difference in success rates between treatments were calculated. Treatment groups were compared by a 2 degree of freedom (d.f.) chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment to account for investigator differences. Safety results including adverse events, laboratory abnormalities and vital signs were analyzed using descriptive statistics.

Efficacy Results:

Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -10.6, 4.0 and -11.0, 4.3, respectively) and at the end of study (95% CI: -10.5, 8.0 and -10.5, 7.5, respectively). Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects are presented in the following tables.

A Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=162) ^a	Clarithromycin 500 mg BID (N=188)	Trovafloxacin 200 mg (N=160)	Clarithromycin 500 mg BID (N=184)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	161 (100%)	188 (100%)	160 (100%)	184 (100%)
Success (Cure + improvement)	136 (84%)	165 (88%)	118 (74%)	138 (75%)
Distribution of Clinical Response:				
Cure	67 (42%)	84 (45%)	85 (53%)	112 (61%)
Improvement	69 (43%)	81 (43%)	33 (21%)	26 (14%)
Failure	25 (16%)	23 (12%)	25 (16%)	23 (13%)
Relapse	NA	NA	17 (11%)	23 (13%)
NA=Not applicable				
a Subject 5077-0052 did not have an end of treatment assessment within the evaluable window.				
Ref.: Table 5.1.1				

A Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinical Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=193)	Clarithromycin 500 mg BID (N=203) ^a	Trovafloxacin 200 mg (N=193)	Clarithromycin 500 mg BID (N=203)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	193 (100%)	202 (100%)	193 (100%)	203 (100%)
Success (Cure + improvement)	154 (80%)	168 (83%)	135 (70%)	145 (71%)
Distribution of Clinical Response:				
Cure	72 (37%)	84 (42%)	94 (49%)	118 (58%)
Improvement	82 (42%)	84 (42%)	41 (21%)	27 (13%)
Failure	39 (20%)	34 (17%)	39 (20%)	35 (17%)
Relapse	NA	NA	19 (10%)	23 (11%)
NA=Not applicable				
a Subject 5078-0238 was not assessed at the end of treatment.				
Ref.: Table 5.1.2				

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg (N=203)	Clarithromycin 500 mg BID (N=214)
Number and Percentage (%) of Subjects		
Adverse Events:		
All Causalities	119 (59%)	124 (58%)
Treatment-Related Adverse Events	76 (37%)	81 (38%)
Discontinuations Due to an Adverse Event ^{a, b}	32 (16%)	12 (6%)
Clinically Significant Laboratory Abnormalities	17/197 (9%)	26/211 (12%)
a With the exception of four subjects in the trovafloxacin 200 mg group and one subject in the clarithromycin group who were discontinued due to unrelated adverse events, all subjects were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related. b One additional subject (5132-0426) in the trovafloxacin group had an unrelated adverse event (ischemic colon) for which the investigator action taken was treatment given; hospitalization for surgery (Table 6.1); however, on the subject summary section of the case report form the investigator classified the reason for withdrawal from the study as adverse event (Table 4.2).		
Ref.: Tables 1.2, 6.1, 6.2, 6.3, and 7.1		

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Two subjects in each treatment group experienced serious adverse events unrelated to study drug. The outcome of one event (presumed myocardial infarction) in the clarithromycin group was death.

Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was statistically equivalent to clarithromycin 500 BID for 14 days for the treatment of acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 16% in the trovafloxacin group and 6% in the clarithromycin group. The overall percentage of adverse events was 59% in the trovafloxacin group and 58% in the clarithromycin group; treatment-related adverse events were also reported at similar rates (37% and 38%, respectively). Subjects in the trovafloxacin group had a lower percentage of adverse events associated with the special senses (6% versus 22%), and a higher percentage of adverse events associated with the central and peripheral nervous system (44% versus 17%) compared to the clarithromycin group; all other adverse events were reported at similar rates for both treatment groups. The most commonly reported adverse events were dizziness and taste perversion in the trovafloxacin and clarithromycin groups, respectively. The frequency and type of adverse laboratory events were comparable between the two treatment groups.

3. Results per Medical Officer

a. Comments on study design: This phase 3 study was designed and conducted to comply with the divisional Points to Consider document. As such, the medical officer has no specific criticisms of this study. The entry criteria, evaluability criteria, and timepoints for post-therapy follow-up are acceptable (and are identical to those enumerated for study 114, above). Although subjects were to be encouraged (but not required) to submit to pre-therapy collection of a sinus aspirate, there were apparently no willing enrollees as there is no microbiology information whatsoever submitted in the final study report.

A total of 36 investigators recruited subjects into this study. The following 20 investigators, presented in descending number of randomized subjects, recruited ten or more subjects into this study:

<u>Investigator</u>	<u>site</u>	<u>location</u>	<u>N</u>
Allen	5141	AL	32
De Abate	5078	LA	32
Durden	5143	AL	28
Bruya	5076	WA	26
Nielsen	5146	UT	24
Adelglass	5096	TX	20
McAdoo	5132	TN	20
Ellison	5079	SC	17
Wolff	5103	NC	16
Bateman	5142	ID	16
VanZandt	5151	NC	13
Garamy	5080	KY	12
Ziering	5092	CA	12
Ruoff	5149	MI	12
Serfer	5102	FL	11
Stoltz	5138	IN	11
Caldwell	5077	FL	10
Handley	5099	AL	10
Hill	5100	FL	10
Stoker	5216	UT	10

In looking at the geographic distribution of the leading enrolling centers in this study, the absence of any site in the Northeastern US is somewhat surprising. Aside from this observation, the geographic distribution of the study sites is certainly acceptable.

In order to verify the results presented by the applicant above, the medical officer undertook an audit of the primary patient data as presented in the ClinView portion of the electronic submission. The data compiled on the CRFs was checked to verify that the same information was present for each patient in the electronic portion of the database, both as presented in the 'Patient Profiles' as well as the data as present in SAS-PH Clinical.

A random sample of 10% of the enrolled subjects was identified by Patient Identification Number. This randomized list was provided by the biostatistical reviewer, Dr. Silliman. These were individually reviewed in order to verify that the data as generated by the investigator had been accurately entered into the electronic database, from which all the applicant's summary tables were generated. They were also scrutinized to determine whether the medical officer was in agreement with the sponsor's interpretation of whether the subject was evaluable or not, and a cure/improve/fail/relapse.

The following patient profiles were examined and compared to the corresponding CRF:

Clarithromycin patients

Patient ID (PID)	Investigator	location	OK?	comments
50760043	Bruya	WA	✓	no post-Rx labs
50760045	" "		✓	
50760248	" "		✓	
50760522	" "		✓	
50780065	DeAbate	LA	✓	
50790007	Ellison	SC	✓	
50960353	Adelglass	TX	✓	
50960358	" "		●	

Comment: this patient was called an 'improvement' by both the investigator and sponsor at EOS (day 32), yet was started on Keflex from day 32 to 36 for 'yellow sputum'. This, technically, does not violate the protocol but nonetheless might have been changed to 'relapse' by the sponsor.

50990090	Handley	AL	✓	
51000100	Hill	FL	✓	
51020124	Serfer	FL	✓	
51020125	" "		✓	
51410338	Allen	AL	✓	
51420350	Bateman	ID	●	

Comment: patient called 'cure' at EOS but was rated as having 3 symptoms (purulent nasal discharge, nasal congestion, and facial pain) as 1 out of 3 (on a zero to 3 rating scale); would probably be more accurately termed 'improvement', as x-ray interpreted as 'better'.

51420480	" "		✓	

Clarithromycin patients (con't)				
Patient ID (PID)	Investigator	location	OK?	comments
51430459	Durden	AL	✓	
51430498	" "		✓	
51460496	Nielsen	UT	✓	
51490312	Ruoff	MI	✓	
51510394	VanZandt	NC	✓	
52160300	Stoker	CA	✓	
52160390	" "		✓	

Trovafloxacin patients				
Patient ID (PID)	Investigator	location	OK?	comments
50760047	Bruya	WA	✓	
50760241	" "		✓	
50920159	Ziering	CA	✓	
50960414	Adelglass	TX	●	

Comment: patient took one dose, had severe dizziness and nausea, and was promptly switched to cefuroxime for 10 days, resulting in clinical cure. Called clinically unevaluable (appropriately) but called a trovafloxacin 'cure' by intent-to-treat. Although this conforms to the stated criteria for inclusion in the ITT analysis, it points out a potential weakness of such an analysis. (Of course, if the patient had not responded to cefuroxime, the same rules would require that this be a trovafloxacin failure.)

50980082	Grossman	AZ	✓	
50990089	Handley	AL	✓	
50990096	" "		✓	
51000101	Hill	FL	✓	
51000226	" "		✓	
51010114	Rudolph	NM	✓	
51240266	Anthony	TX	✓	
51320388	McAdoo	TN	✓	
51410340	Allen	AL	✓	
51420479	Bateman	ID	✓	

Trovafloxacin patients (con't)				
Patient ID (PID)	Investigator	location	OK?	comments
51430330	Durden	AL	✓	
51430331	" "		✓	
51490492	Ruoff	MI	✓	
51510395	VanZandt	NC	✓	
52050022	Bock	PA	✓	
52160389	Stoker	CA	✓	

Medical officer conclusions regarding audit:

With the minor exception of the noted comments, the data as presented in the Patient Profiles was an accurate representation of the information in the actual case report forms. In general, the interpretations of the sponsor were conservative; that is, the sponsor's categorization of cure/improve/fail was the most conservative one, based on the information at hand.

The interpretations of the sponsor were made prior to the breaking of the blind, as detailed in section H.3.A of the NDA. This audit did not detect any indication that the blind was in any way compromised.

Medical officer comments:

- As noted in the summary tables, the end-of-study (EOS) Success rates for the two interventions (i.e., cure + improvement) were equivalent: 135/193 or 70% for trovafloxacin, and 145/203 or 71% for clarithromycin in the ITT subset; and 118/160 or 74% for trovafloxacin and 138/184 or 75% for clarithromycin in the Clin Eval subset. If one looks only at the end-of-study clinical cures in the two arms, however, one sees that the cure rates were 94/193 or 49% for trovafloxacin, vs. 118/203 or 58% for clarithromycin (ITT subset); and 85/160 or 53% for trovafloxacin and 112/184 or 61% for clarithromycin (Clin Eval subset). As there were no microbiology data for this study, there is no way to examine these results by specific pathogen. [For the EOS cure in the ITT subset, the 95% confidence interval for the difference between trovafloxacin and clarithromycin is (119.7%, 0.9%) with a corresponding p-value of 0.06. For EOS cure in the Clin Eval subset, the 95% CI for the difference is (-18.8%, 3.3%), with a p-value of 0.15. Thus, the two arms of this study meet the criteria for equivalence when just the 'cures' are evaluated.]
- Comparatively, the EOS clinical cure rates for study 114, an open noncomparative study, was 77% for the clinically evaluable subset and 73% for the ITT subset.
- The IDSA guidelines (page S76) call for the differentiation of clinical response into dichotomous variables of clinical cure (defined as the complete resolution of signs and symptoms at the conclusion of antimicrobial therapy and at follow-up) and clinical failure, along with categories such as early and late relapse. No provision is made for the clinical response category of 'improvement'. These are guidelines, however, and FDA medical reviewers are not bound by these general recommendations.
- Previous medical officer reviews of this indication have defined 'cure' as the resolution of all baseline signs and symptoms (although it is generally agreed that radiographic cure is not necessary). A category of 'improvement' has not previously been utilized.

Medical officer conclusions regarding efficacy results, study 115:

1. This double-blinded study supports the clinical efficacy of trovafloxacin in the treatment of acute bacterial sinusitis, both when the clinical endpoint is 'success' and when analysis is restricted to the clinical endpoint of 'cure'.
2. The clinical cure rates in this double-blinded study were substantially lower than the rates reported in the open-label, uncontrolled study 114 (77% vs 53% at EOS in the Clin Eval subset). This may reflect the extremely conservative approach taken by the applicant in evaluating the outcomes of subjects prior to the breaking of the blind, as well as some degree of investigator bias in favor of the drug in the open-label phase 2 study 114.

Medical officer review of sinusitis study 154-138

1. Introduction

The applicant conducted two phase 3 studies following the completion of study 114 (reviewed above). Both of these were prospective, randomized, studies using FDA-approved active comparators.

Study 138 was a open-label, comparative, multicenter study conducted exclusively outside of the US, using amoxicillin/clavulanate as the comparator agent. The choice of this agent and the dosage used (500 mg TID for 10 days) constitute an FDA-approved regimen for the treatment of acute sinusitis. (It should, however, be mentioned that although the precise duration of therapy for acute sinusitis is not specified in the approved product labeling, a ten-day course of amoxicillin/clavulanate would be considered the shortest acceptable duration of therapy by most Infectious Disease experts).

2. Results per applicant

The applicant's study synopsis for study 138 follows:

PROTOCOL 154-138: A RANDOMISED, OPEN, MULTI-CENTRE TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (CP-99,219) (200 MG ONCE DAILY) WITH ORAL AMOXYCILLIN/CLAVULANATE (AUGMENTIN, 500/125 MG TID) FOR THE TREATMENT OF ACUTE SINUSITIS.

Principal Investigators:

Professor Jacques Soudant	Dr. F. R. Cranfield	Dr. G. Levi
Professor Jean-Paul Monteil	Dr. I. G. V. James	Frau Dr. Doris Jenner
Professor L. Gilain	Dr. T. K. Khong	Dr. Udo Rahmel
Dr. Perrin	Dr. J. K. Agarwala	Dr. M. Schiffmann
Dr. P. Corlieu	Dr. S. A. Ahmed	Dr. I. Senfleber
Dr. Francoise Vonie	Dr. D. M. Allin	Dr. P. Sann
Professor Stoll	Dr. M. C. Brown	Dr. W. Motzko
Professor Pignat	Dr. J. B. Frazer	Dr. L. Capiou
Professor Chabolle	Dr. Safi U. Khan	Dr. Clarysse
Professor Bernard Meyer	Dr. P. Marazzi	Dr. H. Flore
Dr. Andre Coste	Dr. N. H. Patel	Dr. Lousbergh
Professor Legent	Dr. R. S. Paton	Dr. E. Schatteman
Dr. Denis Lafarge	Dr. J. Qualtrough	Dr. De Vlieger
Professor Morgon	Dr. B. D. Silvert	Dr. Elias Kivisaari
Dr. G. Amsellem	Dr. C. Marshall	Dr. Hannu Markkanen
Dr. J. Danon	Dr. M. L. Mairs	Dr. Juhani Nuutinen
Dr. L. Meaux	Dr. C. Langdon	Dr. Jyrki Nuutinen
Dr. J. Darmon	Dr. P. Horsfield	Dr. Päivi Valkeinen
Dr. F. Nemni	Dr. S. J. Edwards	Dr. J. C. Koster
Dr. N. Tlili	Dr. C. Brunswig-Pitschner	Dr. H. C. C. Christiannse-Vandewalle
Dr. A. Q. D. N'Guyen	Dr. A. Djamchidi	Dr. H. Mulder
Dr. B. Passerat	Dr. Reinhold Eichler	Dr. J. C. Ehrlich
Dr. R. Jacquelin	Dr. J. Horn	

Study Publication: None

Study Dates: 25 May 1995 - 11 April 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin and amoxicillin/clavulanate in the treatment of subjects with acute sinusitis.

Study Design: Study 154-138 was a randomized, open, comparative, multicenter trial.

Evaluation Groups:

	Trovafloxacin (200 mg/day)	Amoxicillin/ Clavulanate (500/125 mg TID)
Randomized	207	211
All Treated	205 (100%)	209 (100%)
Completed Study	191 (93%)	201 (96%)
Completed Treatment	189 (92%)	196 (94%)
Evaluated for Efficacy ^a		
Intent-to-treat	202 (98%)	211 (100%)
Evaluable	189 (91%)	203 (96%)
Assessed for Safety		
Adverse Events	205 (100%)	209 (100%)
Laboratory Tests	200 (98%)	206 (99%)

a. Evaluability was determined at end of treatment.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 18 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray, were eligible to participate in this study.

Drug Administration: Study drug was in the form of trovafloxacin tablets and amoxicillin/clavulanate tablets packaged in bottles or blister packs.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Treatment groups were compared using the confidence interval approach. Confidence intervals (95%) were produced for the difference in success rates between treatments using the normal approximation method. Additionally, a chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment was used to account for investigator differences. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

Efficacy: Comparisons of the difference between the two treatment groups in sponsor -defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -0.8, 8.3 and -1.4, 8.6, respectively) and at the end of study (95% CI: -5.2, 7.2 and -5.2, 7.1, respectively). Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects are presented in the following tables.

ADDITIONAL TABLES

Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinically Evaluable Subjects)					
	End of Treatment			End of Study	
	Trovafloxacin 200 mg (N=189)	Amoxicillin/ Clavulanate 500/125 mg TID (N=203)	Trovafloxacin 200 mg (N=189)	Amoxicillin/ Clavulanate 500/125 mg TID (N=203)	
Number and Percentage (%) of Subjects					
Number of Subjects Assessed	188 (100%)	201 (100%)	175 (100%)	196 (100%)	
Success (Cure + improvement)	181 (96%)	186 (93%)	158 (90%)	175 (89%)	
Distribution of Clinical Response:					
Cure	90 (48%)	80 (40%)	123 (70%)	125 (64%)	
Improvement	91 (48%)	106 (53%)	35 (20%)	50 (26%)	
-Failure	7 (4%)	15 (7%)	7 (4%)	15 (8%)	
Relapse			10 (6%)	6 (3%)	
NA=Not applicable Ref.: Table 5.1.1					
Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinically Intent-to-Treat Subjects)					
	End of Treatment			End of Study	
	Trovafloxacin 200 mg (N=202)	Amoxicillin/ Clavulanate 500/125 mg TID (N=211)	Trovafloxacin 200 mg (N=202)	Amoxicillin/ Clavulanate 500/125 mg TID (N=211)	
Number and Percentage (%) of Subjects					
Number of Subjects Assessed ^a	202 (100%)	210 (100%)	202 (100%)	211 (100%)	
Success (Cure + improvement)	191 (95%)	191 (91%)	180 (89%)	186 (88%)	
Distribution of Clinical Response:					
Cure	93 (46%)	82 (39%)	136 (67%)	132 (63%)	
Improvement	98 (49%)	109 (52%)	44 (22%)	54 (26%)	
Failure	11 (5%)	19 (9%)	11 (5%)	19 (9%)	
Relapse			11 (5%)	6 (3%)	
NA=Not applicable a One subject in the amoxicillin/clavulanate group had a missing assessment at the end of treatment but was assessed at the end of study. Ref.: Table 5.1.2					

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg	Amoxicillin/Clavulanate 500/125 mg TID
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	77/205 (38%)	62/209 (30%)
Treatment-Related Adverse Events	52/205 (25%)	48/209 (23%)
Discontinuations From Treatment Due to an Adverse Event	15/205 (7%)	7/209 (3%)
Clinically Significant Laboratory Abnormalities	38/200 (19%)	56/206 (27%)
Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.2, 6.3, 7.1, and Appendix I, Table 3.1.		

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No deaths were reported during this study. One subject in the trovafloxacin group had a serious adverse event (intentional overdose with Co-proxamol), which occurred ten days after the last treatment dose and led to hospitalization. This serious adverse event was attributed to reactive depression and was noted as having resolved. No serious adverse events were reported during this study for any subject in the amoxicillin/clavulanate group.

Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was statistically equivalent to amoxicillin/clavulanate 500/125 mg three times daily for 10 days for clinical success rates at the end of treatment in subjects with acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 7% in the trovafloxacin group and 3% in the amoxicillin/clavulanate group. The overall percentage of all and treatment-related adverse events for subjects in the trovafloxacin group was comparable to that of subjects in the amoxicillin/clavulanate group (38% and 25% versus 30% and 23%, respectively). The most commonly reported treatment-related adverse events were dizziness in the trovafloxacin group and diarrhea in the amoxicillin/clavulanate group.

3. Results per Medical Officer

a. Comments on study design: This phase 3 study was designed and conducted in compliance with the IDSA Guidelines for the Evaluation of Anti-Infective Drug Products and the Divisional Points To Consider document. The entry criteria, evaluability criteria, and timepoints for post-therapy follow-up are acceptable (and are identical to those enumerated for studies 114 and 115, above). Although subjects were to be encouraged (but not required) to submit to pre-therapy collection of a sinus aspirate, there were very few enrollees willing to do so, as no microbiology information was presented in the study report. (A total of 8 subjects had microbiology data collected, which appears in table 16, Appendix V of the complete study report for study 154-138.)

The choice of duration of therapy should also be mentioned. Since this study was an open label comparison, there would seem to be no reason (from a study design standpoint) that a 14-day regimen for amoxicillin/clavulanate could not have been selected. (In other words, since the study was not double-blinded, it would have been logistically quite easy to design the study in this way.) The previously reviewed study (115) was designed to be double-blinded despite the discrepancy in durations of therapy between the two arms (10 days for trovafloxacin and 14 days for clarithromycin).

Of the 68 principal investigators listed at the beginning of this study report, 42 of them actually enrolled subjects. The greatest number of subjects were enrolled from the UK (149), followed by Germany (99) and France (64). The ten leading investigators in this study were:

Center	Investigator	Location	# randomized
5695	Kivisaari	Finland	39
5722	Brunswig	Germany	31
5274	Cranfield	UK	31
5674	Ahmed	UK	30
5730	Senfleber	Germany	20
5701	Clarysse	Belgium	19
5727	Jenner	Germany	18
5675	Allin	UK	17
6397	Tlili	France	16
5724	Eichler	Germany	16

It would thus appear that enrollment in this study was not dominated by investigators from one particular country, but was relatively well distributed throughout Western Europe.

b. Results of Case report form audit: As was done with the previously reviewed studies in this indication, a random sample of 10% of the subjects was selected by the reviewing biostatistician, Dr. Nancy Silliman. The case record forms of this sample were carefully reviewed to ascertain the consistency of the information therein contained, compared to the data as it appears on the corresponding Patient Profile for that patient. The investigator's and applicant's interpretation of the results for that patient, with regard to whether that patient was considered clinically evaluable or not, and what the final outcome was determined to be, were reviewed for discrepancies from the protocol.

Trovafloxacin subjects

Patient ID (PID)	Investigator	Location	OK?	Comments
52740075	Cranfield	UK	✓	EOT eval < 14 days post Rx
52740085	"_"		✓	
52780513	Khong	UK	✓	
54690321	Vandewalle	Holland	✓	
56890022	Patel	UK	●	No CRFs present
56950403	Kivisaari	Finland	✓	
56950408	"_"		✓	
56950424	"_"		✓	
56950432	"_"		✓	
56950439	"_"		✓	
56990442	Valkeinen	Finland	✓	<i>Comment: called NOT clinically evaluable but called an ITT cure. Patient received one dose of trovafloxacin, then d/c'ed due to rash. Was assessed as a 'cure' by ITT 18 days later; no other antibiotics listed as being administered. Single dose therapy for sinusitis?</i>
57000309	Capiau	Belgium	●	<i>Comment: day 23 x-ray called 'better' on Patient Profile; no mention of x-ray at day 23 on CRF. Also, EOS visit was < 14 days post end of therapy.</i>
57000311	"_"		✓	
57060299	Schatteman	Belgium	✓	
57070617	DeVlieger	Belgium	✓	
57220350	Pitschner	Germany	✓	
57270267	Jenner	Germany	✓	
57300212	Senftleber	Germany	✓	
63200445	Marshall	UK	✓	
63970163	Tlili	France	●	<i>Comment: EOS visit 11 days post-completion of therapy. Still had 2 symptoms listed as 2/3, and one symptom as 1/3 yet considered 'improvement' and therefore a 'successful clinical outcome'.</i>
65040172	Passerat	France	✓	

Amoxicillin/clavulanate subjects

Patient ID (PID)	Investigator	Location	OK?	Comments
52740073	Cranfield	UK	●	EOS eval 10 days post-Rx
52740573	"_"		✓	
52770523	James	UK	✓	
56750066	Allin	UK	✓	
56950430	Kivisaari	Finland	✓	
56950433	"_"		✓	
56990441	Valkeinen	Finland	●	EOS eval day 12 post-Rx
57010288	Clarysse	Belgium	✓	
57010301	"_"		●	
<i>Comment: Patient listed in CRF as being clinically cured at both EOT and EOS visits; sponsor lists EOT visit as day 3 (of 10 day course of therapy) and then carries this forward to EOS (day 27) as an evaluable failure.</i>				
57220352	Pitschner	Germany	✓	
57240251	Eichler	Germany	✓	
57240272	"_"		✓	
57240353	"_"		✓	
57270268	Jenner	Germany	●	EOS eval 12 days post-Rx
57300239	Senfleber	Germany	●	EOS eval 11 days post-Rx
63210457	Mairs	UK	✓	
63220531	Langdon	UK	✓	
63230539	Horsfield	UK	✓	
63970162	Tlili	France	✓	
64620159	N'Guyen	France	●	
<i>Comment: called clinically evaluable failure by sponsor after day 4 called EOT failure then carried forward. EOT was actually day 9, called improved by investigator, then seen at day 28 and still improved. Should actually be nonevaluable due to protocol violation (patient 17 years old, and no written consent was obtained from parents).</i>				
65040171	Passerat	France	●	EOS eval 11 days post-Rx

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Medical officer review of combined safety data Sinusitis studies 154-114, 154-115, and 154-138

1. Introduction

The safety database for the three studies submitted as pivotal to the sinusitis indication consists of a total of 1085 patients, among which 662 received trovafloxacin and 423 received a comparator regimen (either clarithromycin or amoxicillin/clavulanate). All three of these studies utilized the same dosage regimen for trovafloxacin, 200 mg once daily (as two 100 mg tablets) for 10 days.

2. Sponsor's results

The following text and tables are taken from the individual study reports for the three studies:

For study 114:

Five (5) subjects, 5/254 (2%) were discontinued from treatment due to adverse events. Four of these subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related. The most frequently occurring adverse events that led to discontinuation from treatment were those associated with the gastrointestinal system and the central and peripheral nervous system. Two subjects (2/254, <1%) were discontinued due to treatment-related abdominal pain, nausea, and vomiting; and two subjects (2/254, <1%) were discontinued due to treatment-related dizziness, nausea, somnolence, and headache. The remaining subject was discontinued due to epistaxis, headache, and emotional lability, none of which were considered by the investigator to be related to study drug.

When corrected for baseline abnormalities, clinically significant post-baseline laboratory abnormalities were observed for 14% (34/247) of subjects. The majority of these abnormal values were attributed to the subject's underlying condition or represented a sporadic occurrence for a given subject. For liver function parameters, no subjects had clinically significant abnormalities in aspartate aminotransferase (SGOT, >2.0 x ULN) and alanine aminotransferase (SGPT, >2.0 x ULN). In addition, no subjects had clinically significant hemoglobin (<80% of LLN), hematocrit (<80% of LLN), creatinine (>1.3 x ULN), or total bilirubin (>1.5 x ULN) values.

The median changes from baseline to the last observation were small and not clinically meaningful for all laboratory parameters analyzed with the exception of neutrophils which decreased by >10% indicating a reduction in the inflammatory process.

Table A. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects) Study 114	
	Trovafloxacin 200 mg (N=254)
	Number and Percentage (%) of Subjects
Number of Subjects With at Least One Adverse Event ^c	137 (54%)
BODY SYSTEM WHO Term	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	83 (33%)
Dizziness	51 (20%)
Headache	34 (13%)
Vertigo	7 (3%)
GASTROINTESTINAL SYSTEM	40 (16%)
Nausea	30 (12%)
Vomiting	10 (4%)
Diarrhea	7 (3%)
RESPIRATORY SYSTEM	26 (10%)
Epistaxis	9 (4%)
a ≥3 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. Ref.: Tables 6.2 and 6.4	

The majority of adverse events were mild or moderate in intensity (Tables 6.1, 6.4, 6.5, and Appendix I, Table 7). Eight subjects (8/254, 3%) reported 12 adverse events that were considered by the investigator to be of severe intensity. Six severe adverse events were considered to be treatment-related; 6 severe adverse events were considered to be not related to treatment. The most common severe adverse events were those associated with the central and peripheral nervous system and included dizziness, headache, and vertigo.

APPENDIX I
TABLE 7

Table B. Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects) Study 114	
	Trovafloxacin 200 mg (N=254)
	Number and Percentage (%) of Subjects
Number of Subjects With at Least One Adverse Event ^c	87 (34%)
BODY SYSTEM	
WHO Term	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	59 (23%)
Dizziness	45 (18%)
Headache	11 (4%)
Vertigo	6 (2%)
GASTROINTESTINAL SYSTEM	35 (14%)
Nausea	27 (11%)
Vomiting	9 (4%)
Diarrhea	6 (2%)
a ≥ 2 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. Ref.: Tables 6.3 and 6.5	

Medical officer comment: This open label study had an adverse event rate and profile that will be seen to be similar to subsequent, controlled studies. The most common events were dizziness, nausea, and headache. There were no deaths.

For study 115:

Forty-four (44) subjects, 32/203 (16%) in the trovafloxacin group and 12/214 (6%) in the clarithromycin group were discontinued from treatment due to adverse events. With the exception of five subjects (5077-0054, 5090-0129, 5100-0097, 5132-0426, and 5143-0499) in the trovafloxacin group who were discontinued due to adverse events that were attributed to other illnesses, events, or the disease under study and one subject (5102-0125) in the clarithromycin group who was discontinued due to an adverse event that was attributed to other events (hemorrhoids or non-steroidal anti-inflammatory drug [NSAID]-induced), all subjects discontinued from treatment had adverse events that were considered by the investigator to be study drug-related.

One additional subject (5132-0426) in the trovafloxacin group had an unrelated adverse event (ischemic colon). The subject received treatment for this event and was hospitalized for surgery (Table 6.1); however, on the subject summary section of the case report form the investigator classified the reason for withdrawal from the study as adverse event (Table 4.2).

For subjects in the trovafloxacin group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the central and peripheral nervous system. Twenty-six subjects (26/203, 13%) in this group were discontinued due to dizziness, headache, vertigo, paresthesia, and/or hypoesthesia. Four subjects (4/214, 2%) in the clarithromycin group were discontinued due to headache, dizziness, paresthesia and/or hypertonia. For subjects in the clarithromycin group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the gastrointestinal system. Nine subjects (9/214, 4%) in the clarithromycin group were discontinued due to vomiting, nausea, diarrhea, coated tongue, abdominal pain and/or blood in stool. Thirteen subjects (13/203, 6%) in the trovafloxacin group were discontinued due to nausea, vomiting, tongue edema, diarrhea, abdominal pain, and/or loose stools. All other adverse events leading to discontinuation were reported by three or less subjects in either treatment group.

One subject in the trovafloxacin group was discontinued from treatment due to interstitial nephritis (allergic) that was considered by the investigator to be related to study drug as described in the following narrative.

Subject 5083-0108, a 61 year-old white male with a history of chronic interstitial nephritis, confirmed by biopsy, proteinuria and mild renal insufficiency and a present diagnosis of acute sinusitis was treated with trovafloxacin 200 mg for 10 days. At baseline the subject's serum creatinine value was found to be elevated and his urine protein finding was Repeat serum creatinine values on Days 3 and 10 showed further increases. The subject was discontinued from treatment on Day 14 due to what the investigator defined as mild interstitial nephritis (allergic) which was not confirmed by biopsy or any other procedure. On Day 17, decreases in serum creatinine and urine protein were noted. Treatment with prednisone was initiated on Day 18 and this event was considered to be resolved on Day 25.

Table C. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects) Study 115				
	Trovafloxacin 200 mg (N=203)		Clarithromycin 500 mg BID (N=214)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	119	(59%)	124	(58%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	89	(44%)	36	(17%)
Dizziness	69	(34%)	5	(2%)
Headache	29	(14%)	27	(13%)
GASTROINTESTINAL SYSTEM	39	(19%)	52	(24%)
Nausea	23	(11%)	21	(10%)
Diarrhea	8	(4%)	12	(6%)
Abdominal Pain	5	(2%)	6	(3%)
Flatulence	3	(1%)	7	(3%)
Dyspepsia	1	(<1%)	7	(3%)
PSYCHIATRIC SYSTEM	13	(6%)	10	(5%)
Insomnia	5	(2%)	6	(3%)
REPRODUCTIVE SYSTEM	5	(2%)	5	(2%)
Vaginitis ^d	4	(3%)	3	(2%)
SPECIAL SENSES	12	(6%)	48	(22%)
Taste Perversion	2	(<1%)	44	(21%)
a ≥3 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately. Ref.: Tables 6.2 and 6.4				

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Table D. A Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects) Study 115				
	Trovafloxacin 200 mg (N=203)		Clarithromycin 500 mg BID (N=214)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	76	(37%)	81	(38%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	60	(30%)	10	(5%)
Dizziness	54	(27%)	4	(2%)
Headache	7	(3%)	4	(2%)
Paresthesia	4	(2%)	1	(<1%)
GASTROINTESTINAL SYSTEM	30	(15%)	39	(18%)
Nausea	19	(9%)	18	(8%)
Diarrhea	4	(2%)	10	(5%)
Abdominal Pain	4	(2%)	6	(3%)
Flatulence	2	(<1%)	5	(2%)
Vomiting	3	(1%)	4	(2%)
Dyspepsia	1	(<1%)	4	(2%)
REPRODUCTIVE SYSTEM	2	(<1%)	4	(2%)
Vaginitis ^d	2	(2%)	3	(2%)
SPECIAL SENSES	5	(2%)	41	(19%)
Taste Perversion	2	(<1%)	41	(19%)
a ≥2 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately. Ref.: Tables 6.3 and 6.5				

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The majority of adverse events in both treatment groups were mild or moderate in intensity (Table 6.4 and Appendix I, Table 7). Twenty-one subjects in the trovafloxacin group (21/203, 10%) and 18 subjects in clarithromycin group (18/214, 8%) reported adverse events that were considered by the investigator to be of severe intensity. Thirty-two (trovafloxacin: 19; clarithromycin: 13) severe adverse events were considered to be treatment-related; 22 (trovafloxacin: 11; clarithromycin: 11) severe adverse events were considered to be not related to treatment. Within the trovafloxacin group, the most common severe adverse events were those associated with the central and peripheral nervous system and included dizziness, headache, and paresthesia. Within the clarithromycin group, the most common severe adverse events were those associated with the central and peripheral nervous system (headache, dizziness, migraine, and paresthesia) and the gastrointestinal system (flatulence, vomiting, abdominal pain, and nausea).

Two subjects (Subjects: 5132-0462 and 5149-0407) in the trovafloxacin group and two subjects (Subjects: 5076-0045 and 5143-0325) in the clarithromycin group had serious adverse events that were considered by the investigator to be unrelated to study drug. Three of these subjects were hospitalized while receiving study medication within 7 days of last dose for treatment or surgery and the adverse events resolved; for the fourth subject (Subject: 5076-0045) the outcome of the adverse event (presumed myocardial infarction on Day 29) was death. A narrative for the subject who died can be found in Appendix I, Table 5.2.

When corrected for baseline abnormalities, clinically significant post-baseline laboratory abnormalities were observed for 9% (17/197) of subjects in the trovafloxacin group and 12% (26/211) of subjects in the clarithromycin group. The majority of these abnormal values were attributed to the subject's underlying condition or represented a sporadic occurrence for a given subject.

The percentage of subjects with laboratory values that met the criteria for clinical significance during the study was $\leq 4\%$ in both treatment groups for individual laboratory parameters except urine white blood cells $\geq 6/\text{HPF}$ (6 subjects, 4%) in the trovafloxacin group, and urine red blood cells $\geq 6/\text{HPF}$ (8 subjects, 4%) in the clarithromycin group.

For liver function parameters, the percentage of subjects with clinically significant abnormalities in aspartate aminotransferase (SGOT, $>2.0 \times \text{ULN}$) was two subjects (1%) in the trovafloxacin group. The percentage of subjects with clinically significant alanine aminotransferase (SGPT, $>2.0 \times \text{ULN}$), was three subjects (2%) in the trovafloxacin group and two subjects (1%) in the clarithromycin group.

One subject (1%) in the trovafloxacin group had a clinically significant creatinine value ($>1.3 \times \text{ULN}$); one subject ($<1\%$) in the clarithromycin group had a clinically significant total bilirubin value ($>1.5 \times \text{ULN}$); no subject in either group had clinically significant hemoglobin values ($<80\%$ of LLN).

For study 138:

Fourteen subjects (14/205, 7%) in the trovafloxacin group and six subjects (6/209, 3%) in the amoxicillin/clavulanate group were discontinued from treatment due to adverse events. Of these subjects, 13 in the trovafloxacin group and all in the amoxicillin/clavulanate group were discontinued due to adverse events that were considered by the investigator to be study drug-related. The remaining subject (Subject 6504-0169) in the trovafloxacin group was discontinued from treatment due to an adverse event that was attributed to an other event.

In addition, one subject in the trovafloxacin group (Subject 5803-0318) who was discontinued from treatment due to insufficient response and one subject in the

amoxicillin/clavulanate group (Subject 5701-0301) who was discontinued from treatment due to a laboratory abnormality also had adverse events that led to discontinuation from treatment (worsening sinusitis and worsening dyskinesia of the bile ducts, respectively). Therefore, a total of 15 of the 205 subjects (7%) in the trovafloxacin group and seven of the 209 subjects (3%) in the amoxicillin/clavulanate group had adverse events that led to discontinuation from treatment .

For subjects in the trovafloxacin group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the central and peripheral nervous system and gastrointestinal system. Ten subjects were discontinued due to central and peripheral nervous system adverse events including dizziness, paresthesia, headache, vertigo, and/or confusion and six subjects were discontinued due to gastrointestinal system adverse events including nausea, vomiting, and/or abdominal pain.

For subjects in the amoxicillin/clavulanate group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the gastrointestinal system. Six subjects were discontinued due to nausea, vomiting, diarrhea, abdominal pain, dyspepsia, and/or gastrointestinal disorder.

Table E. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects) Study 138				
	Trovafloxacin (N=205)		Amoxicillin/ Clavulanate (N=209)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	77	(38%)	62	(30%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	46	(22%)	9	(4%)
Dizziness	34	(17%)	2	(<1%)
Headache	15	(7%)	4	(2%)
GASTROINTESTINAL SYSTEM	19	(9%)	43	(21%)
Diarrhea	1	(<1%)	19	(9%)
Dyspepsia	0		6	(3%)
Nausea	9	(4%)	9	(4%)
REPRODUCTIVE SYSTEM	1	(<1%)	6	(3%)
Vaginitis ^c	1	(<1%)	5	(4%)
a ≥3% of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				
c Preferred term is gender-specific; the percentages are based on the number of males and females, appropriately.				
Ref.: Tables 6.2 and 6.4				

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Table F. Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects) Study 138		
	Trovafloxacin (N=205)	Amoxicillin/Clavulanate (N=209)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	52 (25%)	48 (23%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	36 (18%)	4 (2%)
Dizziness	30 (15%)	2 (<1%)
Headache	9 (4%)	1 (<1%)
GASTROINTESTINAL SYSTEM	11 (5%)	39 (19%)
Diarrhea	1 (<1%)	19 (9%)
Dyspepsia	0	6 (3%)
Nausea	6 (3%)	9 (4%)
REPRODUCTIVE SYSTEM	1 (<1%)	6 (3%)
Vaginitis ^c	1 (<1%)	5 (4%)
a ≥2% of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication. c Preferred term is gender-specific and the percentages are based on the number of males and females, appropriately. Ref.: Tables 6.3 and 6.5		

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No deaths were reported during this study.

Medical officer comments on combined sinusitis safety data:

It is interesting to look at the reported treatment-related adverse events for the three studies side-by-side, as the comparator regimens and blinding was different between the three studies:

Study #	114	115		138	
Design	open	double-blinded		open	
Arms/N	trova/254	trova/203	clarithro/214	trova/205	AC/209
Subjects (%) with drug-related d/c	4 (2%)	27 (13%)	11 (5%)	13 (7%)	6 (3%)
Subjects (%) with Rx-related Adverse Event:					
dizziness	45 (18%)	54 (27%)	4 (2%)	30 (15%)	2 (<1%)
nausea	27 (11%)	19 (9%)	18 (8%)	6 (3%)	9 (4%)
headache	11 (4%)	7 (3%)	4 (2%)	9 (4%)	1 (<1%)
vertigo	6 (2%)	--	--	--	--
paresthesia	--	4 (2%)	1 (<1%)	--	--
Death, any cause	0	0	1	0	0

As can be clearly seen, study discontinuations due to drug-related adverse events are more common in the trovafloxacin subjects than in the comparator subjects. Among AEs considered to be treatment-related by the investigator, over one-fourth of subjects in the double-blinded study 115 experienced dizziness, compared to 2% of clarithromycin subjects. Nausea was also a prominent trovafloxacin AE, though roughly comparable to the rate seen in both comparator arms.

There were no trovafloxacin-related adverse laboratory events that were noted to be prominent compared to comparators. The case of interstitial nephritis reported in study 115 is of interest, as the patient appeared to have a drug-related increase in serum creatinine well above his presumed baseline. The return to baseline following discontinuation of trovafloxacin would indicate some degree of causality, though the mechanism in this situation is unclear. There did not appear to be any other trovafloxacin-related increases in serum creatinine seen in the other studies, which is not surprising as the kidney is not the major route of elimination for this drug. Unfortunately the investigator caring for the patient (who had a known history of interstitial nephritis) did not obtain a urinary eosinophil study to see if the impairment in renal function was a manifestation of an allergic response to the presence of trovafloxacin (or the ester glucuronide, the major urinary metabolite) in the renal tissue.

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Overall Medical Officer Conclusions
Sinusitis Indication

1. Study 114 is an acceptable phase 2 study as described in the divisional Points To Consider document and the IDSA Guidelines. It adequately demonstrates (that is, has a clinical and presumed microbiological response rate of $\geq 70\%$) the activity of trovafloxacin in patients with acute bacterial sinusitis. Adequate numbers of the primary pathogens were obtained, with the possible exception of *Moraxella catarrhalis*. *Staphylococcus aureus* was not adequately demonstrated to be a pathogen responsible for acute sinusitis in this study.
2. Study 115 is an acceptable phase 3 study which demonstrates statistical equivalence to an approved comparator regimen. The design and conduct of this double-blinded, double-dummy study was of high quality. Although the confidence intervals are wide when just 'cures' in the two treatment arms are taken into consideration, they remain within the definition of statistical equivalence. The audit of CRFs for this study indicated that the sponsor was fairly conservative in interpreting the results of this study.
3. Study 138 should be considered supportive, at best. This study was open-label, non-US, and used a minimally acceptable comparator regimen. Audit of CRFs suggested that the open-label nature of this study may have influenced some investigators' interpretation of patient outcomes.
4. Safety results from these three studies demonstrated that up to 27% of trovafloxacin treated sinusitis patients can be expected to experience drug-related CNS adverse events, most prominently dizziness and headache. In both comparative studies, twice as many trovafloxacin-treated subjects withdrew from the study due to treatment-related AEs compared to either clarithromycin or amoxicillin/clavulanate.

Medical Officer Recommendation

It is recommended that the indication of acute sinusitis be included in the product labeling for trovafloxacin. The recommended dose should be 200 mg daily for 10 days. Listed organisms should include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and (depending on the results of the community-acquired pneumonia and acute exacerbation of chronic bronchitis indications) *Moraxella catarrhalis*.

/S/

Philip E. Coyne, Jr., MD
Medical Officer
HFD-590

concurrency: HFD-590/DivDir/Goldberger /S/
HFD-590/TL/Leissa /S/

cc:

original NDA 20-759, 20-760
HFD-590
HFD-590/DepDivDir/Albrecht
HFD-590/MO/Alivasatos
HFD-590/Pharm/Ellis
HFD-590/Biopharm/Colangelo
HFD-590/Stats/Silliman
HFD-590/CSO/

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APPENDIX I

Medical Officer's Review of NDA 20-759

Date Received: December 19, 1996
Date Assigned: December 29, 1996
Date Review Started: March 20, 1997
Date 1st Draft Completed: April 17, 1997
Date 2nd Draft Completed: July 20, 1997

DEC 17 1997

Applicant: Pfizer Central Research
Medical Research Laboratory
Eastern Point Road
Groton, CT 06340

Drug Name: Trovafloxacin Mesylate

Proprietary Name: Trovan

Pharmacologic Category: a fluoronaphthyridone related to the fluoroquinolone antibacterials

Chemical Name: (1a,5a,6a)-7-(6-amino-3-azabicyclo{3.1.0}hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate

Dosage Form: Tablet/Intravenous solution

Route of Administration: Oral/Intravenous

Strengths: 100mg
200 mg

Proposed Indication and Usage: Treatment of acute bacterial infections
Prophylaxis of infections following elective surgical procedures

Specific to this review: Uncomplicated Urinary Tract Infections including cystitis caused by *Escherichia coli*

Bacterial Prostatitis caused by *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis*,
Staphylococcus haemolyticus, or coagulase-negative Staphylococci.

Proposed Dosage and Administration: Uncomplicated Urinary Tract Infections including cystitis: 100 mg PO once a day for 3 days

Bacterial Prostatitis: 200 mg oral for 28 days

Related INDs and NDAs: NDA 20-760
IND
IND

List of Currently Approved Indications: None

Materials Reviewed: Electronic Submission/December 29, 1996
Fax/March 10, 1997 containing Tables showing the EOT and EOS assessment windows for patients in Studies 103 and 116
Fax/March 26, 1998 containing Tables showing the EOT and EOS assessment windows for patients in Studies 117 and 118 as well as efficacy Tables for 103 and 116.
Fax/April 14, 1997 containing Tables generated in SAS by Pfizer with FDA evaluable population for study 116
Fax/April 15, 1997 containing Tables generated in SAS by Pfizer with FDA evaluable population for study 103

Fax /April 16, 1997 containing Tables generated in SAS by Pfizer with FDA evaluable patients for studies 103, 116, 117, and 118

Fax/May 1, 1997 containing Tables generated in SAS by Pfizer with FDA evaluable patients for studies 117 and 118.

Fax/July 11, 1997 containing Tables generated in SAS by Pfizer with FDA evaluable patients for study 119

Oral Antimicrobial Agents Currently Approved for the Uncomplicated UTI Indication:

Ciprofloxacin®: Acute uncomplicated UTI in females caused by *Escherichia coli* and *Staphylococcus saprophyticus*.
Urinary Tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

Floxin®: Uncomplicated cystitis due to *Citrobacter diversus*, *Enterobacter aerogenes*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa*.

Lorabid®: Uncomplicated UTI (cystitis) caused by *Escherichia coli* or *Staphylococcus saprophyticus*.
Uncomplicated Pyelonephritis caused by *Escherichia coli*.

Macrobid®: indicated only for the treatment of acute uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of *Escherichia coli* and *Staphylococcus saprophyticus*.

Maxaquin®: Uncomplicated UTI (cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*.

Noroxin®: Uncomplicated UTI (including cystitis) caused by *Escherichia coli*.

Fosfomycin®: Indicated only for the treatment of uncomplicated UTIs (acute cystitis) in women due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*.

Vantin®: Uncomplicated UTI (cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*.

Ceftin®: Uncomplicated UTI caused by *Escherichia coli* or *Klebsiella pneumoniae*.

Bactrim®: for the treatment of UTIs due to susceptible strains of the following organisms: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Morganella morganii*, and *Proteus vulgaris*.

Suprax®: Uncomplicated UTI caused by *Escherichia coli* and *Proteus mirabilis*.

Enoxacin: Uncomplicated UTI (cystitis) due to *Escherichia coli*, *Staphylococcus epidermidis*, or *Staphylococcus saprophyticus*.

**Other Antimicrobial Agents Currently Approved for UTI caused by *Escherichia coli*:
(Not listed above)**

- Ancef®
- Augmentin®
- Cefizox®
- Cefobid®
- Ceptaz®
- Claforan®
- Duricef®
- Fortaz®
- Geocillin®
- Keflex®
- Macrochantin®
- Mandol®
- Keftab®
- Kefurox®
- Kefzol®
- Mefoxin®
- Mezlin®
- Monocid®
- Monurol®
- Nebcin®
- Negram®
- Netromycin®*
- Omnipen®
- Pipracil®
- Primaxin®
- Proloprim®*
- Sepra®
- Rocephin®*
- Seromycin®
- Spectrobid®
- Streptomycin®*
- Suprax®

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Tazicef®
 Tazidime®
 Ticar®
 Timentin®
 Trimex®*
 Zinacef®

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* Denotes agents also approved for UTI caused by *Klebsiella pneumoniae*

Chemistry/Manufacturing Controls: Please the Chemistry Review

Microbiology: This is a new quinolone antibacterial characterized by a novel 3-azabicyclo{3.1.0}hexyl substituent at the C-7 position which provides improved anti-bacterial activity as compared to other quinolones against Gram (+) organisms and anaerobes as well as against Gram (-) organisms. The MIC-90 values against Staphylococci are in the range _____, but less potent against Enterococci with MIC-90s in the range _____

Pertinent to the indications in this review, the MIC-90's against *Escherichia coli* are in the range _____ for *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Citrobacter freundii*. Against *Pseudomonas aeruginosa*, the range _____

Human Pharmacokinetics: Mean serum concentrations after single oral doses of 100 and 200 mg are approximately 1.0 and 2.0 mcg/mL respectively. These levels are attained approximately 1 -2 hours after dosing. With once daily dosing, the serum concentrations increase with an accumulation factor of 1.3.

Steady state concentrations are achieved by the third daily dose and the biologic half-life is approximately 9 - 11 hours. 50% of a trovafloxacin dose is excreted unchanged, (43% in the bile and 6% in the urine), while another 13% appears in the urine in the form of the ester glucuronide and 9% appears in the feces as the N-acetyl metabolite.

Mean urine concentration after single oral doses of 100 and 200 mg are approximately 2.3 mcg/mL and 4.4 mcg/mL respectively, during the 24-hour post-dosing period. After multiple 100 mg doses, the mean urinary concentrations ranged from 4.4 mcg/mL during the 0 - 2 hour interval to 2.1 mcg/mL during the 12 -24 hour interval.

Age and gender do not affect pharmacokinetics and trovafloxacin is well absorbed from the GI tract.

For further information, refer to the pharmacokinetic review.

Human Clinical Experience: The clinical development program consisted of 45 Phase I studies of oral trovafloxacin or IV alatrofloxacin. The Phase II/III program consisted of 33 studies assessing the efficacy and safety for a variety of indications.

Clinical Studies: Pertinent to this review were:

For Uncomplicated Urinary Tract Infections: Two double blind, comparative trials where the comparator agents were ciprofloxacin and norfloxacin.

For Bacterial Prostatitis: One double blind, comparative trial versus ofloxacin.

All of the above trials were designed in accordance with the DAIDP's "Points-to-Consider" document and in accordance with IDSA guidelines.

Introduction to UTI Studies:

The sponsor is seeking approval for the treatment of uncomplicated UTI including cystitis at a dose of 100 mg PO once a day for 3 days (b)(4)

Background and Definitions:

As per IDSA Guidelines, the DAIDP Guidance Document (1997), and the March 1997 Advisory Committee, there are 2 broad categories of UTI.

- Uncomplicated Urinary Tract Infections including cystitis.

Bacterial Prostatitis is not treated as a UTI and will be considered separately.

This differentiation of these clinical entities into 2 categories differs from IDSA Guidelines which divided the pathology of the urinary tract into 5 separate clinical entities. The most significant difference is that IDSA suggests that pyelonephritis, be studied separately as opposed to the DAIDPs where it has been studied in conjunction with other complicated UTIs. The Division has currently determined that the type and duration of treatment of these entities are the same and therefore should be studied together.

Additionally, IDSA recognizes uncomplicated UTI in men including prostatitis, as separate clinical entities, whereas the Division differentiates prostatitis

For the purposes of this review, uncomplicated UTI is defined as a clinical syndrome, predominantly seen in women, characterized by dysuria, increased frequency, and/or urgency in combination with pyuria and bacteruria.

For Uncomplicated UTI the MO accepted the following:

- non-pregnant adult females
- clinical signs and symptoms of an uncomplicated UTI with onset of symptoms at least 72 hours before study entry but not for longer than 1 week
- pyuria, defined as >10 leukocytes/mm³ when unspun urine was examined in a counting chamber
- a positive pretreatment urine culture within 48 hours of enrollment, defined as $\geq 10^5$ CFU/mL (it should be noted that IDSA recommends 10^3 CFU/mL)
- susceptibility testing to both test and control drug

Excluded were:

- males

- pregnant women
- patients who had 3 or more episodes of acute uncomplicated UTI in the past 12 months
- patients with evidence of factors predisposing to the development of UTI including calculi, stricture, neurogenic bladder or primary renal disease
- patients with symptoms suggestive of upper tract disease including temperature >101 F, flank pain, and chills
- patients with known hypersensitivity to one of the study drugs
- patients who had received treatment with an appropriate course of antimicrobial therapy within 48 hours of the study start.
- patients who received one dose of an antimicrobial with 24 hours of study were accepted if they meet the prerequisite colony count.

Regarding Pretreatment Colony Counts:

Traditionally, growth of bacteria in the amount of $\geq 10^5$ CFU/mL from a midstream clean catch urine, (MSU), has been required to establish the diagnosis of UTI. The IDSA guidelines of 1992, lowered this threshold to $\geq 10^3$ CFU/mL. The sponsor has adhered to the lower threshold in this application for uncomplicated UTI. IDSA Guidelines suggested that increased sensitivity might be achieved through the use of lower threshold colony counts. Kunin, in a response to IDSA in 1992 determined not to accept a lower threshold for any of the UT clinical entities so as not to lose specificity. The DAIDP's AC, 1997 also determined that loss of specificity was not acceptable in the context of clinical trials and that a threshold of $\geq 10^5$ CFU/mL should be adhered to.

Therefore, although the sponsor used $\geq 10^3$ CFU/mL as a threshold for uncomplicated UTI and $\geq 10^4$ CFU/mL for pyelonephritis, the MO adhered to current guidance and used $\geq 10^5$ CFU/mL as the threshold.

This determination was communicated to the sponsor who provided reanalysis of the data with the exclusion of patients below this threshold.

Regarding Pathogens:

In the majority of case of uncomplicated UTI the causative pathogens are *Enterobacteriaceae*, Enterococci, and *Staphylococcus saprophyticus*.

Medical Officer's Comment: *The MO did not accept patients with Uncomplicated UTI due to coagulase-negative staphylococci within the exception of Staphylococcus saprophyticus. Group B streptococci which are considered to represent perineal contamination were also not accepted.*

Trovafloxacin/Uncomplicated UTI /Special Evaluability Issues:

Prior to the presentation of the studies, a special section and analysis have been added to present certain issues with regards to the first post-study evaluability window. This issue developed during the preliminary review of the data.

Evaluability Issues:

There was discussion between the MO and the Pfizer team as to where to set the lower bound of the evaluability window for the first post-therapy visit which is also the MO TOC visit for this indication (as per the Advisory Committee, 1997). This pertained only to that population that had no growth on repeat urine culture. If a patient had between 1 and 9 colonies, they were not classified as cures, but were re-evaluated at the later 4 - 6 week visit and if they were then "cured", they were categorized as "late cures." This classification is different than that developed for those patients who were "cures" at the first visit (that is those with $< 10^3$ CFU/mL), who developed "relapses.")

At issue in these discussions were the following:

As per the protocols, the EOT visit was to have been set at 5 - 9 days post-therapy.

In contrast to this, the lower bound of the window, was arbitrarily set at 2 days post-therapy and the upper at 11. There was no commitment on DAIDP in reference to this issue.

This discussion centers on the lower bound in conjunction with the pharmacokinetics of the study drug.

The PK argument is as follows: Trovafloxacin has a long half-life of approximately 12 hours. 10 % of the oral dose is excreted into the urine and as per the sponsor's calculation, at 12 hours on a 100 mg daily dose, after multiple doses, the drug level is 4 ug/ml. At 24 hours, this would be at 2. The MIC-90 for most common Gram (-) organisms is between 0.03 - 0.06 ug/ml.

Based on this information it is expected that drug levels would decline in the following manner:

36 hours : 1.0
 48 hours : 0.5
 60 hours : 0.25
 72 hours : 0.125
 84 hours : 0.062
 96 hours : 0.03

96 hours is between 4 and 5 days after the last day of therapy.

Based on this argument by the MO and the PK information provided by the sponsor, (clinical study #154-002-503/Mean Urine Concentrations of Trovafloxacin in Healthy Male Volunteers Following Oral Administration of a Single Dose of either 100 or 300 mg), the following were determined:

Where the mean urine concentration at 72 hours is 0.2 mcg/mL for the 100 mg dose and 0.3 mcg/mL for the 300 mg dose, the MO elected to set the lower boundary of the evaluability window at study day 13 or 5 days post-therapy for the 7-day patients and at study day 9 for the 3-day patients.

The MO elected not to set an upper boundary for the first post-visit window.

The MO accepted "early failures," that is patients who were evaluated between days 3 -5 and who were changed to another antimicrobial usually for "incomplete response."

These determinations were made in accordance with IDSA Guidelines and FDA evaluability criteria that state that:

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In a study where patients receive 7 days of therapy, the first post-therapy window should be set at study days 12 -16.

In a study where the patients receive 3 days of therapy, the first post-therapy window should be set a study days 8 - 12.

As pertained to the studies under review, in study 103, there were 3 treatment arms, (trovafloxacin 100 mg qd, trovafloxacin 100 mg bid, and ciprofloxacin 250 mg bid) and 87 patients that met the MO criterion of $\geq 10^5$ CFU/mL (30, 26, and 31 patients per arm respectively). The duration of therapy was 7 days on all arms. In Table 1, the MO presented the number of patients evaluated per arm per study day (first post-therapy evaluation in relation to study day).

Table 1
Study 103/comparison of date of first post-therapy evaluation date/FDA TOC
(Dates are Study day)

Day of EOT Eval.	Trova 100 qd	Trova 100 bid	Cipro 250 bid
Study Day 3	0	0	0
5	0	0	0
7	0	0	0
8	0	0	0
9	1	0	0
10	2	0	0
11	3	0	1
12	2	4	1
13 lower bound	1	0	3
14	7	4	9
15	8	14	8
16	3	3	5
17	3	1	1
TOTAL	30	26	31

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From this Table, it became apparent that if the protocol/IDSA Guidelines and FDA Guidance had been adhered to, the lower bound of the window should have been set at study day 13, thus rendering 6 patients unevaluable on the trovafloxacin 100 qd arm and 1 unevaluable on the ciprofloxacin arm.

Thus the evaluable population would be 24, 26 and 30 patients respectively.

However, because of the long half-life of the drug in the urine, the lower bound was set at 5 days, thus there were 22, 22 and 26 evaluable patients per arm respectively.

Table 2
Study 116/comparison of date of first post-therapy evaluation date/FDA TOC
(Dates are Study Day)

Day of EOT Eval.	Trova 100 qd x 3 days	Trova 100 qd x 7 days	Norflox 400 bid x 3 days
Study Day 5	0	0	0
8	0	0	0
9	2	1	3
10	6	8	2
11	38	29	24
12	25	27	35
13	31	30	27
14	10	8	7
15	2	7	6
16	1	2	0
17	1	1	1
TOTAL	116	113	105

From this table it is apparent that if the lower bound of the window were set at day 13 for the 7-day arm, there would be 65 patients excluded, thus rendering only 48 patients evaluable.

For the patients on the 3-day arms a lower boundary set at day 9 of the study, rendered no patients unevaluable on the trovafloxacin and the norfloxacin arms, thus the evaluable population would remain at 116 and 105 patients respectively.

Overview of UTI studies:

Medical Officer's Comment: *As the sponsor stated that all of the studies pertaining to UT indications were conducted using a common procedure, the protocol overview provided in this section is common to all the studies. Any deviations were noted in each study review separately.*

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Description of Clinical Trials:

(Copied from section H of the electronic submission is Table 6 which provides an overview of all trials conducted for the treatment of urinary tract infections)

Protocol	Trovafloxacin		Comparator		Type of Study
	Dose	N ^a	Dose	N ^a	
Uncomplicated Urinary Tract Infection					
154-103	100 mg QD (7 days)	72	Ciprofloxacin 250 mg BID (7 days)	75	Phase II DB
	100 mg BID (7 days) ^b	74			
154-116	100 mg QD (3 days)	182	Norfloxacin 400 mg BID (3 days)	178	Phase III DB
	100 mg QD (7 days)	182			

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Medical Officer's Comment: *Both the MO and the sponsor considered Study 116 pivotal for the uncomplicated UTI indication.*

Definitions (as per the sponsor):

Acute uncomplicated UTI was defined as follows:

- the presence of any combination of UTI symptoms (dysuria, frequency, suprapubic pain or urgency) for 7 days or less in protocol 154-116 and 10 days or less in protocol 154-103,
- no general or regional signs of infection (chills/fever, flank pain, costovertebral angle tenderness and nausea/vomiting),
- pyuria (> 10 WBCs per mm³ of unspun urine), bacteruria ($\geq 10^3$ CFU/mL for all subjects in protocol 154-116 and women in protocol 154-103; $\geq 10^4$ CFU/mL for men in protocol 154-103), and
- no history of UTI symptoms within 4 weeks prior to the current episode for all subjects in protocol 154-116 and for women in protocol 154-103, or within 6 months prior to the current episode for men in protocol 154-103.

Subjects were excluded from protocol 154-116 if they had an actual or estimated creatinine clearance of less than 30 mL/min, an indwelling urinary catheter, or underlying structural or functional defects of the urinary system.

Medical Officer's Comment: *As stated previously, the MO accepted only those patients with a baseline colony count of $\geq 10^5$ CFU/mL except for *Staphylococcus saprophyticus* where $\geq 10^4$ CFU/mL was accepted.*

Systemic Antibiotic Usage:

(Copied from section H of the electronic submission)

Subjects could not have taken any systemic antibiotic treatment for more than 24 hours within 72 hours prior to baseline. Subjects with infections that may have required treatment with an antibiotic other than study drug were also excluded.

Medical Officer's Comment: *The MO agreed with the above statement, however, patients who received only 1 dose of another systemic antimicrobial within 24 hours of study entry were considered evaluable in the face of a positive urine culture. Additionally, any patient who was switched to another effective antimicrobial during the course of therapy was considered evaluable as a "valid failure."*

Data Analysis:

(Copied from section H of the electronic submission):

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Subject Subsets:

- **All Randomized (Double-Blind Studies) or Enrolled (Open Study) Subjects:**
The all randomized or enrolled subjects subsets included all subjects who were randomized or enrolled to a treatment group, regardless of whether or not a particular subject received any study medication.
- **All Treated Subjects:**
The all treated subject subset included all subjects who received one or more doses of study medication (active double-blind study medication for the double-blind studies).
- **Bacteriological Intent-to-Treat Subjects:**
The bacteriological intent-to-treat subjects subset included those subjects in the all randomized or enrolled subject subsets who had a baseline diagnosis of the disease under investigation as determined by protocol specific inclusion and exclusion criteria), pyuria (> 10 WBC/mm³) and at least one uropathogen identified at baseline with $\geq 10^3$ CFU/mL for uncomplicated UTI studies

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Some subjects in this subset may never have received any study medication.

Medical Officer's Comment: *The MO again states that only those patients with colony counts of $\geq 10^5$ CFU/mL were considered evaluable. All patients who received one dose of study drug were considered evaluable for safety.*

- **Bacteriologically Evaluable Subjects:**
The bacteriologically evaluable subjects subset included all subjects in the bacteriologically intent-to-treat subset who received study medication, unless one or more of the criteria for non-evaluability applied.
- **Clinical Intent-to-Treat Subjects:**
The clinical intent-to-treat subjects subset included those subjects in the all randomized or enrolled subset who had a baseline diagnosis of the disease or condition under investigation as determined by protocol specific inclusion and exclusion criteria. Some subjects in this subset may never have received any study medication.
- **Clinically Evaluable Subjects:**
The clinically evaluable subjects subset included all subjects in the bacteriologically intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied.

The following population was also defined for the uncomplicated UTI studies only:

- **Bacteriologically Evaluable Subjects with a Baseline Uropathogen $\geq 10^5$ CFU/mL:** all subjects in the bacteriologically evaluable subset with a baseline uropathogen of $\geq 10^5$ CFU/mL.

Medical Officer's Comment: *This population was the MO's evaluable population.*

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Evaluability Criteria:

As per the original protocols, the presence of any of the following conditions, rendered a patient ineligible for bacteriologic evaluability:

- insufficient therapy (less than 3 or 4 days, depending on the protocol, for uncomplicated UTI) (b)(4)
- (b)(4)
- baseline culture outside baseline visit window (> 2 days before the first dose of study medication);
- no post-baseline culture unless antibiotic for insufficient response;
- prior antibiotic usage (i.e., for > 24 hours within 3 days before Day 1 of the study);
- use of a concomitant antibiotic, given for intercurrent illness or adverse event, that was potentially effective against the condition under study unless antibiotic for insufficient response.

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Patients were included in the EOS analyses if they were the following:

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- was bacteriologically evaluable at the end of treatment visit
- had a culture within the appropriate window (unless antibiotic given for insufficient response)
- was not given antibiotics for intercurrent illness before the assessment at the end of study visit (unless given for insufficient response).

Subjects in Phase III studies with a bacteriologic evaluation of persistence or presumed persistence at the end of treatment visit but who did not have a culture determination at the end of study had the pathogen present at the end of treatment evaluation carried forward.

Medical Officer's Comment: The MO agreed with the sponsor's evaluability criteria and noted that the relationship between the above and the windows of evaluation ultimately utilized by the sponsor, was unclear. (b)(4)

(b)(4)

As per the original protocols, the presence of any of the following conditions, rendered a patient ineligible for clinical efficacy:

- insufficient therapy (less than 3 or 4 days, depending on the protocol, for uncomplicated UTI) (b)(4)
- (b)(4)
- prior antibiotic usage (i.e., for > 24 hours within 3 days before Day 1 of the study);

- use of a concomitant antibiotic, given for intercurrent illness or adverse event, that was potentially effective against the condition under study; or intercurrent illness that could confound clinical evaluation of the condition under study (unless given for insufficient response).

Subjects in the Phase II protocol were also non-evaluable for clinical efficacy if they were lost to follow-up (i.e., completed protocol specific minimum of study treatment but failed to return for the end of treatment or end of study visits). However, subjects who discontinued due to lack of efficacy or subjects who were clinical failures at the end of treatment visit and failed to return for the end of study visit were evaluable.

Subjects in Phase III studies were also non-evaluable for clinical efficacy if either of the following applied:

- no post-baseline assessment in the evaluable analysis window (unless, in the uncomplicated UTI study, the investigator's clinical response was failure before the beginning of the end of treatment window, or unless, in complicated UTI studies only, the subject was discontinued due to insufficient response);
- an antibiotic for insufficient response was given.

Patients were included in the EOS analyses (phase III studies), if they were the following:

- clinically evaluable at the end of treatment visit
- not given any antibiotics for intercurrent illness before the assessment at the end of study visit (unless given for insufficient response)
- had a clinical assessment in an appropriate window (unless antibiotic was given for insufficient response), or the subject
- had a sponsor-defined clinical response of failure or relapse.

Medical Officer's Comment: *The MO agreed with the sponsor's evaluability criteria. The only point of disagreement is that of the first window. The MO also points out that the MO TOC was applied to the EOT visit and not to the EOS. This decision was based on the recent AC meeting regarding evaluability criteria (March, 1997).*

Primary and Secondary Efficacy Endpoints:
(Copied from section H of the electronic submission)

The primary efficacy endpoint was:

- Sponsor-defined subject bacteriological response rate at the end of treatment visit.

Secondary efficacy endpoints were:

- Sponsor-defined subject bacteriological response rate at the end of study visit
- Sponsor-defined subject clinical response at the end of treatment and end of study visits
- Pathogen eradication rates at the end of treatment and end of study visits;
- (Uncomplicated UTI studies only) Investigator-defined subject clinical response at the end of treatment and end of study visits.

The definitions of the efficacy variables are provided below:

Sponsor-Defined Subject Bacteriological Response:

The sponsor-defined subject bacteriological responses, based on pathogen outcomes described in the following section, were defined as follows:

1. Eradication: eradication of all baseline uropathogens.
2. Persistence: persistence or presumed persistence of at least one baseline uropathogen.

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Sponsor-Defined Pathogen Outcome

The sponsor classified each baseline organism as a pathogen or as a non-pathogen.

Each baseline organism classified as a pathogen was assigned a sponsor-defined pathogen outcome. Multiple pathogens identified in culture samples from the same subject were assigned separate outcomes.

Baseline pathogens were assigned a separate outcome for the end of treatment and end of study visits.

The sponsor-defined pathogen outcomes were defined as follows:

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1. Eradication: Baseline pathogen absent from urine culture or reduced to $\leq 10^3$ CFU/mL for uncomplicated UTI studies,

Medical Officer's Comment: The MO agreed with the definition of "eradication" Specifically for the purposes of this review, eradication was defined as a urine culture taken within the MO defined post-therapy window that revealed that all uropathogens isolated ($\geq 10^5$ CFU/mL), at entry were reduced to $< 10^3$ CFU/mL for uncomplicated UTI.

Although the AC suggested that those patients with colony counts between 10^3 CFU/mL and 10^4 CFU/mL at the first post-therapy visit NOT be considered failures but rather be reevaluated at a later time point and be called "late cures", the MO elected NOT to apply this to the current review because of difficulties with data access.

2. Persistence: Baseline pathogen present in urine culture sample at $\geq 10^3$ CFU/mL for uncomplicated UTI studies

For the Phase II study only, an outcome of persistence was also assigned if the subject was given a concomitant antibiotic for insufficient bacteriological response at any prior time point.

Medical Officer's Comment: The MO agreed with the sponsor's definition of "persistence" which was stricter than that of the DAIDP where the presence of the original uropathogen in a urine culture taken at any time after completion of therapy in an amount of 10^5 or greater is defined as persistence.

3. Presumed Persistence: For Phase II study only: Use of concomitant antibiotic therapy due to continued clinical symptoms of the disease or condition under investigation in the absence of microbiological data.

For the Phase III studies only: Use of concomitant antibiotic therapy due to insufficient response in the absence of prior microbiological data or in the presence of microbiological data, if given at least one day before a culture.

The baseline pathogen of subjects who were lost to follow-up at either the end of treatment or end of study visits was assigned the outcome of presumed persistence if the pathogen was persistent at any previous visit.

4. Not Assessed: The baseline pathogen of subjects with no data at the end of study analysis window were treated as not assessed if they were found to be eradicated or presumed eradicated at end of treatment.

Medical Officer's Comment: The above were acceptable to the MO as the MO's TOC applied to the first post-therapy visit and not to the second.

The baseline pathogen of subjects with no positive baseline cultures and no antibiotics given for insufficient response were considered not assessed.

Medical Officer's Comment: *The MO did not understand this comment and requested clarification on March 25, 1997. The sponsor's representative responded that the above statement contained a typographical error. The word "positive" should be substituted by the word "post." Therefore this statement meant that patients without a repeat post-therapy culture in whom a "cure" could not be definitively determined despite clinical outcome, were not assessed.*

Superinfection and Colonization:
(as per the sponsor)

Pathogens not present at baseline were classified as superinfection or colonization, defined as follows:

Each non-baseline organism isolated with a colony count $\geq 10^3$ CFU/mL (uncomplicated UTI) on Day 10 (first day of end of treatment window) or after was classified as a superinfecting pathogen or colonizing organism by applying the following hierarchy. (When making these classifications, a baseline organism was defined to be any pathogen isolated within the baseline visit window with an adequate colony count).

Condition Classification:

1. Organism not on list of potential superinfecting pathogens: Colonizing Organism
2. Antibiotic given for inadequate response prior to culture: Superinfecting Pathogen
3. In the absence of antibiotic use, pyuria was present: Superinfecting Pathogen
4. All other cases Colonizing Organism

As with other culture results, if both local lab and Scior results are available for a particular patient visit, the local lab results were ignored, and no colonizing/superinfecting classifications were made for these organisms.

If a non-baseline organism was isolated on Day 10 or after, but with a missing count, then no colonization/superinfection classification was made on that organism.

Medical Officer's Comment: *The MO noted the sponsor's definition of superinfecting organisms. However, the MO adhered to the definition as it appears in the DAIDP Guidance document which states that "superinfection is defined as growth of $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen during the course of therapy". The sponsor's analysis was stricter than that of the DAIDP.*

As per Divisional policy, the MO utilized the categories of Recurrence, that is a positive culture defined as $\geq 10^5$ CFU/mL of the original uropathogen taken anytime after documented eradication at the first follow-up visit, up to and including the 4-6 week post-therapy visit, and that of New Infection, defined as a pathogen, other than the species found at baseline at a level of $\geq 10^5$ CFU/mL, present at a level $\geq 10^5$ CFU/mL anytime after treatment is finished.

Clinical Response:
(Copied from section H of the electronic submission)

Sponsor-Defined Subject Clinical Response:

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the global evaluations made by the investigator at the end of treatment and end of study visits.

The investigator classified the clinical response of the subject as cure (resolution of all signs and symptoms of the disease under study to the level that existed before baseline), improvement (uncomplicated UTI studies only; incomplete resolution

of signs and symptoms of the disease under study) or failure (lack of resolution of any of the signs and symptoms of the disease under study).

The occurrence of the following conditions superseded the investigator's assessment:

Failure: If the investigator-defined subject clinical response was failure at the end of treatment visit, then the sponsor-defined subject clinical response was failure at all subsequent visits.

Failure: If a subject was given a concomitant antibiotic for insufficient clinical response or failure at any time before the assessment plus one day, the sponsor clinical response was failure at that assessment and all subsequent assessments. If a subject did not have an assessment in a particular window and was given an antibiotic for insufficient response in that assessment window then the sponsor-defined clinical response was a failure at that timepoint and all subsequent assessments.

Failure: If a subject had no post-baseline assessment, that subject was classified as a clinical failure at both the end of treatment and end of study visits (intent-to-treat only).

Relapse:

If a subject was a clinical cure (cure or improvement for uncomplicated UTI studies) at the end of treatment visit, and was assessed by the investigator to be a failure at a subsequent visit, then that subject was classified as a clinical relapse at the end of study visit.

If a subject was a clinical cure (cure or improvement for uncomplicated UTI studies) at the end of treatment visit, but required an additional antibiotic therapy for the primary disease before the end of study visit, then the subject was classified as a clinical relapse at the end of study visit.

For the analysis of the *Clinically Intent-to-Treat Subject* subset, a 'last observation carried forward' strategy will be used for subjects who are lost to follow-up before the End of Study Visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment will be treated as missing data.

Medical Officer's Comment: *The MO agreed with the sponsor's definitions. In the MO's analysis the TOC was applied to the first post-therapy visit and the categories of "cure" and "improvement" were combined in order to provide a dichotomous cure/failed analysis.*

APPEARS THIS WAY
O.F ORIGINAL

NDA 20-759/Uncomplicated UTI

Study 154 -103:**TITLE:**

A Randomized, Double-Blind, Multicenter Trial Comparing 7 Days of Oral Therapy with Trovafloxacin (100 mg or 200 mg daily) or Ciprofloxacin (500 mg daily) for the Treatment of Uncomplicated Urinary Tract Infections.

List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5003	James McCarty, M.D.
	5005	Willis Manford Gooch, III, M.D.
	5006	Corey Tancik, M.D.
	5008	Stephen Gordon, M.D.
	5009	Robert Bedinger, Jr, M.D.
	5010	Caryn Nesbitt, M.D.
	5011	Anthony Puopolo, M.D.
	5012	Z.A. Dalu, M.D.
	5013	Larry Gideman, D.O.
	5014	Ira Klimberg, M.D.
	5017	John Gezon, M.D.
	5040	Theodore Appel, M.D.
	5041	Robert Fiddes, M.D.
	5042	Joseph Scott, M.D.
5043	Daniel Wermeling, Pharm. D.	
5044	Charles Jenkins, M.D.	

APPROVED FOR
SUBMISSION

Study Dates: December 10, 1993 - June 16, 1994

Objective: The objective of this phase II study was to compare the efficacy and safety of two doses of trovafloxacin and ciprofloxacin in the treatment of subjects with uncomplicated urinary tract infection (UTI).

Treatments: Trovafloxacin 100 mg PO daily for 7 days
 Trovafloxacin 100 mg PO twice a day for 7 days
 Ciprofloxacin 250 mg PO twice a day for 7 days

APPROVED FOR
SUBMISSION

Study Design: This was a Phase II, randomized, double-blind, double-dummy, comparative, multi-center trial of trovafloxacin 100 mg as a single dose in the morning, or trovafloxacin as a 100 mg dose twice daily or ciprofloxacin as a 250 mg dose twice daily, administered orally for 7 days.

APPROVED FOR
SUBMISSION

Protocol Overview:

(Copied from the electronic submission, is the sponsor's Schedule of Visits and Procedures):

Schedule Of Study Visits and Procedures

Visit Number:	1	2 (by phone)	3	4
Study Day:	Day 1	Day 5	Day 15	Day 36
Allowable Window:	Day 1	Day 4-6	Day 11-19	Day 29-43
Treatment Period:	Day 1 to Day 8			
Follow-up Period:			Day 9 to Day 36	

Informed Consent	X			
Demographic Information	X			
Medical History	X			
Physical Examination	X			
Concomitant Medication	X		X	X
Vital Signs	X		X	X
Dosing Record			X	
Adverse Experiences		X	X	X
Clinical Signs and Symptoms ¹	X	X ⁸	X	X
Urine assessments				
pyuria ²	X		X	X
quantitative urine culture and sensitivity ³	X		X	X
Safety Laboratory				
ESR, PT, APTT ⁴	X		X	abn
CBC + chemistry ⁵	X		X	abn
urinalysis ⁶	X		X	abn
Pregnancy Test ⁷	X			
Investigator's Clinical Evaluation		X	X	

ADVERSE EXPERIENCES
TABLE

1. includes assessment of dysuria, frequency, urgency, suprapubic pain, flank pain, and costovertebral angle tenderness
 2. to be done by local site
 3. to be done initially by the local laboratory with pure culture sent to the central laboratory for reanalysis and storage
 4. to be done by local site
 5. to be done by central laboratory and includes CBC with differential and platelet count, ALT, AST, AP, GGT, serum total protein and albumin, serum bilirubin, LDH, BUN, serum creatinine, serum calcium and phosphorus, electrolytes, blood glucose, uric acid, serum cholesterol and triglycerides
 6. to be done by central laboratory
 7. to be done by local site for women of childbearing potential only
 8. pyuria, urine culture and sensitivity, and urine drug levels to be determined for subjects returning to clinic at this time (see text)
- abn only for clinically significant abnormalities persisting at Visit 3

As noted from the schedule, on Day 1, (Visit 1), the subjects who met the criteria for clinical diagnosis of uncomplicated UTI, gave informed consent, and if they met all the inclusion and exclusion criteria, were eligible for randomization. The baseline assessment included the collection of demographic information, medical history, physical exam, concomitant medication use, and vital signs.

The presence of pyuria was to have been established within 48 hours prior to study entry and the finding of ≥ 10 WBCs/hpf at baseline was required for entry. Any intercurrent illness was also recorded.

Susceptibility testing to the study drugs was determined for all potentially significant organisms isolated and hematology, serum chemistry and urinalysis were also performed. Randomization occurred prior to the availability of the culture report, however, if no pathogen was isolated, continuation of the study drug was at the discretion of the investigator. Additionally, if a pathogen was resistant to the study agents, therapy could have been continued in the face of clinical improvement ONLY and again at the discretion of the investigator.

At Visit 2, (Day 5 or the DURING therapy visit), the subjects were contacted by phone. If they had had no signs of clinical improvement they were asked to return within 48 hours for a formal clinical and bacteriological evaluation. Additionally, if the phone contact elicited any concerns about adverse events, the subjects were instructed to return for a formal visit.

At Visit 3, (Day 15 OR 1 week after study drug completion), a microbiological and clinical assessment of the signs and symptoms of UTI was performed. Hematology, chemistry, and urinalysis were also performed at this visit. The investigator was asked to provide an evaluation of clinical response.

At Visit 4, (Day 36 OR 4 weeks following study drug completion), the subjects underwent a similar assessment to that at Visit 3. Laboratory evaluations were performed only if a clinically significant abnormality was present at Visit 3. The investigator was to provide a final determination of clinical response.

During the study, patients were not to be treated with any other systemic antimicrobial active against the pathogens under evaluation. If this became necessary, the study drug was to have been discontinued and the appropriate alternative therapy instituted.

Patients taking theophylline or warfarin had levels monitored at each study visit and dose adjustments were made if necessary. Any concomitant medication used was recorded in the CRF.

The investigator was to discontinue therapy in the event of the isolation of a resistant pathogen to either study drug during the study period ONLY if there was no indication of clinical improvement OR if there was no improvement by visit 2. Additionally, patients could be discontinued for any AE that occurred independent of their relationship to the study drug.

Any patient who was discontinued was to be followed for the whole study period.

Protocol Amendments:

The protocol was amended once, on December 14, 1993:

- to update the introduction to reflect pharmacokinetic data.
- to indicate that sensitivity testing at the local laboratory was only to be performed on urine specimens from some centers rather than ALL centers.
- to reflect monitoring procedures for subjects taking theophylline and warfarin.

STUDY POPULATION:

As per the original protocol, approximately 200 subjects were expected to be randomized in this study with 150 expected to be bacteriologically evaluable. Each participating center was to enroll a minimum of 15 evaluable subjects.

Inclusion and Exclusion Criteria:

(Copied from the electronic submission)

Inclusions:

1. Age . . . at baseline.
2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or $\leq$ one year post-menopausal) must have a negative gonadotrophin pregnancy test immediately prior to entry in the study and must use adequate contraception both during and for one month after the end of the study.
3. Clinically documented uncomplicated urinary tract infection as defined below.
4. Written informed consent must be obtained.

Exclusions:

1. Pregnant women or nursing mothers.
2. Known hypersensitivity or intolerance to any quinolone antibiotics.
4. Subjects who are currently hospitalized for any reason.
3. Treatment with any other systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline visit.
5. Subjects with infections that may require treatment with an antibiotic other than the study drugs.
4. Subjects with significant gastrointestinal or other conditions which may affect study drug absorption.
6. Subjects with evidence or history of significant hematological, renal, hepatic, or cardiovascular disease or immunologic compromise (i.e. neutropenia, ARC/AIDS, non-skin cancers, or malignant melanoma).
7. Subjects with any significant neurologic disease including all forms of epilepsy or any other condition that increases the risk of seizure (e.g. significant head injury, intracranial hemorrhage).
8. Treatment with another investigational drug within four weeks prior to the baseline visit.
9. Prior enrollment in this protocol.
10. Evidence of drug or alcohol abuse or dependence.

Medical Officer's Comment: The MO agreed with the standard criteria listed above. The MO would like to clarify that, as stated in the introduction, if a patient received only one dose of another antimicrobial prior to the start of the study and still had a microbiologically documented infection, that patient was considered evaluable by the MO.

Randomization and Blinding:

The investigator was provided with a masked randomization schedule consisting of a list of randomization numbers to which the study drugs had been randomly allocated. The investigator assigned study numbers sequentially to the subjects as they were determined to be eligible for treatment. The study number was entered onto the subject's case report form and the subject received study medication with the corresponding number.

All study personnel who evaluated subjects, and all monitors, statisticians and any other personnel who reviewed data, remained blinded during the course of the study.

Dosage and Administration:

The study drugs were in the form of tablets and capsules and packaged in blister cards using a double-dummy technique to maintain blinding. The patients received one of the 3 aforementioned regimes. All patients were to receive study medication in the morning and evening in combinations of active drug and placebos for active drug. Each card contained sufficient medication for an 8 day course of treatment, (one extra day as needed), and at the EOT visit or earlier in the case of a premature discontinuation, the appropriate entries for the tablets/capsules taken and returned was completed on the CRF and the Pfizer inventory record. Missing doses were also recorded.

Copied below from the original protocol is the administration schedule:

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloxacin (100 mg/d)	1-placebo for Ciprofloxacin 1-Trovafloxacin x 100 mg	1-placebo for Ciprofloxacin 1-placebo for Trovafloxacin
Trovafloxacin (200 mg/d)	1-placebo for Ciprofloxacin 1-Trovafloxacin x 100 mg	1-placebo for Ciprofloxacin 1-Trovafloxacin x 100 mg
Ciprofloxacin (500 mg/d)	1-Ciprofloxacin x 250 mg 1-placebo for Trovafloxacin	1-Ciprofloxacin x 250 mg 1-placebo for Trovafloxacin

Patients were instructed to start with the AM dose on Day 1, even if it was not morning and to complete a full day of medication. The investigator was to have reviewed the labeling instructions with the patients, making clear the AM and PM doses. Initially, the patients were told not to take the medication with meals, however, this was later amended to reflect only that morning and evening dosing should be approximately 12 hours apart.

The protocol reflected that mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids should not be taken within (before or after) two hours of dosing.

Microbiologic Methods:

Susceptibility to the study drugs was determined for all causative organisms isolated. Disk susceptibility and minimum inhibitory concentrations (MIC) for isolates were determined by both the local and the central laboratory using standard techniques. Each time an organism was isolated, susceptibility to the study drugs was re-established. Susceptibility to both study drugs was recorded on the subject's case report form for all isolates.

Criteria for determining susceptibility to the study drugs are summarized below:

CRITERIA	<u>Trovafloxacin</u>	<u>Ciprofloxacin⁺</u>	
	MIC* (mg/mL)	MIC (mg/mL)	Zone Diameter (mm) (5 mg Disk)
SUSCEPTIBLE	≤ 2	≤ 1	≥ 21
INTERMEDIATE	4	> 1 to ≤ 2	16-20
RESISTANT	≥ 8	> 2	≤ 15

* tentative criteria based on projections from pharmacokinetic data and in vitro susceptibility testing.

+ NCCLS criteria for organisms other than *Haemophilus influenzae* and *Neisseria gonorrhoeae*.

Efficacy and Safety evaluations:

Efficacy evaluations included assessments of bacteriological response by pathogen (assessed as eradicated, persisted, presumed persisted,) evaluation of clinical signs and symptoms, and clinical response rates (assessed as cure, improvement, failure or relapse).

The primary efficacy endpoint was the subject bacteriologic response rate at the EOT visit. Secondary endpoints were subject bacteriological response rate at the EOS visit and clinical response at the EOT and EOS visits. Pathogen eradication rates were also secondary endpoints at the EOT and EOS visits.

Safety assessments included the incidence of treatment-related adverse events, laboratory tests as noted above, and physical examinations including vital signs.

Data Analysis:

Please refer to the introduction for the sponsor's subsets.

EVALUABILITY CRITERIA:

Please refer to the introduction for an overview of the sponsor's evaluability criteria

Medical Officer's Comments:

- The MO considered any patient who received 3 days of therapy evaluable.
- Any patient who received an antimicrobial for less than 24 hours and who had a culture with $\geq 10^5$ CFU/mL of a pathogen was considered evaluable by the MO.
- The MO considered evaluable failures those patients who received an alternative antimicrobial at any time after the 3 days of therapy if appropriate follow-up had been completed.

Windows for Analysis:

(Copied from the electronic submission):

The extended windows for the intent-to-treat subjects analysis were designed to include additional subjects excluded from the evaluable subjects analysis. If a subject had two assessments in an intent-to-treat window, one of which was also in the evaluable window, the record that was in the evaluable window was to be used for the intent-to-treat analysis.

Analysis Windows			
Visit	Nominal Day Relative to Treatment Start	Window for Evaluable Analysis	Window for Intent-to-Treat Analysis
Baseline	1	-2 to 1	-2 to 1
End of Treatment	15	9 to 17	2 to 17
End of Study	36	18 to 48	18 to 55

Medical Officer's Comment: Please refer to the introduction to view the MO's determination of the analysis windows. For this study the EOT window for analysis was set at study days 13 - 18.

Primary and Secondary Efficacy Endpoints:

Medical Officer's Comment: Please refer to the introduction for the sponsor's endpoints.

Sponsor-Defined Subject Bacteriological Response:

Medical Officer's Comment: Please refer to the introduction for the sponsor's definitions of response.

DEMOGRAPHICS:

221 patients were enrolled at 13 centers. Copied and modified below is the sponsor's Table 1.3 from the Esub:

**Table 103.1
Number of Subjects Enrolled By Center: All Randomized Patients
(As per the sponsor)**

Center	Trovafoxacin						Trovafoxacin				Ciprofloxacin			
	Total Randomized N=221 (100%)		100 mg				100 mg b. i. d.				250 mg b. i. d.			
			Randomized N= 72 (32.5%)		Treated N= 72 (32.5%)		Randomized N= 74 (33.4%)		Treated N= 74 (33.4%)		Randomized N= 75 (33.9%)		Treated N= 75 (33.9%)	
5003	53	(23.9%)	18	(25.0%)	18	(25.0%)	17	(22.9%)	17	(22.9%)	18	(24.0%)	18	(24.0%)
5005	42	(19.0%)	14	(19.4%)	14	(19.4%)	14	(19.4%)	14	(19.4%)	14	(18.6%)	14	(18.6%)
5006	4	(1.8%)	1	(1.38%)	1	(1.38%)	1	(1.35%)	1	(1.35%)	2	(2.66%)	2	(2.66%)
5008	10	(4.52%)	4	(5.55%)	4	(5.55%)	3	(4.05%)	3	(4.05%)	3	(4.00%)	3	(4.00%)
5009	4	(1.8%)	0	(0%)	0	(0%)	2	(2.70%)	2	(2.70%)	2	(2.66%)	2	(2.66%)
5010	6	(2.71%)	2	(2.77%)	2	(2.77%)	2	(2.70%)	2	(2.70%)	2	(2.66%)	2	(2.66%)
5011	29	(13.1%)	10	(13.8%)	10	(13.8%)	9	(12.1%)	9	(12.1%)	10	(13.3%)	10	(13.3%)
5012	12	(5.42%)	4	(5.55%)	4	(5.55%)	4	(5.40%)	4	(5.40%)	4	(5.33%)	4	(5.33%)
5013	30	(13.5%)	10	(13.8%)	10	(13.8%)	10	(13.5%)	10	(13.5%)	10	(13.3%)	10	(13.3%)
5014	12	(5.42%)	4	(5.55%)	4	(5.55%)	4	(5.40%)	4	(5.40%)	4	(5.33%)	4	(5.33%)
5040	4	(1.8%)	2	(2.77%)	2	(2.77%)	2	(2.70%)	2	(2.70%)	0	(0%)	0	(0%)
5041	4	(1.8%)	0	(0%)	0	(0%)	2	(2.70%)	2	(2.70%)	2	(2.66%)	2	(2.66%)
5042	11	(4.97%)	3	(4.16%)	3	(4.16%)	4	(5.40%)	4	(5.40%)	4	(5.33%)	4	(5.33%)

Medical Officer's Comment: All 221 randomized patients were treated. Additionally, the majority of patients were randomized at centers 5003 (23.9%), 5005 (19%) and 5011 (13%) respectively. Of the 221 treated patients, 203 completed treatment as can be seen in MO Table 103.2 (copied from the Esub and modified by MO).

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Table 103.2
Subject Disposition, All Enrolled Patients

		Trovafloxacin 100 mg	Trovafloxacin 100 mg bid	Ciprofloxacin 250 mg bid
Subjects with Signed Consent	221			
Withdrawn Prior to Randomization	0			
Randomized		72	74	75
Randomized, But Not Treated		0	0	0
All Treated Subjects		72 (100%)	74 (100%)	75 (100%)
Withdrawn During Treatment		3 (4%)	9 (12%)	6 (8%)
Completed Treatment		69 (96%)	65 (88%)	69 (92%)
Withdrawn During Follow-up		4 (6%)	1 (1%)	1 (1%)
Completed Study		65 (90%)	64 (86%)	68 (91%)
Completed Treatment and Study		65 (90%)	64 (86%)	68 (91%)
Withdrawn During Treatment and Study		7 (10%)	10 (14%)	7 (9%)

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Medical Officer's Comment: *Of the 203 patients who completed the study, (18 withdrawn), 69/72 (96%) were on the trovafloxacin 100 mg arm, 65/74 (88%) were on the trovafloxacin 100 mg bid arm, and 69/75 (92%) were on the ciprofloxacin arm.*

Copied below from the Esub is the sponsor's further analysis of the patient population followed by the sponsor's Table 1.2 as modified by the MO.

Of the 221 treated subjects, 203 completed treatment (69/72 [96%] in the trovafloxacin 100 mg group; 65/74 [88%] in the trovafloxacin 100 mg BID group; and 69/75 [92%] in the ciprofloxacin group. One hundred and sixty-four (164) of the randomized subjects were included in the bacteriological intent-to-treat analyses (56, trovafloxacin 100 mg; 57, trovafloxacin 100 mg BID; and 51, ciprofloxacin) and 220 of the randomized subjects were included in the clinical intent-to-treat analyses (71, trovafloxacin 100 mg; 74, trovafloxacin 100 mg BID; and 75, ciprofloxacin). All treated subjects were included in analysis of adverse events (72, trovafloxacin 100 mg; 74, trovafloxacin 100 mg BID; and 75, ciprofloxacin); one hundred nineteen (119) subjects with on-treatment laboratory evaluations were included in the analysis of laboratory data (40, trovafloxacin 100 mg; 35, trovafloxacin 100 mg BID; and 44, ciprofloxacin).

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Table 103.3
Study Evaluation Groups/All Randomized Patients

	Trovafloxacin 100 mg	Trovafloxacin 100 mg bid	Ciprofloxacin 250 mg bid
All Randomized Subjects	72 (100%)	74 (100%)	75 (100%)
All Treated Subjects	72 (100%)	74 (100%)	75 (100%)
Subjects with Low Baseline Colony Count or No Pyuria	15 (21%)	17 (23%)	24 (32%)
Subjects with Inappropriate Baseline Diagnosis	1 (1%)	0	0
Bacteriologically Intent- to- Treat Subjects	56 (78%)	57 (77%)	51 (68%)
Bacteriologically Evaluable Subjects	43 (60%)	40 (54%)	41 (55%)
Bacteriologically Not Evaluable Subjects	13 (18%)	17 (23%)	10 (13%)
No post- baseline cultures	12 (17%)	14 (19%)	9 (12%)
Insufficient Therapy	1 (1%)	5 (7%)	1 (1%)
Prior Antibiotic Therapy	0	1 (1%)	0
Concomitant Antibiotic Therapy	1 (1%)	2 (3%)	1 (1%)
Bacteriologically Evaluable at End of Study Visit	40 (56%)	39 (53%)	39 (52%)
Bact. Evaluable w/ Baseline Uropathogen >10** 5 cfu/ ml	30 (42%)	26 (35%)	31 (41%)
Bact. Evaluable w/ Baseline Uropathogen >10** 5 cfu/ ml at EOS	28 (39%)	25 (34%)	29 (39%)
Subjects with Inappropriate Baseline Diagnosis	1 (1%)	0	0
Clinically Intent- to- Treat Subjects	71 (99%)	74 (100%)	75 (100%)
Clinically Evaluable Subjects	54 (75%)	50 (68%)	49 (65%)
Clinically Not Evaluable Subjects	2 (3%)	7 (9%)	2 (3%)
Lost to Follow- up	0	1 (1%)	1 (1%)
Insufficient Therapy	1 (1%)	5 (7%)	1 (1%)
Prior Antibiotic Therapy	0	1 (1%)	0
Concomitant Antibiotic Therapy	1 (1%)	2 (3%)	1 (1%)
Clinically Evaluable at End of Study Visit	46 (64%)	44 (59%)	44 (59%)
Analyzed for Safety			
Adverse Events	72 (100%)	74 (100%)	75 (100%)
Laboratory Data	40 (56%)	35 (47%)	44 (59%)

Medical Officer's Comment: The MO determined that the MO's evaluable population consisted of the subset of patients with a baseline culture of $\geq 10^5$ CFU/mL uropathogen. From Table 3, this group was comprised of 39 (42%) trovafloxacin 100 mg qd, 26 (35%) trovafloxacin 100 mg bid, and 31 (41%) ciprofloxacin patients per arm respectively.

The MO independently reviewed the CRFs and patient profile summaries on all of the patients who were withdrawn from the study, (3: trovafloxacin 100, 9: trovafloxacin 100 bid, and 6 ciprofloxacin). The MO determined that the sponsor's judgment in determining the non-evaluability of all patients was accurate. Patients excluded despite the fact that they had received >4 days of therapy, and who would have been "cures" if included, were excluded because of lack of repeat cultures. The MO did not find any cases of "early failures" that were not carried forward.

The MO determined that there was general agreement between the Reviewer's and the sponsor's determination of evaluability and outcome. Therefore the MO's analysis presented the sponsor's determinations of outcome and merely changed evaluability on those patients who had a baseline culture with $< 10^5$ CFU/mL baseline uropathogen as well as on those patients who were not within the predetermined by the MO window.

Baseline Characteristics:

The three treatment groups were comparable with respect to age, race, and weight. 2 subjects in the trovafloxacin 100 mg group, two subjects in the trovafloxacin 100 mg BID group, and five subjects in the ciprofloxacin group were males, all other subjects were female.

The median duration since onset of urinary tract symptoms was 4 days for the subjects on the trovafloxacin 100 and ciprofloxacin arms as compared to 3 days for the subjects on the trovafloxacin 100 bid arm.

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Concomitant Medications:

The majority of patients in the study received a variety of concomitant medications, however, only 4 patients received concomitant antimicrobials. These patients were reviewed. All were switched to another antimicrobial because of adverse events and NOT because of an inadequate response. None of these patients was bacteriologically evaluable.

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Protocol Deviations:

There were 19 deviations however none of these affected evaluability and were limited to age, out of order randomization, and underlying illness.

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Exclusions from Evaluation:

Please refer to MO Table 103.2. Of the 221 patients randomized, 164 were included in the bacteriological ITT analysis. The 57 patients who were excluded from the analysis were excluded because of negative baseline cultures (trovafloxacin 100: 15/72 (21%), trovafloxacin 100 bid: 17/74 (23%), ciprofloxacin 24/75 (32%) and 1 additional ciprofloxacin patient who was excluded due to an inappropriate diagnosis.

Of these 164, 124 were bacteriologically evaluable. The remaining 40 patients (trovafloxacin 100: 13/72 (18%), trovafloxacin 100 bid: 17/74 (23%), ciprofloxacin 24/75 (32%)) were excluded from the analysis because of no follow-up cultures in 12, 14 and 9 patients respectively. The remainder were excluded because of insufficient therapy and concomitant antimicrobials and have been referred to in detail previously.

The sponsor's bacteriologically evaluable population at EOT was 43, 40 and 41 patients per arm respectively.

For the sponsor's clinically evaluable population, of the 221 randomized patients, 68 were not evaluable. This included the 57 patients excluded from the bacteriologically ITT population and an additional 11 subjects (trovafloxacin 100: 2/72 (3%), trovafloxacin 100 bid 5/74 (7%), and ciprofloxacin 1/75 (1%). These patients are those who received insufficient therapy, concomitant antimicrobials or were lost to follow-up and have been referred to previously.

The sponsor's clinically evaluable population at EOT was 54, 50 and 49 patients per arm respectively.

Sponsor's Efficacy Analysis:

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Bacteriologic Response:

(Copied below from page 32 of the study report is the sponsor's Table A)

Table A. Summary of Sponsor-Defined Subject Bacteriological Response Rates at the End of Treatment and at the End of Study (Bacteriologically Evaluable Subjects)				
	Trovafloxacin 100 mg (N=43)	Trovafloxacin 100 mg BID (N=40)	Ciprofloxacin 250 mg BID (N=41)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	43 (100%)	40 (100%)	41 (100%)	
Eradication	41 (95%)	37 (93%)	38 (93%)	
Persistence	2 (5%)	3 (8%)	3 (7%)	(-7.5, 13.2)
Trova 100 mg vs. Trova 100 mg BID				(-7.5, 12.8)
Trova 100 mg vs. Ciprofloxacin				(-11.6, 11.2)
Trova 100 mg BID vs. Ciprofloxacin				
End of Study:				
Number of Subjects Assessed	39 (100%)	39 (100%)	39 (100%)	
Eradication	31 (79%)	34 (87%)	31 (79%)	
Persistence	8 (21%)	5 (13%)	8 (21%)	(-24.1, 8.8)
Trova 100 mg vs. Trova 100 mg BID				(-17.9, 17.9)
Trova 100 mg vs. Ciprofloxacin				(-8.8, 24.1)
Trova 100 mg BID vs. Ciprofloxacin				

Comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined subject bacteriological eradication rates at both the end of treatment and at the end of study showed that the three treatment groups were similar. Because this study was not powered to fall within the limits for equivalence, no definitive conclusions regarding equivalency of the three treatments could be drawn.

Medical Officer's Comment: The MO agreed with the sponsor's analysis. It appeared as if the 3 groups had numerically comparable eradication rates. The MO points out that this analysis has been done on patients with $\geq 10^3$ CFU/mL. This population can be broken down into those patients with $\geq 10^3$ CFU/mL but $< 10^5$ CFU/mL (13, 14 and 10 patients per arm respectively at EOT), and those with $\geq 10^5$ CFU/mL (28, 23 and 29 patients per arm respectively at EOT). The bacteriologic response rate for these subgroups can be seen in MO Table 103.4

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Table 103.4
Bacteriologic Response by Baseline Titer (as per the sponsor)
Population: Sponsor's Bacteriologically Evaluable

Timepoint	Treatment	$\leq 10^5$			$\geq 10^5$			Total Eradicated		
		N	n	%	N	n	%	N	n	%
EOT	Trova qd	13	13	100	30	28	93.3	43	41	95.3
	Trova bid	14	14	100	26	23	88.5	40	37	92.5
	Cipro bid	10	9	90	31	29	93.5	41	38	92.7
EOS	Trova qd	12	11	91.7	27	20	74.1	39	31	79.5
	Trova bid	14	12	85.7	25	22	88	39	34	87.2
	Cipro bid	10	7	70	29	24	82.8	39	31	79.5

Numerically comparable response rates are seen per arm at EOT and at EOS but no significant conclusions could be drawn. It is also apparent that there were 2 failures on the trovafloxacin 100 arm at EOT as compared to 3 on each of the other 2 treatment arms.

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Sponsor-Defined Pathogen Eradication Rates:

The sponsor's Table of Sponsor-Defined Pathogen Eradication Rates at EOT and at EOS for the most frequently found baseline pathogen has been copied from page 33 of the study report.

Pathogen	Trovaflloxacin 100 mg	Trovaflloxacin 100 mg BID	Ciproflloxacin 250 mg BID	95% Confidence Intervals		
				Trova 100 mg vs. Trova 100 mg BID	Trova 100 mg vs. Cipro	Trova 100 mg BID vs. Cipro
End of Treatment						
<i>E. coli</i>	37/38 (97%)	32/33 (97%)	30/31 (97%)	-7.4, 8.2	-7.4, 8.6	-8.3, 8.7
End of Study						
<i>E. coli</i>	27/34 (79%)	29/32 (91%)	25/30 (83%)	-28.1, 5.7	-23.0, 15.1	-9.4, 24.0

^a ≥ 10 isolates of a given pathogen in any treatment group.
 Ref.: Table 5.5.1

Medical Officer's comment: The sponsor's analysis showed comparable eradication rates for all 3 arms against the most frequently isolated baseline pathogen, *Escherichia coli*. The sponsor provided a similar table for patients with a baseline titer of $\geq 10^5$ CFU/mL.

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Table C. Summary of Sponsor-Defined Subject Bacteriological Response Rates at the End of Treatment and at the End of Study (Bacteriologically Evaluable Subjects With A Baseline Uropathogen $\geq 10^5$ CFU/mL)

	Trovafloxacin 100 mg (N=30)	Trovafloxacin 100 mg BID (N=26)	Ciprofloxacin 250 mg BID (N=31)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	30 (100%)	26 (100%)	31 (100%)	
Eradication	28 (93%)	23 (88%)	29 (94%)	
Persistence	2 (7%)	3 (12%)	2 (6%)	
Trova 100 mg vs. Trova 100 mg BID				(-10.3, 20.1)
Trova 100 mg vs. Ciprofloxacin				(-12.6, 12.6)
Trova 100 mg BID vs. Ciprofloxacin				(-20.1, 9.9)
End of Study:				
Number of Subjects Assessed	27 (100%)	25 (100%)	29 (100%)	
Eradication	20 (74%)	22 (88%)	24 (83%)	
Persistence	7 (26%)	3 (12%)	5 (17%)	
Trova 100 mg vs. Trova 100 mg BID				(-34.8, 6.9)
Trova 100 mg vs. Ciprofloxacin				(-30.2, 12.8)
Trova 100 mg BID vs. Ciprofloxacin				(-13.5, 24.0)

Ref.: Table 5.9

Medical Officer's Comment: The 3 arms appeared numerically comparable at the EOT although the trovafloxacin 100 qd regimen appeared less effective at the EOS visit.

Below is MO's Table 103.5, a partially copied and modified Table from the Esub. This Table shows the by-pathogen response rate in bacteriologically evaluable patients.

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Table 103.5
Table of Sponsor-Defined Pathogen Eradication Rates at the EOT
(Bacteriologically evaluable patients with baseline pathogen $\geq 10^3$ CFU/mL)

Pathogen	Trovafloracin 100			Trovafloracin 100 bid			Ciprofloracin		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
<i>Escherichia coli</i>	38	37	97.3	33	32	96.9	31	30	96.7
<i>Enterococcus faecalis</i>	3	3	100	2	2	100	1	0	50
<i>Proteus mirabilis</i>	1	1	100	-	-	-	-	-	-
<i>Acinetobacter spp.</i>	-	-	-	-	-	-	1	1	100
<i>Staphylococcus saprophyticus</i>	-	-	-	1	1	100	3	3	100
<i>Staphylococcus epidermidis</i>	-	-	-	1	1	100	-	-	-
<i>Staphylococcus haemolyticus</i>	-	-	-	-	-	-	1	1	100
<i>Pseudomonas aeruginosa</i>	-	-	-	-	-	-	1	0	0
<i>Staphylococcus aureus</i>	1	1	100	1	1	100	-	-	-
<i>Enterobacter aerogenes</i>	-	-	-	-	-	-	2	2	100
<i>Enterobacter cloacae</i>	-	-	-	-	-	-	1	1	100
<i>Serratia marcescens</i>	-	-	-	1	0	0	-	-	-
Group B streptococcus	1	1	100	-	-	-	-	-	-
<i>Klebsiella pneumoniae</i>	2	1	50	3	2		2	2	100
Total	46	44	95.6	42	39	92.8	43	40	93

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Medical Officer's Comment: The bacterial eradication rates were comparable for all 3 arms of this study.

Copied below, is sponsor's Table F, The Summary of Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS for the Most Frequently Isolated Baseline Uropathogen, (*Escherichia coli*), in subjects with baseline colony counts $\geq 10^5$ CFU/mL.

Table D. Summary of Sponsor-Defined Pathogen Eradication Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Uropathogens $\geq 10^6$ CFU/mL ^a (Bacteriologically Evaluable Subjects)						
Pathogen	Trovafloracin 100 mg	Trovafloracin 100 mg BID	Ciprofloracin 250 mg BID	95% Confidence Intervals		
				Trova 100 mg vs. Trova 100 mg BID	Trova 100 mg vs. Cipro	Trova 100 mg BID vs. Cipro
End of Treatment						
<i>E. coli</i>	26/27 (96%)	20/21 (95%)	23/23 (100%)	-10.5, 12.6	-10.8, 3.4	-13.9, 4.3
End of Study						
<i>E. coli</i>	18/24 (75%)	19/20 (95%)	20/22 (91%)	-39.8, -0.2	-37.0, 5.2	-11.3, 19.4

^a ≥ 10 isolates of a given pathogen in any treatment group.
 Ref.: Table 5.10

Medical Officer's Comment: The 3 arms appeared comparable at the EOT but there appeared to have been a higher number of relapses amongst the patients on the trovafloracin 100 arm at the EOS as compared to the other 2 arms. Due to the small number of isolates, a 95% CI was not applied. No conclusions could be drawn with regard to the other isolates.

Superinfecting Pathogens and Colonizing Organisms:

The sponsor's text has been copied and modified from page 35 of the study report:

Superinfecting organisms were isolated from three subjects (4%) in the trovafloracin 100 mg group (*Enterococcus faecalis*, *Escherichia coli*, and *Citrobacter freundii*), from two subjects (3%) in the trovafloracin 100 mg BID group (*Enterococcus faecalis* [two isolates] and *Escherichia coli*), and three subjects (4%) in the ciprofloracin group (*Enterococcus faecalis* [two isolates], *Escherichia coli*, *S. hominis*, and streptococcus Group D [enterococcus]). Colonizing organisms were isolated from 18 subjects (25%) in the trovafloracin 100 mg group, 18 subjects (24%) in the trovafloracin 100 mg BID group, and 22 subjects (29%) in the ciprofloracin group.

Medical Officer's Comment: The most common "colonizing" organisms were gram (+) cocci and specifically Group B streptococci with 5, 4, and 8 per treatment arm.

Resistance:

None of the pathogens isolated in this study developed resistance to either study drug.

Sponsor's Analysis of Clinical Response:

Copied below from page 38 of the study report is the sponsor's table of clinical response rates for clinically evaluable subjects:

Table E. Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study (Clinically Evaluable Subjects)				
	Trovafloxacin 100 mg (N=54)	Trovafloxacin 100 mg BID (N=50)	Ciprofloxacin 250 mg BID (N=49)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	44 (100%)	42 (100%)	45 (100%)	
Success (Cure + Improvement)	42 (95%)	41 (98%)	41 (91%)	
Trova 100 mg vs. Trova 100 mg BID				(-9.9, 5.5)
Trova 100 mg vs. Ciprofloxacin				(-6.0, 14.7)
Trova 100 mg BID vs. Ciprofloxacin				(-3.0, 16.0)
Distribution of Clinical Response:				
Cure	37 (84%)	33 (79%)	39 (87%)	
Improvement	5 (11%)	8 (19%)	2 (4%)	
Failure	2 (5%)	1 (2%)	4 (9%)	
End of Study:				
Number of Subjects Assessed	46 (100%)	44 (100%)	44 (100%)	
Success (Cure + Improvement)	42 (91%)	41 (93%)	37 (84%)	
Trova 100 mg vs. Trova 100 mg BID				(-12.9, 9.2)
Trova 100 mg vs. Ciprofloxacin				(-6.3, 20.7)
Trova 100 mg BID vs. Ciprofloxacin				(-4.0, 22.2)
Distribution of Clinical Response:				
Cure	41 (89%)	40 (91%)	35 (80%)	
Improvement	1 (2%)	1 (2%)	2 (5%)	
Failure	2 (4%)	1 (2%)	4 (9%)	
Relapse	2 (4%)	2 (5%)	3 (7%)	

Ref.: Table 5.2.1

The sponsor stated that 7 of the clinically evaluable subjects were designated as clinical relapses at the EOS (2 trovafloxacin 100 mg qd patients, both with *Escherichia coli*; 2 trovafloxacin 100 mg bid patients, 1 with *Escherichia coli* and 1 with *Klebsiella pneumoniae*; and 3 ciprofloxacin patients, one each with *Enterobacter aerogenes*, *Escherichia coli*, and *Klebsiella pneumoniae*).

Medical Officer's Comment: It appeared as if all 3 treatment regimens were numerically comparable in terms of clinical efficacy. The MO was unclear as to why the initially evaluable populations of 54, 50, and 49 per arm respectively, decreased to 44, 42 and 45 per arm respectively, at the EOT visit and then changed to 46, 44 and 44 at the EOS visit. The sponsor's representative was queried as to this numerical discrepancy and responded that there was a "floating population" of patients. That is that not all patients were evaluated at both visits and that if someone had been seen at EOT, they were not necessarily seen at EOS and the opposite was true. The MO requested a list of these patients for independent review. The sponsor faxed a list of 6 trovafloxacin 100 patients, 5 trovafloxacin bid patients, and 4 ciprofloxacin patients who were seen at EOT but not at EOS. The MO is in agreement with these patients being included in the evaluable analysis as the Reviewer's TOC is at the EOT. There are however patients that have yet to be accounted for, because this list applies only to those patients with baseline $\geq 10^5$ CFU/mL, and not to the population in Table I.

The reviewer elected to accept the sponsor's explanation of this discrepancy between the total number of clinically evaluable and the number actually evaluated. The sponsor also faxed a list of patients who were evaluated only at EOS but not at EOT (clinically evaluable only). This list consisted of 3 ciprofloxacin patients, 8 trovafloxacin 100 patients, and 7 trovafloxacin bid patients. These patients were only those with baseline counts $\geq 10^5$ CFU/mL.

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The MO independently reviewed all of the cases where there was a difference between the investigator and the sponsor's assessment. Overall, the Reviewer determined that the sponsor acted appropriately and within the protocol guidelines in their reassessment of patient outcome. Differences occurred most commonly because of the receipt of another antimicrobial after the EOT (usually for another disease process), thus leading to the by-protocol exclusion of many "cures." Specifically, for the trovafloxacin 100 arm, there was a difference of opinion at the EOT in 1 patient and in 11 at the EOS; for the trovafloxacin bid arm there were 8 differences at the EOS; and for the ciprofloxacin arm, 9 at the EOS. The MO agreed with the sponsor's determination of outcome in all cases, and verified that these patients were included in the analyses when appropriate.

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Clinical Response by Baseline Pathogen:

Copied from page 42 of the study report is the sponsor's summary of clinical response in patients with *Escherichia coli* as the baseline pathogen. Following below this is the MO's review of the sponsor's Table 5.4, (clinical response for all isolates in clinically evaluable patients).

Among clinically evaluable subjects with *Escherichia coli* isolated at baseline, sponsor-defined clinical success rates (cure + improvement) at the end of treatment were 97% in all three treatment groups.

Table F. Summary of Clinical Success Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens* (Clinically Evaluable Subjects)						
	Trovafloxacin 100 mg (N=54)	Trovafloxacin 100 mg BID (N=50)	Ciprofloxacin 250 mg BID (N=49)	Trovafloxacin 100 mg (N=46)	Trovafloxacin 100 mg BID (N=44)	Ciprofloxacin 250 mg BID (N=44)
	Number of Subjects					
Pathogen	End of Treatment			End of Study		
<i>E. coli</i>	38/39 (97%)	34/35 (97%)	32/33 (97%)	35/38 (92%)	36/38 (95%)	31/33 (94%)

a ≥10 isolates of a given pathogen in any treatment group.
Several subjects were not evaluated clinically at the end of treatment.
Ref: Table 5.4

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Among subjects with baseline isolates of *Escherichia coli*, two subjects in the trovafloxacin 100 mg group, one subject in the trovafloxacin 100 mg BID group, and one subject in the ciprofloxacin group who were clinical successes at the end of treatment had relapses at the end of study.

Medical Officer's Comment: From sponsor table 5.4, the MO ascertained that at the EOT, of the 39 evaluable patients with *Escherichia coli* as the baseline pathogen, on the trovafloxacin 100 arm, there were 34 patients cured, 4 improved and 1 failure. At the EOS, the number of patients cured remained at 34, 1 was still classified as improved and 3 as failures.

On the trovafloxacin 100 bid arm, of 35 evaluable patients, 29 were cured, 5 had improved, and 1 had failed at the EOT. At the EOS, there were 38 evaluable patients, of whom, 35 were cured, 1 improved and 2 were classified as failures.

On the ciprofloxacin arm, there were 33 evaluable patients at the EOT, 31 cured, 1 improved and 1 failed. At the EOS, there were 33 evaluable patients, 30 cured, 1 improved and 2 failed.

The MO elected not to present similar data for the remaining isolates as there were < 3 evaluable patients with each isolate on all 3 arms of the study and therefore no conclusions could be drawn.

The only conclusion that was drawn from the above information was that:

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- All 3 treatment arms appeared equivalent in their effectiveness against *Escherichia coli*.

Cross-tabulation of Sponsor-Defined Subject Clinical Response, Bacteriologic Response, and Pathogen Outcome:

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The Sponsor submitted table 5.6.1 which was reviewed by the MO and which revealed that there were 9 inconsistencies between sponsor-defined clinical response and pathogen outcome at the EOT and 9 at the EOS. Specifically, on the trovafloxacin 100 mg arm, there was 1 clinical cure with bacteriologic persistence at the EOT and 2 at the EOS. There were no clinical failures with eradication on this arm.

On the trovafloxacin bid arm, there were 3 clinical successes with bacteriologic persistence and 1 clinical failure with eradication at the EOT. There were no inconsistencies at the EOS.

On the ciprofloxacin arm, there were 2 clinical successes with bacteriologic persistence and 2 failures with eradication at the EOT. At the EOS, there were 5 clinical successes with persistence and 4 clinical failures with eradication.

Copied below is sponsor's Table G from page 43 of the study report which reviews these inconsistencies:

**Table G. Summary of Inconsistencies Between Sponsor-Defined Clinical Response and Sponsor-Defined Subject Bacteriological Response and Pathogen Outcome
Clinically and Bacteriologically Evaluable Subjects**

Subject Number	Baseline Pathogen	Baseline MIC (µg/mL) Trovafloxacin ^a	Baseline MIC (µg/mL) ^a Ciprofloxacin	Clinical Response	Subject BT Response	Pathogen BT Response
Trovafloxacin 100 mg BID						
5003-0023	<i>E. coli</i>	≤0.03 µg/mL	0.03 µg/mL	Failure	Eradication	Eradication
5005-0183	<i>K. pneumoniae</i>	0.06 µg/mL	0.03 µg/mL	Improvement	Persistent	Persistent
5011-0206	<i>S. marcescens</i>	0.25 µg/mL	0.12 µg/mL	Cure	Persistent	Persistent
5042-0275	<i>E. coli</i>	≤0.03 µg/mL	0.015 µg/mL	Cure	Persistent	Persistent
Ciprofloxacin						
5005-0181	<i>P. aeruginosa</i>	0.25 µg/mL	0.12 µg/mL	Cure	Persistent	Persistent
5005-0198	<i>K. pneumoniae</i>	0.06 µg/mL	0.06 µg/mL	Failure	Eradication	Eradication
5006-0027	<i>E. faecalis</i>	0.12 µg/mL	1 µg/mL	Cure	Persistent	Persistent
	<i>E. coli</i>	≤0.03 µg/mL	0.03 µg/mL	Cure	Persistent ^b	Eradication
5042-0219	<i>S. haemolyticus</i>	1 µg/mL	8 µg/mL ^c	Failure	Eradication	Eradication

BT=Bacteriological
 a Susceptibility breakpoints for trovafloxacin are tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. Susceptibility breakpoints for ciprofloxacin are based on NCCLS criteria.
 b Subject response was persistent if any baseline pathogen was persistent.
 c Resistant to study drug at baseline.
 Ref.: Tables 5.6.1, 5.7.1 and Appendix I, Tables 8 and 8a

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Medical Officer's Comment: The MO agreed with the sponsor's determination in all subjects. No significant trends were noted.

Sponsor's Summary and Conclusions (copied from page 50 of the study report):

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Two hundred twenty-one (221) subjects were randomized to treatment with trovafloxacin 100 mg once daily, trovafloxacin 100 mg twice daily, or ciprofloxacin 250 mg twice daily for 7 days. The three treatment groups were generally comparable with respect to demographic characteristics at baseline, medical history, and prior and concomitant medications. One hundred and twenty-four (124) subjects were bacteriologically evaluable (43, trovafloxacin 100 mg; 40, trovafloxacin 100 mg BID; and 41, ciprofloxacin) and 153 subjects were clinically evaluable (54, trovafloxacin 100 mg; 50, trovafloxacin 100 mg BID; and 49, ciprofloxacin). All treated subjects were included in the analysis of adverse events.

Administration of trovafloxacin 100 mg once daily for seven days or trovafloxacin 100 mg twice daily for 7 days were shown to be effective for the treatment of uncomplicated urinary tract infections. Trovafloxacin 100 mg once daily and trovafloxacin 100 mg BID were found to be similar to ciprofloxacin 250 mg twice daily for 7 days as observed in subject bacteriological eradication rates (primary efficacy analysis) at the end of treatment for bacteriologically evaluable subjects (trovafloxacin 100 mg: 95% [41/43]; trovafloxacin 100 mg BID 93% [37/40]; and ciprofloxacin 93% [38/41]). Additionally, comparisons (95% confidence intervals) of the difference between groups in sponsor-defined pathogen eradication rates for the most frequently isolated baseline pathogen (*Escherichia coli*) showed that the three treatment groups were similar at the end of treatment and at the end of study. Because this study was not powered to fall within the limits for

equivalence, no definitive conclusions regarding equivalency of the three treatment groups could be drawn. Similar results were observed among bacteriologically intent-to-treat subjects.

Comparisons of the difference between treatment groups in sponsor-defined clinical success rates (cure + improvement) showed that the three treatment groups were similar at both evaluations. Success rates among clinically evaluable subjects ranged (b)(4) at the end of treatment and at the end of study. These findings were supported by marked decreases in the presence of clinical signs and symptoms of infection from baseline to the end of treatment and to the end of study in all three treatment groups.

Medical Officer's Analysis of Efficacy:

The MO elected not to accept as the MO evaluable population, the sponsor's bacteriologically evaluable population with baseline counts of $\geq 10^5$ CFU/mL as presented. As stated in the introduction, the MO determined that the sponsor did not adhere to the protocol-defined lower bound of the analysis window set for the EOT visit. Therefore, the MO elected to utilize a different population that that of the sponsor. The MO excluded patients from the analysis based on baseline colony counts and relative date of evaluation with day 13 of the study being the lower bound of the window.

The MO performed a random audit of every 7th patient via review of the CRFs and the electronic data set. The MO found NO inconsistencies in data transfer.

All cases of patients excluded from the analyses for protocol violations, including the use of alternative antimicrobials were reviewed and the MO found that the sponsor exercised very conservative judgment in the inclusion/exclusion of these patients. All failures were carried forward appropriately.

Of the original 221 patients, 0 were withdrawn prior to randomization and all were treated. 72 were randomized to the trovafloxacin 100 arm, 74 to the trovafloxacin 100 bid arm, and 75 to the ciprofloxacin arm.

The MO has already provided an analysis of the excluded patients. The sponsor's bacteriologically evaluable population was 43, 40, and 41 patients per arm respectively, as compared to the MO's, which was 22, 22, and 29 patients per arm respectively. This difference of 21, 18 and 12 patients is due to the exclusion by the MO of those patients with baseline colony counts of $\leq 10^5$ CFU/mL (10, 13 and 8), and the setting of the lower bound of the EOT window at Day 13 thus excluding an additional 8, 4, and 2 patients per arm respectively. The patients evaluated at the EOS were a subset of those evaluated at the EOT.

**Table 103.6
Bacteriologically Evaluable Population (as per the MO)**

Bacteriologically Evaluable Population (Baseline Pathogen $\geq 10^5$ CFU/mL)			
Reason for exclusion	Trova 100/ day	Trova 100 bid	Cipro 250 bid
	N= 221		
Total Randomized	N=72	N=74	N=75
No Baseline Pathogen	1	0	0
BSL count < 10³	15	17	24
BSL count > 10³ but < 10⁵	13	14	10
Withdrawn because of insufficient R/x/ con. AB or no consent prior to EOT	13	17	10
Out of window for EOT	8	4	2
Total Evaluable at EOT	22	22	29
Total Evaluated at EOS	20	21	27

The MO's clinically evaluable population is the same as the bacteriologically evaluable.

A by-center breakdown of the MO's evaluable population is presented in Table 103.7:

MO Table 103.7
Bacteriologically Evaluable Patients by Center/Sponsor/MO

Center	Total Randomized N = 221 (100%)		Trovafoxacin		Trovafoxacin		Ciprofloxacin		Total evaluable N = 73 (100%)	
			100 mg		100 mg b. i. d.		250 mg b. i. d.			
			Sponsor and MO Evaluable N = 22	100 %	Sponsor and MO Evaluable N = 22	100 %	Sponsor and MO Evaluable N = 29	100 %		
5003	53	(23.9%)	6	27.3	4	18.2	9	31.0	19	26.0
5005	42	(19.0%)	4	18.2	1	4.5	4	13.8	9	12.3
5006	4	(1.8%)	1	4.5	0	0	2	6.9	3	4.1
5008	10	(4.52%)	1	4.5	0	0	1	3.4	2	2.7
5009	4	(1.8%)	0	0	0	0	1	3.4	1	1.4
5010	6	(2.71%)	0	0	0	0	1	3.4	1	1.4
5011	29	(13.1%)	1	4.5	5	22.7	3	10.3	9	12.3
5012	12	(5.42%)	1	4.5	1	4.5	2	6.9	4	5.5
5013	30	(13.5%)	5	22.7	4	18.2	2	6.9	11	15.1
5014	12	(5.42%)	0	0	2	9.1	2	6.9	4	5.5
5040	4	(1.8%)	1	4.5	0	0	0	0	1	1.4
5041	4	(1.8%)	0	0	1	4.5	1	3.4	2	2.7
5042	11	(4.97%)	2	9.1	4	18.2	1	3.4	7	9.6

Approximately of the patients per arm, were from centers 5003, 5011, and 5005. However, the number of patients in this study is very small and therefore all centers were pooled.

The demographics of the FDA evaluable population can be seen in Table 103.8.

Table 103.8
Demographic Characteristics of the FDA Evaluable Population:

Characteristics	Trova 100 N = 22	Trova 100 bid N = 22	Cipro 250 bid N = 29
Sex (Female)	21	22	27
Age (years) 16 -44	14	14	22
45 - 64	6	7	7
≥ 65	2	1	0
Mean	39	38.9	36.1
Race:			
Asian	0	1	0
Black	0	2	2
White	22	19	23
Hispanic	0	0	3
Nat Am.	0	0	1
Body weight (kg) mean	65.6	69.5	72.3

Most of the subjects were female and all 3 arms consisted of a comparable population in terms of weight and age.

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Table 103.9
Bacteriologic Efficacy by Patient (Per the MO)

Timepoint	Trova 100			Trova 100 bid			Ciprofloxacin bid		
	N	no. Erad	%	N	no. Erad	%	N	no. Erad.	%
EOT	22	21	95.5	22	19	86.4	29	27	93.1
EOS	21	15	75	21	18	85.7	27	22	81.5

The MO elected not to apply a 95% CI to this analysis because of the small number of patients involved per study arm.

Trovafoxacin 100 was more numerically more effective than ciprofloxacin, and ciprofloxacin was more effective than trovafloxacin bid at the EOT. Interestingly, at the EOS, both the trovafloxacin bid and the ciprofloxacin arms were numerically superior to the trovafloxacin 100 arm. A by-pathogen analysis is presented in Table 103.10.

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Table 103.10
Bacteriologic Efficacy by Pathogen at EOT

Pathogen	Trova 100			Trova 100 bid			Ciprofloxacin bid		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
<i>Escherichia coli</i>	19	19	100	18	17	94.4	21	21	100
<i>Enterococcus faecalis</i>	-	-	-	-	-	-	1	0	0
<i>Proteus mirabilis</i>	1	1	100	-	-	-	-	-	-
<i>Enterobacter aerogenes</i>	-	-	-	-	-	-	2	2	100
<i>Pseudomonas aeruginosa</i>	-	-	-	-	-	-	1	0	0
<i>Klebsiella pneumoniae</i>	2	1	50	2	1	50	2	2	100
<i>Staphylococcus aureus</i>	-	-	-	1	1	100	-	-	-
<i>Staphylococcus saprophyticus</i>	-	-	-	1	1	100	3	3	100
<i>Serratia Marcescens</i>	-	-	-	1	0	0	-	-	-
Total	22	21	95.4	23	20	86.9	30	28	89.2

From the by-pathogen analysis, it appeared as if the trovafloxacin 100 bid arm and the ciprofloxacin arm were numerically comparable versus *Escherichia coli* and that the trovafloxacin 100 arm was numerically superior to both.

The value of applying a confidence interval to these results is again questionable. At best only numeric conclusions could be drawn from this small and underpowered study.

Clinical Efficacy Analysis:

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Table 103.11
Clinical Efficacy (FDA Bacteriologically Evaluable Population)

Timepoint	Trova 100			Trova 100 bid			Ciprofloxacin bid		
	N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
EOT	22	21	95.5	22	21	95.5	29	28	96.6
EOS	18	16	88.9	19	17	89.5	26	22	84.6

Overall, the sample sizes in this study were too small to provide any meaningful conclusions, however, all 3 arms appeared numerically comparable at the EOT, and the trovafloxacin bid arm was marginally superior at the EOS.

Table 103.12
Cross Tabulation of Clinical and Bacteriological Efficacy at the EOT for FDA Evaluable Population:

Clinical Assessment	Trova 100 N = 22				Trova 100 bid N = 22				Cipro 250 bid N = 29							
	Bact. Assessment								Bact. Assessment							
	Erad.		Pers		Erad.		Pers		Erad.		Pers					
	N	%	N	%	N	%	N	%	N	%	N	%				
Success	21	95.5	-	-	18	81.8	3	13.6	26	89.7	2	6.9				
Failure	-	-	1	4.5	1	4.5	-	-	1	3.4	-	-				
Total	21	95.5	1	4.5	19	86.4	3	13.6	27	93.1	2	6.9				

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As seen in Table 103.12, there was a lack of concurrence between clinical success and bacteriologic eradication in 3 of the 19 clinical successes on the trovafloxacin 100 bid arm and 2 of the 27 clinical successes on the ciprofloxacin arm. There were no inconsistencies on the trovafloxacin 100 arm That is these 3 and 2 patients per arm were clinical successes combined with bacteriologic persistence.

Additionally, there was 1 clinical failure with bacteriologic eradication on the trovafloxacin bid arm and 1 on the ciprofloxacin arm.

The MO identified these subjects from the line listings provided. These patients are reviewed below:

Trovafloxacin 100 bid (N=4):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp	Sup/inf. Y/N	Reviewer Determination
50110206:	Persistent	Cure	Persistent	Not assessable	N	<i>Serratia marcescens Pers./Maxaquin R/x, N</i>
50420275:	Persistent	Cure	Eradicated	Not assessable	N	<i>Escherichia coli Pers., Enterobacter Erad/ Escherichia coli Erad EOS, N</i>
50050183:	Persistent	Improvement	Persistent	Relapse	N	<i>Klebsiella pneumoniae Pers. at EOT; R/x Keflex, N</i>
50030023:	Eradicated	Failure	Persistent	Failure	N	<i>Escherichia coli Erad. at EOT/Bactrim R/x, NG at 31 day, N</i>
Ciprofloxacin (N = 3):						
50050181:	Persistent	Cure	Persistent	Improvement	N	<i>Pseudomonas aeruginosa Pers./ Noroxin, N</i>
50060027:	Persistent	Cure	Persistent	Not assessable	N	<i>Enterococcus faecalis Pers., Btacin day 30, Escherichia coli Erad., N</i>
50050198:	Eradicated	Failure	Eradicated	Failure	N	<i>Klebsiella pneumoniae Erad./ Escherichia coli day 35, Superinfection Y</i>

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There were not enough patients in this study to determine any trends. The Reviewer disagreed with the sponsor in the categorization of 1 patient on the ciprofloxacin arm as a superinfection.

Overall, the MO agreed with the sponsor's determination of outcome and ascertained that conservative judgment was used.

Clinical Relapses:

The following patients were classified as relapses, (where applicable, the patients from the previous list who are included in this list have their PIDs Bolded):

Trovafloxacin 100 (N = 1):

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PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf. Y /N	Reviewer Determination
50110201:	Eradicated	Cure	Persistent	Relapse	N	RECURRENCE with Erad. of initial <i>Escherichia coli</i> , N
Trovafloxacin 100 bid (N = 1):						
50050183:	Persistent	Improvement	Persistent	Relapse	N	<i>Klebsiella pneumoniae</i> Pers. at EOT, Keflex R/x, eradicated, N APPROVED BY [Signature]
Ciprofloxacin (N = 3):						
50030144:	Eradicated	Cure	Eradicated	Relapse	N	<i>Klebsiella pneumoniae/Enterobacter</i> Erad./ <i>Enterococcus faecalis</i> Superinfection, MIC = 2;Y
50050265:	Eradicated	Improvement	Persistent	Relapse	N	<i>Klebsiella pneumoniae</i> Erad/Macrobid R/x, N
50130264:	Eradicated	Cure	Eradicated	Relapse	N	<i>Escherichia coli</i> Erad., no r/x, N

The MO determined that there were no significant trends. There was 1 clinical relapse on the trovafloxacin 100 arm, which the MO determined to be a recurrence with initial eradication of the original pathogen. There was 1 relapse on the trovafloxacin bid arm that the reviewer agreed with and there were 3 relapses on the ciprofloxacin arm, one of which the reviewer determined to be a clinical relapse with a superinfecting organism.

Bacterial Superinfections:

The MO ascertained that there was 1 superinfection per arm for the trovafloxacin-treated patients and 2 for the ciprofloxacin-treated patients. These cases are reviewed below:

Trovafloxacin 100:

50130259: Clinical cure at EOT with *Citrobacter freundii* superinfection/MO agreed.

Trovafloxacin bid:

50130124: Clinical cure at EOT with *Enterococcus faecalis* superinfection/MO agreed.

Ciprofloxacin:

50030015: Clinical cure with *Enterococcus faecalis* superinfection/MO disagreed. Initial *Escherichia coli* was eradicated but *Enterococcus faecalis* was also present at $\geq 10^5$ CFU/mL at baseline and persistent.

In addition to the above, the MO added 1 patient to the ciprofloxacin arm: #50030144.

Overall, there were few superinfections or recurrences in this study. 2 of the 3 superinfections were due to *Enterococcus faecalis*. No conclusions could be drawn based on the small number of patients analyzed.

Safety Analysis:

All 221 patients were eligible for the safety analysis, (72 trovafloxacin 100, 74 trovafloxacin bid, and 75 ciprofloxacin).

There were no deaths and only one patient had an adverse event that was classified as serious. This patient was hospitalized on study day 13 for a hysterectomy. The investigator classified this event as not related to the study drug.

3/72 (4%) of the trovafloxacin 100 patients, 8/74 (11%) of the trovafloxacin bid patients, and 2/75 (3%) of the ciprofloxacin patients were discontinued from the study because of an AE. 2, 7, and 1 of these events were treatment-related.

In both of the trovafloxacin 100 patients and in 3 of the 7 trovafloxacin bid patients that were discontinued, these events were related to the CNS (headache and/or dizziness). These complaints were also elicited from an additional trovafloxacin 100 patient who discontinued therapy but in that case, the investigator determined that the complaints were unrelated to the study drug.

The additional ciprofloxacin patients who discontinued therapy did so because of GI side effects (abdominal pain and/or nausea).

Copied below is sponsor's Table 6.1 which is a summary of all AEs, all causalities. This Table has been modified by the MO.

Table 103.13
Summary of All AEs/All Causality/All Randomized Patients

	Trovafloxacin 100	Trovafloxacin bid	Ciprofloxacin
Number of Subjects Treated	72 (100%)	74 (100%)	75 (100%)
Subjects With At Least One Event	40 (56%)	48 (65%)	42 (56%)
Number of Adverse Events	81	108	79
Subjects with Serious Adverse Events	0	1 (1%)	0
Subjects with Severe Adverse Events	2 (3%)	7 (9%)	3 (4%)
Subjects Discontinued Due to Adverse Events	3 (4%)	8 (11%)	2 (3%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0	0
Subjects Discontinued Due to Objective Test Findings	0	0	0
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Finding	0	0	0

Medical Officer's Comment: Copied below is sponsor's Table 6.2, a summary of the most commonly reported AEs by body system. This Table has been modified by the MO:

Table 103.14
Summary of Most Commonly Reported AEs by Body System (All causality/All Randomized Patients)

	Trovafloxacin 100	Trovafloxacin bid	Ciprofloxacin
NUMBER OF SUBJECTS:			
Evaluable for Adverse Events	72 (100%)	74 (100%)	75 (100%)
Subjects With At Least One Event	40 (56%)	48 (65%)	42 (56%)
Subjects Discontinued due to Adverse Event	3 (4%)	8 (11%)	2 (3%)
ADVERSE EVENTS BY BODY SYSTEM:			
Autonomic Nervous	3 (4%)	2 (3%)	0
Cardiovascular	0	0	1 (1%)
Centr. & Periph. Nerv.	26 (36%)	21 (28%)	18 (24%)
Gastrointestinal	9 (13%)	12 (16%)	18 (24%)
General	4 (6%)	9 (12%)	5 (7%)
Metabolic/ Nutritional	0	0	1 (1%)
Musculoskeletal	0	2 (3%)	3 (4%)
Other Adverse Events	2 (3%)	1 (1%)	0
Psychiatric	4 (6%)	10 (14%)	5 (7%)
Reproductive	5 (7%)	8 (11%)	5 (7%)
Respiratory	3 (4%)	7 (9%)	5 (7%)
Skin/ Appendages	5 (7%)	8 (11%)	6 (8%)
Special Senses	4 (6%)	6 (8%)	2 (3%)
Urinary System	1 (1%)	0	1 (1%)

Medical Officer's Comment: Notable from these Tables is the large number of AEs reported from the peripheral and central nervous systems. These events appeared more frequently on the trovafloxacin arms.

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Additionally, GI side effects appeared to be relatively frequent on all arms but more so on the ciprofloxacin arm.

A breakdown of these 2 systems, revealed the following:

Table 103.15
Most Common AEs from the CNS and GI Systems
(All Causality/All Randomized Patients)

	Trovafoxacin 100 N= 72		Trovafoxacin bid N = 74		Ciprofloxacin bid N = 75	
Nervous System	26	(36%)	21	(28%)	18	(24%)
Headache	18	25	15	20	15	20
Dizziness	12	17	9	12	5	7
GI System	9	(13%)	12	(16%)	18	(24%)
Nausea	4	6	8	11	7	9
Abdominal Pain	1	1	2	3	6	8
Diarrhea	2	3	0	0	5	7

The adverse events that were classified by the investigators as treatment-related are listed below in MO Table 103.16 (modified sponsor table 6.3):

Table 103.16
Summary of Treatment-Related AEs by Body System

	Trovafoxacin 100	Trovafoxacin bid	Ciprofloxacin
NUMBER OF SUBJECTS:			
Evaluable for Adverse Events	72 (100%)	74 (100%)	75 (100%)
Subjects With At Least One Event	26 (36%)	36 (49%)	21 (28%)
Subjects Discontinued due to Adverse Event	2 (3%)	7 (9%)	1 (1%)
ADVERSE EVENTS BY BODY SYSTEM:			
Autonomic Nervous	2 (3%)	2 (3%)	0
Centr. & Periph. Nerv.	16 (22%)	17 (23%)	9 (12%)
Gastrointestinal	6 (8%)	10 (14%)	13 (17%)
General	1 (1%)	2 (3%)	1 (1%)
Metabolic/ Nutritional	0	0	1 (1%)
Musculoskeletal	0	0	1 (1%)
Psychiatric	4 (6%)	9 (12%)	4 (5%)
Reproductive	3 (4%)	3 (4%)	2 (3%)
Respiratory	0	1 (1%)	0
Skin/ Appendages	4 (6%)	7 (9%)	2 (3%)
Special Senses	2 (3%)	4 (5%)	1 (1%)

Medical Officer's Comment: It appeared that the central and peripheral nervous systems as well as the GI system were those most commonly affected by treatment. The majority of the reported adverse events were of mild or moderate severity on all treatment groups.

All severe AEs were considered to be treatment-related with the exception of one subject with dysmenorrhea on the trovafoxacin 100 arm, 2 subjects with dizziness, abdominal pain, and nausea on the trovafoxacin bid arm, and one subject with TMJ on the ciprofloxacin arm. 2, 7, and 3 severe events per arm were reported and 1, 5, and 2 of these were considered to be treatment-related.

These events and patients are listed below:

Trovafoxacin 100 (N= 2):

- 50030173: increased sweating, dizziness, headache, and abnormal vision. Treatment-related, R/x stopped.

- 5008053: *dysmenorrhea, unrelated to treatment.*

Trovafloxacin bid (N = 7):

- 50030017: *dysphoria, vaginal burning, treatment-related.*
- 50050011: *dizziness, headache, nausea, unrelated to study drug.*
- 50030169: *headache, treatment-related.*
- 50100006: *vertigo, treatment-related.*
- 50080051: *abdominal pain, unrelated to study drug.*
- 50090037: *nausea, treatment-related.*
- 50030280: *eye pain, treatment-related.*

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Ciprofloxacin bid (N=3):

- 50050156: *diarrhea, skin ulceration*
- 50060027: *TMJ, unrelated*
- 50030133: *insomnia*

Other AEs that occurred in > 1% of the patients included: somnolence in 3 (4%) of the trovafloxacin 100 patients and 4 (5%) of the trovafloxacin bid patients as compared to 1 (1%) ciprofloxacin patient. Vaginitis occurred in 3 (4%) of the patients on both trovafloxacin arms and 2 (3%) of the patients on the ciprofloxacin arm.

Rash (macular-papular), occurred in 2 (3%), 4 (5%), and 1 (1%) of patients respectively, generalized itching in 1 (1%), 2 (3%), and 1 (1%) of patients and an erythematous rash, (no further details), in 2 (3%) of the trovafloxacin bid patients.

Photophobia occurred in 1(1%) trovafloxacin 100 patient, 2 (3%) trovafloxacin bid patients and none of the ciprofloxacin patients.

Clinical Laboratory Abnormalities:

None of the subjects in this study were discontinued from therapy because of abnormal laboratory results.

Clinically significant abnormalities were found in 9/40 (23%) of the trovafloxacin 100 patients, 5/35 (14%) of the trovafloxacin bid patients and 11/44 (25%) of the ciprofloxacin patients.

Copied from page 49 of the study report is the sponsor's analysis of these abnormalities:

The percentage of subjects with laboratory values that met the criteria for clinical significance during the study was 3% in all three treatment groups for individual laboratory parameters except for triglycerides >1.3 x ULN (10%, 4/ 41 subjects in the ciprofloxacin group), urine red blood cells > 6/ HPF (8%, 3/ 40 subjects and 10%, 4/ 41 subjects in the trovafloxacin 100 mg and ciprofloxacin groups, respectively), and urine white blood cells > 6/ HPF (10%, 4/ 40 subjects, 9%, 3/ 34 subjects, and 7%, 3/ 41 subjects in the trovafloxacin 100 mg, trovafloxacin 100 mg BiD, and ciprofloxacin groups, respectively).

For liver function parameters, the percentage of subjects with clinically significant abnormalities was: alanine aminotransferase (SGPT, >2.0 x ULN) and aspartate aminotransferase (SGOT, >2.0 x ULN), each 3% (1/ 40) in the trovafloxacin 100 mg group. No other clinically significant liver function abnormalities were reported in any of the three treatment groups.

No subject in any of the three treatment groups had clinically significant hemoglobin, total bilirubin, and and/ or creatinine values.

Medical Officer's Comment:

A review of the sponsor's Tables, 4.1 4.2, and 4.3 in Appendix 1 revealed nonsignificant laboratory abnormalities on all 3 arms.

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Specifically, on the trovafloxacin 100 mg arm there were 3 patients with ≥ 6 RBCs per HPF in the urine and 4 with ≥ 6 WBCs in the urine between days 10 and 14 of the study. These patients were recovering from UTI and these abnormalities can be attributed to the underlying disease process.

One patient had an increase in triglycerides to twice baseline but had an initially elevated baseline count.

Patient #50030134 had a significant increase in SGOT.
These values normalized post-therapy
further information was available.

The SGPT in this patient also increased from
This patient also had a urine protein No

A second patient #50140119, a 31 YO female, developed minor LFT abnormalities with baseline SGOT and SGPT respectively, and EOS values
The sponsor stated that this patient had moderate ETOH consumption of ounces of alcohol/week.

On the trovafloxacin 100 bid arm, there was one patient with a significant decrease in peripheral WBC which did not recover by the end of the study, 3 patients with ≥ 6 WBCs per HPF in the urine and 1 with ≥ 6 RBCs per HPF in the urine. One patient had an increase in platelets, which was not significant.

On the ciprofloxacin 250 bid arm, 4 patients had increases in serum triglycerides but had initially high baseline counts, one had an elevated platelet count, and 4 had increased urine RBCs and 3 had increased urine WBCs.

Overall, the incidence of clinically laboratory abnormalities did not appear significant.

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Reviewer's Conclusion:

The MO concluded that trovafloxacin 100 qd and ciprofloxacin appeared to be equally effective in the treatment of uncomplicated UTI in this small pilot study, however no statistically valid conclusions could be drawn because of the small sample sizes.

Overall bacteriologic efficacy at the EOT, (TOC), was 21/22 (95.5%) for the trovafloxacin 100 mg qd arm, 19/22 (86.4%) for the trovafloxacin bid arm, and 27/29 (93.1%) for the ciprofloxacin arm. The respective values at the EOS were 15/21 (75%), 18/21 (85.7%), and 22/27 (81.5%).

Bacteriologic efficacy by baseline pathogen for the most commonly isolated pathogen, *Escherichia coli*, was 19/19 (100%) for the trovafloxacin 100 arm, 17/18 (94.4%) for the trovafloxacin bid arm, and 21/21 (100%) for the ciprofloxacin arm.

Clinical efficacy at the EOT was also comparable, with cure rates of 21/22 (95.5%) for the trovafloxacin 100 arm, 21/22 (95.5%) for the trovafloxacin bid arm and 28/29 (96.6%) for the ciprofloxacin arm. The respective EOS values were 16/18 (88.9%), 17/19 (89.5%), and 28/29 (96.6%).

Superinfection and relapse rates were comparable between all arms.

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From a safety standpoint, the type of AEs appeared similar between the 3 groups with the most frequently reported AE being headache and dizziness in both trovafloxacin groups and headache, dizziness, nausea, and diarrhea in the ciprofloxacin group.

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Study 154 - 116

TITLE:

A Randomized Double-Blind, Multicenter Trial Comparing 3 Days and 7 Days of Oral Therapy with Trovafloxacin (100 mg PO daily) and 3 Days with Norfloxacin (400 mg PO bid) for the treatment of Uncomplicated Acute Urinary Tract Infections.

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List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5003	James McCarty, M. D. Jose Ibarra, M. D.
	5005	Willis Gooch, III, M. D.
	5011	Anthony Puopolo, M. D.
	5013	Larry Gilderman, D. O.
	5041	Robert Fiddes, M. D.
	5138	Randall Stoltz, M. D.
	5492	Nicholas Creel, M. D.
	5630	Ronald Castellanos, M. D.
	5632	Ronald Gove, M. D.
	5633	Gholam Malek, M. D.
	5635	Marcia Montgomery, M. D.
	5636	Stuart Sarshik, M. D.
	5637	Alan Tice, M. D.
	5681	Abdollah Iravani, M. D.
	5733	Ellen Guthrie, M. D.
	The Netherlands	5468
5803		Hendrik Mulder, M. D.
5804		Hans Prak, M. D.
France	5821	Harry Fransen, M. D.
	5783	Philippe Angeli, M. D.
	5784	Marc Hindamian, M. D.
	5785	Max Labyod, M. D.
	5786	Jacques Sultan, M. D.
Sweden	5787	Sylvanie Dumas, M. D.
	5790	Gosta Granberg, M. D.
	5791	Elisabeth Weiner, M. D.
	5792	Anders Henriksson, M. D.
Germany	5793	Leif Weiner, M. D.
	5794	Bengt Widgren, M. D.
	5797	Roland Weil, M. D.
	5798	Reinhard Schorten, M. D.
	5799	Christian Saul, M. D.
	5801	Jens Herold, M. D.
	5802	Constantin Aurel Baran, M. D.

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Study Dates: March 15, 1995 - November 13, 1995

Objective: The objective of this pivotal, phase III study was to evaluate the safety and efficacy of trovafloxacin for 3 days and 7 days compared to 3 days of norfloxacin in the treatment of subjects with uncomplicated acute urinary tract infections.

Treatment Arms: Trovafloxacin 100 mg PO daily for 3 days
 Trovafloxacin 100 mg PO daily for 7 days
 Norfloxacin 400 mg PO bid for 3 days

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Study Design: This was a Phase III, randomized, double-blind, double-dummy, comparative, multi-center trial of trovafloxacin 100 mg once daily for 3 or 7 days versus norfloxacin 400 mg twice daily for 3 days.

Protocol Overview: Copied from the electronic submission (page 22 of the original protocol) is the Sponsor's Schedule of Visits and Procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number	1	2	3
Study day:	Day 1	Day 12	Day 42
Allowable Window:	-48 hours	Day 11-13	Day 35-49
Treatment Period	Day 1 to Day 7		
Follow-up period	Day 8 to Day 42		
Informed consent	X		
Demographic Information	X		
Physical Examination	X		
Concomitant Medication	X	X	X
Vital Signs	X	X	X
Dosing Record		X	
Clinical Signs & Symptoms	X	X	X
Microbiology			
Analysis of unspun urine culture & sensitivity	X	X	X
Safety laboratory tests			
hematology	X	X	abn
biochemistry	X	X	abn
urinalysis	X	X	abn
Pregnancy test*	X		
Adverse events			
routine events		X	X
serious adverse events		X	X
Investigator's evaluation			
clinical		X	X

abn= abnormal at previous visit or clinically significant adverse event

As noted from the above schedule, all baseline assessments were to be completed within the 48 hours prior to the start of the study. At Visit 1, subjects who met the diagnostic criteria for a clinically uncomplicated UTI, (characterized by symptoms including any combination of dysuria, frequency, suprapubic pain or urgency, and pyuria), in the absence of chills/fever, flank pain, costovertebral angle tenderness, and nausea/vomiting, and who had bacteruria confirmed by a culture of $\geq 10^3$ CFU/mL per organism isolated from a clean-catch midstream urine specimen, could be enrolled. These symptoms were to have been present 7 days or less and additionally no UTI symptoms were to have been present in the 4 weeks prior to this episode.

Those subjects who met the criteria as defined above, were eligible for randomization, if they gave informed consent and met the additional inclusion and exclusion criteria. The baseline assessment included the collection of demographic information, medical history, physical exam, concomitant medication use, and vital signs. The presence of the signs and symptoms of uncomplicated UTI was also assessed. The presence of pyuria was to have been established within 48 hours prior to study entry and the finding of ≥ 10 WBCs/hpf at baseline was required for entry. Any intercurrent illness was also recorded.

Susceptibility testing to the study drugs (trovafloxacin and norfloxacin) was determined for all potentially significant organisms isolated, and hematology, serum chemistry and urinalysis were performed. Randomization occurred prior to the availability of the culture report. However, if no pathogen was isolated, continuation of the study drug was at the discretion of the investigator. Additionally, if a pathogen was resistant to the study agents, therapy could have been continued in the face of clinical improvement ONLY and again at the discretion of the investigator.

DURING therapy, at study day 5, the subjects were contacted by phone and if they had had no signs of clinical improvement were requested to return within 48 hours for a formal clinical and bacteriological evaluation. Additionally, if the phone contact elicited any concerns about adverse events, the subjects were instructed to return for a formal visit.

At Visit 2, (day 12 OR between 9 days (3 days arms) and 5 days (7 day arm) after study drug completion), a microbiological and clinical assessment of the signs and symptoms of UTI were performed. Hematology, chemistry, and urinalysis were also performed at this visit. The investigator was asked to provide an evaluation of clinical response and bacteriological response.

At Visit 3 (day 42), the subjects underwent a similar assessment to that at Visit 2. Laboratory evaluations were performed only if a clinically significant abnormality was present at Visit 2. The investigator was to provide a final determination of clinical response and bacteriological response.

During the study, patients were not treated with any other systemic antimicrobial active against the pathogens under evaluation. If this became necessary, the study drug was to have been discontinued and the appropriate alternative therapy instituted.

Patients taking theophylline or warfarin had levels monitored at each study visit and dose adjustments made if necessary. Any concomitant medication use was recorded on the CRF.

The investigator was allowed to discontinue therapy in the event of the isolation of a resistant pathogen to either study drug during the study period ONLY if there was no indication of clinical improvement OR if there was no improvement by the follow-up phone visit. Additionally, patients could be discontinued for any AE that occurred independent of their relationship to the study drug.

Any patient who was discontinued was to be followed for the whole study period.

Protocol Amendments:

The protocol was amended on December 13, 1993 and on January 10, 1994 to reflect the following:

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- to reflect monitoring procedures for subjects taking theophylline and warfarin.
- to reflect that overall clinical response was not to be determined by the Investigator at the time of discontinuation due to lack of efficacy.
- that bacteriological response was not to be determined by the sponsor at the time of discontinuation due to lack of efficacy
- that subjects who discontinued treatment for any reason were not to have been discontinued from the study, but rather followed to the last scheduled visit
- that the requirement for a final efficacy assessment and follow-up safety assessment in the event that an antibiotic was taken during the study period was deleted from the protocol.

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STUDY POPULATION:

It was expected that a total of 540 subjects were to be enrolled in this study with 270 expected to be microbiologically evaluable. Approximately 30 sites were expected to participate which should have attempted to enrol at least 20 subjects each.

Medical Officer's Comment: *The inclusion and exclusion criteria were the same as those in study 103 with the exception that the lower age limit was lowered to age ≥ 16 at baseline. As noted by the MO previously, those patients who received only one dose of another antimicrobial prior to the study start and who had a microbiologically documented infection, were considered evaluable.*

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Randomisation and Blinding:

The investigator assigned study numbers sequentially to the subjects as they were determined to be eligible for treatment. The study number was entered onto the patient's case report form and the patient received study medication with the corresponding number. Study medication was blinded by a double-dummy technique.

Study drug was in the form of tablets and was packaged in blister cards. The study drug administration schedule provided one of the following three dosage regimens of study drug, dependent on the random assignment:

- Trovafloxacin: 100 mg daily (1 x 100 mg tablets) as a single dose in the morning for three days.
- Trovafloxacin: 100 mg daily (1 x 100 mg tablets) as a single dose in the morning for seven days.
- Norfloxacin: 800 mg daily in two equally divided doses (morning, evening) for three days.

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The blister cards contained sufficient supplies for a 7-day course of treatment.

In order to maintain blinding, subjects were instructed to take the following tablets during each day of the 7 days of treatment:

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloxacin (100 mg/d x 3 days)	1-placebo for Norfloxacin x 3 days 1-trovafloxacin- 100 mg x first 3 days (1-placebo for trovafloxacin x last 4 days)	1-placebo for Norfloxacin x 3d
Trovafloxacin (100 mg/d x 7days)	1-placebo for Norfloxacin x 3 days 1-trovafloxacin - 100 mg x 7 days	1-placebo for Norfloxacin x 3d
Norfloxacin (800 mg/d x 3 days)	1-Norfloxacin 400 mg x 3 days 1-placebo for trovafloxacin x 7 days	1-Norfloxacin 400 mg x 3d

Patients were instructed to start with the AM dose on Day 1, even if it was not morning and to complete a full day of medication. The investigator was to have reviewed the labeling instructions with the patients, making clear the AM and PM doses. The patients were instructed to take their doses at least 1 hour before or 2 hours after a meal and that morning and evening dosing should be approximately 12 hours apart

The protocol continued to reflect that mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids should not be taken within (before or after) two hours of dosing.

Microbiologic Methods:

Susceptibility to the study drugs was determined for all causative organisms isolated. Both the local and the central laboratory using standard techniques determined disk susceptibility and minimum inhibitory concentrations (MIC) for isolates. Each time an organism was isolated, susceptibility to the study drugs was re-established. Susceptibility to both study drugs was recorded on the subject's case report form for all isolates.

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 17 of the Study Report)

Criteria	Trovafloxacin		Norfloxacin	
	Zone size(mm) 5µg disc	MIC µg/ml	Zone Size(mm) 10 µg disc	MIC µg/ml
Susceptible	≥15	≤2	≥17	≤4
Intermediate	11-14	4	13-16	5-15
Resistant	≤10	≥8	≤12	≥16

Clinical Response:

Clinical response was determined by the sponsor at visit 2 (EOT) and at Visit 3 (EOS). Response was based on a global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. This assessment was also to be based upon resolution or improvement of clinical and laboratory signs of infection as well as improvement in general condition.

All signs and symptoms were recorded on the CRFs at each visit and the severity of each was rated on the following scale: 0 = Absent, 1 = Mild, 2 = Moderate, and 3 = Severe.

The investigator classified the clinical response as cure; improvement or failure as defined previously in the MOR of study 103.

Medical Officer's Comment: *Notable is the use of a scoring system for severity of illness which was not used in study 103. As in 103 however, the sponsor made the ultimate determination of outcome.*

Bacteriological Response:

This was determined by the sponsor at the EOT and EOS and classified as eradication or persistence as defined previously in the MOR of study 103.

Safety Assessments:

All AEs were recorded on the CRFs and classified as described in the MOR of study 103.

Data Analysis:

Please refer to the MOR of study 103 for a review of the sponsor's subsets and their definitions.

Medical Officer's Comment: *As stated previously the MO's evaluable population consisted of only those patients with a baseline uropathogen $\geq 10^5$ CFU/mL. Clinically evaluable subjects were a subset of this group.*

Evaluability Criteria:

The reader is referred to the introductory section of the MOR for a detailed analysis as well as to the MOR of study 103. The criteria and the MO's comments are the same.

Windows for analysis:

Medical Officer's Comment: *Please refer to the introduction to view the MO's determination of the analysis windows. For this study the lower boundary for the EOT window for analysis, (MO TOC), was set at study day 9 and greater for the patients on 3-day regimens and Day 13 and greater for the patients on 7-day regimens.*

Primary and Secondary endpoints for Efficacy and Definitions of Response

Please refer to of the MOR of study 103.

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DEMOGRAPHICS:

560 subjects were enrolled at 34 centers. 15 centers were in the US and the remainder were in Europe including the Netherlands, France, Germany and Sweden.

Of the enrolled subjects, 18 were withdrawn prior to randomization because they did not meet the study criteria. There were 182 subjects randomized to the trovafloxacin 3-day regimen, 182 to the trovafloxacin 7-day regimen, and 178 to the norfloxacin 3-day regimen. All randomized patients received study drug.

6 trovafloxacin 3-day, 9 trovafloxacin 7-day, and 6 norfloxacin subjects were withdrawn from treatment. Of these 3, 3 and 2 respectively, completed the study and thus a total of 176 trovafloxacin 3-day, 173 trovafloxacin 7-day, and 172 norfloxacin randomized subjects completed treatment.

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Copied and modified below is the sponsor's table 1.3 from the Esub:

Table 116.1:

Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor, Modified by MO)

Center	Trovafoxacin														Norfloxacin			
	Total Randomized N = 542 (100%)		100 mg x 3 days				100 mg x 7 days				400 mg b. i. d. x 3 days							
			Randomized N = 182 (33.5%)		Treated N = 182		Randomized N = 182 (33.5%)		Treated N = 182 (33.5%)		Randomized N = 178 (32.8%)		Treated N = 178 (33.9%)					
5003 *	35	6.4	12	6.5	12	6.5	11	6.0	11	6.0	12	6.7	12	6.7				
5005*	54	9.9	18	9.8	18	9.8	18	9.0	18	9.0	18	10.1	18	10.1				
5011 *	18	3.3	6	3.2	6	3.2	6	3.2	6	3.2	6	3.3	6	3.3				
5013 *	27	4.9	10	5.4	10	5.4	9	4.9	9	4.9	8	4.4	8	4.4				
5041 *	27	4.9	9	4.9	9	4.9	9	4.9	9	4.9	9	5.0	9	5.0				
5138 *	14	2.5	4	0.7	4	0.7	5	2.7	5	2.7	5	2.8	5	2.8				
5492 *	48	8.8	16	8.7	16	8.7	16	8.0	16	8.0	16	8.9	16	8.9				
5630 *	13	2.3	4	0.7	4	0.7	5	2.7	5	2.7	4	2.2	4	2.2				
5632 *	28	5.1	9	4.9	9	4.9	9	4.9	9	4.9	10	5.6	10	5.6				
5633 *	7	1.2	2	1.0	2	1.0	3	1.6	3	1.6	2	1.1	2	1.1				
5635 *	8	1.4	2	1.0	2	1.0	3	1.6	3	1.6	3	1.6	3	1.6				
5636 *	8	1.4	3	1.6	3	1.6	2	1.0	2	1.0	3	1.6	3	1.6				
5637 *	10	1.8	4	0.7	4	0.7	2	1.0	2	1.0	4	2.2	4	2.2				
5681 *	54	9.9	18	9.8	18	9.8	18	9.0	18	9.0	18	10.1	18	10.1				
5733 *	29	5.3	10	5.4	10	5.4	9	4.9	9	4.9	10	5.6	10	5.6				
5783	18	3.3	6	3.2	6	3.2	6	3.2	6	3.2	6	3.3	6	3.3				
5784	17	3.1	6	3.2	6	3.2	6	3.2	6	3.2	5	2.8	5	2.8				
5785	6	1.1	2	1.0	2	1.0	2	1.0	2	1.0	2	1.1	2	1.1				
5786	6	1.1	2	1.0	2	1.0	2	1.0	2	1.0	2	1.1	2	1.1				
5787	19	3.5	6	3.2	6	3.2	6	3.2	6	3.2	7	3.9	7	3.9				
5792	2	0.3	0	0	0	0	2	1.0	2	1.0	0	0	0	0				
5794	13	2.3	4	0.7	4	0.7	5	2.7	5	2.7	4	2.2	4	2.2				
5797	2	0.3	1	0.5	1	0.5	1	0.5	1	0.5	0	0	0	0				
5798	7	1.2	2	1.0	2	1.0	3	1.6	3	1.6	2	1.1	2	1.1				
5799	5	1.4	2	1.0	2	1.0	2	1.0	2	1.0	1	0.5	1	0.5				
5801	12	2.2	4	0.7	4	0.7	4	2.1	4	2.1	4	2.2	4	2.2				
5802	10	1.8	4	0.7	4	0.7	3	1.6	3	1.6	3	1.6	3	1.6				
5803	4	0.7	2	1.0	2	0.7	1	0.5	1	0.5	1	0.5	1	0.5				
5804	24	4.4	8	4.3	8	4.3	8	4.3	8	4.3	8	4.4	8	4.4				
5821	17	3.1	6	3.2	6	3.2	6	3.2	6	3.2	5	2.8	5	2.8				

* denotes US centers

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Medical Officer's Comment: It appeared as if the patients were randomized equally between treatment arms and centers. No center had greater than 10% of the total patients. 340 patients or 70.1% were enrolled at US centers.

Table 116.2:
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin 100 mg x 3 days	Trovafloxacin 100 mg x 7 days	Norfloxacin 400 mg bid x 7 days
Subjects with Signed Consent	560			
Withdrawn Prior to Randomization	0			
Randomized		182	182	178
Randomized, But Not Treated		0	0	0
All Treated Subjects		182 (100%)	182 (100%)	178 (100%)
Withdrawn During Treatment		6 (3%)	9 (5%)	6 (3%)
Completed Treatment		178 (97%)	173 (95%)	172 (97%)
Withdrawn During Follow- up		6 (3%)	6 (3%)	4 (2%)
Completed Study		173 (95%)	170 (93%)	170 (96%)
Completed Treatment and Study		170 (93%)	167 (92%)	168 (94%)
Withdrawn During Treatment and Study		3 (2%)	6 (3%)	4 (2%)

Medical Officer's Comment: From 116. 2 it is apparent that as stated above, 3 trovafloxacin 3-day patients, 6 trovafloxacin 7-day patients, and 4 norfloxacin patients did not complete the study, thus 173, 170, and 170 subjects per arm respectively, completed the study.

Copied below, from page 25 of the study report is the sponsor's analysis of these patients:

One-hundred forty-seven (147) trovafloxacin 3-day, 152 trovafloxacin 7-day, and 130, norfloxacin subjects were included in the bacteriological intent-to-treat analyses and 182 trovafloxacin 3-day, 182 trovafloxacin 7-day, and 178 norfloxacin subjects were included in the clinical intent-to-treat analyses. All treated subjects were included in the analysis of adverse events (182, trovafloxacin 3-day; 182 trovafloxacin 7-day; and 178, norfloxacin).

One hundred seventy-nine (179) subjects with on-treatment laboratory evaluations were included in the analysis of laboratory data (17, trovafloxacin 3-day; 154 trovafloxacin 7-day; and 8, norfloxacin). The difference in the number of subjects analyzed for laboratory data among the three treatment groups is due to the standard method of laboratory data collection which was to have been during the study or within 7 days of the last dose.

Medical Officer's Comment: The difference in the numbers of patients analyzed for laboratory data is because 2 arms of the study had a duration of 3 days as opposed to the one 7 day arm

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Copied below is the sponsor's table 1.2 (Modified by MO)

Table 116.3:

Study Evaluation Groups/All Randomized Patients (As per the Sponsor, Modified by MO)

	Trovafloxacin 100 mg x 3 days	Trovafloxacin 100 mg x 7 days	Norfloxacin 400 mg bid x 7 days
All Randomized Subjects	182 (100%)	182 (100%)	178 (100%)
All Treated Subjects	182 (100%)	182 (100%)	178 (100%)
Subjects with Low Baseline Colony Count or No Pyuria	32 (18%)	27 (15%)	44 (25%)
Subjects with Inappropriate Baseline Diagnosis	3 (2%)	3 (2%)	4 (2%)
Bacteriologically Intent- to- Treat Subjects	147 (81%)	152 (84%)	130 (73%)
Bacteriologically Evaluable Subjects	143 (79%)	142 (78%)	125 (70%)
Bacteriologically Not Evaluable Subjects	4 (2%)	10 (5%)	5 (3%)
No post- baseline cultures	3 (2%)	7 (4%)	3 (2%)
Insufficient Therapy	1 (< 1%)	4 (2%)	3 (2%)
Concomitant Antibiotic Therapy	1 (< 1%)	3 (2%)	1 (< 1%)
Bacteriologically Evaluable at End of Study Visit	128 (70%)	118 (65%)	109 (61%)
Act. Evaluable w/ Baseline uropathy. >10** 5 cfu/ ml	120 (66%)	113 (62%)	106 (60%)
Act. Evaluable w/ Baseline Uropathy. >10** 5 cfu/ ml at EOS	108 (59%)	98 (54%)	94 (53%)
Clinically Intent- to- Treat Subjects	182 (100%)	182 (100%)	178 (100%)
Clinically Evaluable Subjects	144 (79%)	144 (79%)	125 (70%)
Clinically Not Evaluable Subjects	3 (2%)	8 (4%)	5 (3%)
No post baseline assessment	1 (< 1%)	5 (3%)	1 (< 1%)
Insufficient Therapy	1 (< 1%)	5 (3%)	3 (2%)
No post baseline assessment in window	2 (1%)	4 (2%)	3 (2%)
Concomitant Antibiotic Therapy	1 (< 1%)	3 (2%)	1 (< 1%)
Clinically Evaluable at End of Study Visit	133 (73%)	127 (70%)	114 (64%)
Analyzed for Safety			
Adverse Events	182 (100%)	182 (100%)	178 (100%)
Laboratory Data	17 (9%)	154 (85%)	8 (4%)

Medical Officer's Comment: The MO determined that the MO's evaluable population would be comprised of only those subjects with a baseline culture with $\geq 10^5$ CFU/mL. From table 116.3, it appeared as if this group was comprised of 120 trovafloxacin 3-day, 113 trovafloxacin 7-day, and 109 norfloxacin patients per arm respectively, or approximately 60% of the randomized population.

The MO independently reviewed the CRFs and patient profiles on all patients who were withdrawn from the study and agreed with the sponsor's determination of unevaluability.

The sponsor provided 4 tables of the patients who were withdrawn for the study (4.2 and 4.3.2) and 2 for those who discontinued treatment (4.1 and 4.3.1)

There were 29 patients (9 trovafloxacin 3-day, 12 trovafloxacin 7-day, and 8 norfloxacin) who discontinued from the study. Of the 9 trovafloxacin 3-day patients, 3 did not complete therapy. The respective numbers for the two other treatment arms were 6 and 4. The MO reviewed all of the case report forms and found NO inconsistencies. Most common was that these patients did not follow-up after therapy and therefore could not be evaluated. Other causes for withdrawal included immediate allergic reactions and GI side effects.

The MO determined that there was agreement between the MO's and the sponsor's determination of evaluability and outcome. Therefore the MO presented the sponsor's data and merely changed the evaluability on those patients who had a baseline culture with $< 10^5$ CFU/mL and on those patients who were not within the, predetermined by the MO window.

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Baseline Characteristics:

Copied below from page 26 of the study report is the sponsor's text regarding baseline characteristics.

All randomized subjects were females. The three treatment groups were comparable with respect to age, race, and weight. Similar results were observed in the bacteriologically evaluable group.

The mean age for subjects in the trovafloxacin 3-day, trovafloxacin 7-day, and norfloxacin groups was 39.8, 38.8 and 39.8 years, respectively.

The median duration since onset of UTI was 3.0 days for both bacteriologically evaluable and intent-to-treat subjects in all treatment groups.

There were no marked differences among subjects in the three treatment groups with respect to physical examination findings at baseline.

Study Drug Administration:

The median duration of treatment was 3 days for the 3-day patients and 7 days for the 7-day patients.

Concomitant Medications:

During the study, 29 patients in the trovafloxacin 3-day group, 21 in the trovafloxacin 7-day and 28 in the norfloxacin group received concomitant antimicrobials for:

- inadequate response 20, 9 and 22 respectively.
- adverse event 2, 1 and 0
- other illnesses 7, 11 and 6.

The MO reviewed the tables provided by the sponsor as well as the CRFs for these patients and determined that in ALL cases of insufficient response, the failures were carried forward.

Protocol Deviations:

There were 19 deviations, none of which affected evaluability.

Evaluable Population:

(Copied from page 28 of the study report):

Of the randomized subjects, 35 trovafloxacin 3-day subjects, 30 trovafloxacin 7-day subjects and 48 norfloxacin subjects had no baseline urinary pathogen, or low colony counts or no evidence of pyuria and were excluded from the bacteriological intent-to-treat and evaluable analyses. Thus, 147 trovafloxacin 3-day, 152 trovafloxacin 7-day and 130, norfloxacin subjects were included in the bacteriologic intent-to-treat analysis.

Of the bacteriological intent-to-treat subjects, four subjects in the trovafloxacin 3-day group, 10 subjects in the trovafloxacin 7-day group and 5 subjects in the norfloxacin group were not bacteriologically evaluable; thus, 143 trovafloxacin 3-day, 142 trovafloxacin 7-day, and 125 norfloxacin subjects were bacteriologically evaluable.

The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline cultures in evaluable windows (3, trovafloxacin 3-day; 7, trovafloxacin 7-day and 3, norfloxacin). Other reasons were insufficient therapy and concomitant antibiotic therapy.

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All randomized subjects were assumed to have uncomplicated UTI and were, therefore, included in the clinical intent-to-treat analysis (182, trovafloxacin 3-day; 182, trovafloxacin 7-day and 178, norfloxacin).

Of the bacteriological intent-to-treat subjects, 16 subjects were not included in the clinically evaluable analysis. Thus, 144 trovafloxacin 3-day, 144 trovafloxacin 7-day, and 125, norfloxacin subjects were clinically evaluable.

The most common reason for exclusion from clinical evaluability was no post-baseline clinical assessment (1, trovafloxacin 3-day; 5, trovafloxacin 7-day and 1, norfloxacin), no post-baseline assessment in evaluable analysis window (2, trovafloxacin 3-day; 5, trovafloxacin 7-day and 3, norfloxacin), insufficient therapy (1, trovafloxacin 3-day; 4, trovafloxacin 7-day and 3, norfloxacin) and concomitant antibiotic therapy (1, trovafloxacin 3-day; 3, trovafloxacin 7-day and 1, norfloxacin).

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Sponsor's Efficacy Analysis:

Bacteriological Response:

(Copied below is the sponsor's text from pages 29 and 30 of the study report):

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined subject bacteriological eradication rates at the end of treatment supported equivalence of both trovafloxacin regimens versus norfloxacin (trovafloxacin 3-day, 86% versus norfloxacin, 88% [95% CI: -9.7, 6.5] and trovafloxacin 7-day, 93% versus norfloxacin, 88% [95% CI: -2.1, 12.2]).

Sponsor-defined subject bacteriological eradication rates were comparable among the trovafloxacin 3-day (74%), trovafloxacin 7-day (84%), and norfloxacin (73%) groups at the end of study.

A summary of sponsor-defined bacteriological response rates for bacteriologically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in the following table.

Table A. Summary of Sponsor-Defined Subject Bacteriologic Response Rates at the End of Treatment and at the End of Study (Bacteriologically Evaluable Subjects)				
	Trovafloxacin 100 mg/day 3 Days (N=143)	Trovafloxacin 100 mg/day 7 Days (N=142)	Norfloxacin 400 mg BID 3 Days (N=125)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	139 (100%)	142 (100%)	124 (100%)	
Eradication	120 (86%)	132 (93%)	109 (88%)	
Persistence	19 (14%)	10 (7%)	15 (12%)	
Trova 3 days vs. Trova 7 days				(-13.7, 0.5)
Trova 3 days vs. Norfloxacin				(-9.7, 6.5)
Trova 7 days vs. Norfloxacin				(-2.1, 12.2)
End of Study:				
Number of Subjects Assessed	128 (100%)	118 (100%)	109 (100%)	
Eradication	95 (74%)	99 (84%)	80 (73%)	
Persistence	33 (26%)	19 (16%)	29 (27%)	
Trova 3 days vs. Trova 7 days				(-19.7, 0.4)
Trova 3 days vs. Norfloxacin				(-10.4, 12.1)
Trova 7 days vs. Norfloxacin				(-0.1, 21.1)

Medical Officer's Comment: From sponsor's table C which includes all bacteriologically evaluable patients, ($\geq 10^3$ CFU/mL at baseline), it was apparent that there was equivalence between the 3-day treatment arms and that the 7-day regimen was equivalent to the norfloxacin arm.

APPENDIX 1, TABLE 5.5.1
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Sponsor-Defined Pathogen Eradication Rates:

(Copied below is the sponsor's text and Table B from pages 30 and 31 of the study report):

Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates were comparable among the three treatment groups for the most frequently isolated baseline pathogen (*Escherichia coli*), at both the end of treatment and the end of study.

A summary of sponsor- defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in the following table.

Table B. Summary of Sponsor-Defined Pathogen Eradication Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

Pathogen	Trova 100 mg/day 3 Days	Trova 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days	95% Confidence Intervals		
				Trova 3 days vs. Trova 7 days	Trova 3 days vs. Norfloxacin	Trova 7 days vs. Norfloxacin
End of Treatment						
<i>E. coli</i>	105/114 (92%)	103/108 (95%)	87/97 (90%)	-9.6, 3.1	-5.4, 10.2	-1.6, 12.9
<i>E. faecalis</i>	3/10	4/6	4/6	ND	ND	ND
End of Study						
<i>E. coli</i>	85/105 (81%)	74/89 (83%)	62/84 (74%)	-13.0, 8.6	-4.9, 19.2	-2.9, 21.5
<i>E. faecalis</i>	1/9	3/5	3/6	ND	ND	ND

Trova=trovaflaxacin; ND=not done.
^a ≥ 10 isolates of a given pathogen in any treatment group; percents displayed only when the denominator is ≥ 15 .
 Ref.: Table 5.5.1

Medical Officer's Comment: The sponsor has provided a list of all pathogens and their eradication rates in Appendix 1, Table 5.5.1. This table has been reproduced by the MO below:

APPENDIX 1, TABLE 5.5.1
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Table 116.4:
Table of Sponsor-Defined Pathogen Eradication Rates at the EOT (Modified by MO)
(Table includes all relevant sponsor-evaluable isolates)

Pathogen	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
<i>Escherichia coli</i>	114	105	92	108	103	95	97	87	90
<i>Enterococcus faecalis</i>	10	3	30	6	4	67	6	4	67
<i>Proteus mirabilis</i>	8	7	88	5	5	100	4	4	100
<i>Citrobacter freundii</i>	2	1	50	-	-	-	-	-	-
<i>Pseudomonas aeruginosa</i>	1	1	100	1	0	0	-	-	-
<i>Pseudomonas fluorescens</i>	-	-	-	1	1	100	-	-	-
<i>Staphylococcus haemolyticus</i>	4	3	75	3	2	67	1	1	100
<i>Citrobacter diversus</i>	-	-	-	-	-	-	2	2	100
<i>Staphylococcus aureus</i>	2	2	100	1	1	100	4	3	75
<i>Enterobacter aerogenes</i>	1	1	100	1	1	100	-	-	-
<i>Enterobacter agglomerans</i>	-	-	-	1	1	100	-	-	-
<i>Enterobacter cloacae</i>	3	2	67	2	2	100	1	1	100
<i>Morganella morganii</i>	1	1	100	1	1	100	1	1	100
<i>Klebsiella oxytoca</i>	-	-	-	1	1	100	1	1	100
<i>Klebsiella pneumoniae</i>	3	2	67	6	5	83	5	3	60
Total	146	128	87.6	137	127	92.7	122	107	87.7

Medical Officer's Comment: There was equivalence between the 3 arms at EOT and EOS for *Escherichia coli*, the most frequently isolated pathogen. A distant second isolate, *Enterococcus faecalis*, appeared to be much less sensitive to the trovafloxacin 3-day regimen with eradication rates of 30% or less as compared to the 3-day norfloxacin or the 7-day trovafloxacin (60% or greater). A statistical analysis was not provided. Additionally, although the numbers are few, the trovafloxacin 3-day regimen appeared less effective against other Gram (-) organisms as compared to the 7-day regimen.

Overall, there was numerical equivalence between the 3-day regimens and superiority of the 7-day compared to both.

Bacteriologically Evaluable Subjects with a Baseline Uropathogen of $\geq 10^5$ CFU/mL:
(Copied below is the sponsor's text and Table C):

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined subject bacteriological eradication rates supported equivalence of trovafloxacin 7-day versus norfloxacin at the end of treatment (trovafloxacin 7-days 93% versus norfloxacin 90% [95% CI: -4.1, 10.9]).

Sponsor-defined subject bacteriological eradication rates were comparable among the trovafloxacin 3-day (75%), trovafloxacin 7-day (83%), and norfloxacin (74%) groups at the end of study.

A summary of sponsor-defined bacteriologic response rates for bacteriologically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in the following table.

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Table C. Summary of Sponsor-Defined Subject Bacteriologic Response Rates at the End of Treatment and at the End of Study (Bacteriologically Evaluable Subjects With A Baseline Uropathogen $\geq 10^5$ CFU/ML)				
	Trovafloxacin 100 mg/day 3 Days (N=120)	Trovafloxacin 100 mg/day 7 Days (N=113)	Norfloxacin 400 mg BID 3 Days (N=106)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	116 (100%)	113 (100%)	105 (100%)	
Eradication	101 (87%)	105 (93%)	94 (90%)	
Persistence	15 (13%)	8 (7%)	11 (10%)	
Trova 3 days vs. Trova 7 days				(-13.6, 1.9)
Trova 3 days vs. Norfloxacin				(-10.9, 6.0)
Trova 7 days vs. Norfloxacin				(-4.1, 10.9)
End of Study:				
Number of Subjects Assessed	108 (100%)	98 (100%)	94 (100%)	
Eradication	81 (75%)	81 (83%)	70 (74%)	
Persistence	27 (25%)	17 (17%)	24 (26%)	
Trova 3 days vs. Trova 7 days				(-18.7, 3.4)
Trova 3 days vs. Norfloxacin				(-11.5, 12.5)
Trova 7 days vs. Norfloxacin				(-3.4, 19.8)
Trova=trovafloxacin; CI=confidence interval				
Ref.: Table 5.9				

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Medical Officer's Comment: *In this population of patients which can be corresponds to that of the MO, the 3-day trovafloxacin regimen was NOT EQUIVALENT to the 7-day trovafloxacin regimen, however it was equivalent to the comparator, (norfloxacin), at the EOT which was the MO's TOC. The MO requested comment from the FDA statistical reviewer, Dr. Jiang.*

Dr. Jiang provided a statistical analysis which revealed equivalence between the trovafloxacin 3-day arm, (sponsor's requested dose), and the comparator, norfloxacin. Specifically, for trovafloxacin 3-day vs. norfloxacin, the lower bound of the C.I. is -11.8% and the upper is 6,9% with CCF.

Sponsor-Defined Pathogen Eradication Rates for Baseline Pathogens $\geq 10^5$ CFU/mL:
(Copied from pages 32 and 33 of the study report are the sponsor's text and Table D)

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Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates for baseline isolates of *Escherichia coli* $\geq 10^5$ cfu/ mL were comparable among the three treatment groups at both the end of treatment and the end of study.

A summary of sponsor- defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline uropathogen $\geq 10^5$ cfu/ mL is presented for bacteriologically evaluable subjects in the following table.

APPROPRIATE WAY
01/01/01

Table D. Summary of Sponsor-Defined Pathogen Eradication Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Uropathogens 10⁵ CFU/ML^a (Bacteriologically Evaluable Subjects)

Pathogen	Trovafloxacin 100 mg/day 3 Days	Trovafloxacin 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days	95% Confidence Intervals		
	End of Treatment			Trova 3 days vs. Trova 7 days	Trova 3 days vs. Norfloxacin	Trova 7 days vs. Norfloxacin
<i>E. coli</i>	88/96 (92%)	85/90 (94%)	75/81 (93%)	-10.1, 4.5	-8.9, 7.0	-5.6, 9.3
End of Study						
<i>E. coli</i>	73/90 (81%)	64/77 (83%)	54/72 (75%)	-13.6, 9.6	-6.8, 19.0	-4.9, 21.2

Trova=trovafloxacin.
a ≥10 isolates of a given pathogen in any treatment group.
Ref: Table 5.10

Medical Officer's Comment: The sponsor has provided a list of all pathogens and their eradication rates in Table 5.10. This table was reproduced and modified by the MO below:

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Table 116.5:
Table of Sponsor-Defined Pathogen Eradication Rates at the EOT (Modified by MO)
 (Table includes all relevant sponsor-evaluable uropathogens ≥ 10⁵ at baseline)

Pathogen	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
<i>Escherichia coli</i>	96	88	92	90	85	94	81	75	93
<i>Enterococcus faecalis</i>	5	1	20	3	2	67	5	3	60
<i>Proteus mirabilis</i>	8	7	88	4	4	100	4	4	100
<i>Pseudomonas aeruginosa</i>	1	1	100	1	0	0	0	0	0
<i>Pseudomonas fluorescens</i>	-	-	-	1	1	100	-	-	-
<i>Staphylococcus aureus</i>	2	2	100	-	-	-	3	2	66.6
<i>Enterobacter aerogenes</i>	1	1	100	1	1	100	-	-	-
<i>Enterobacter cloacae</i>	2	1	50	1	1	100	1	1	100
<i>Morganella morganii.</i>	-	-	-	-	-	-	1	1	100
<i>Klebsiella oxytoca</i>	-	-	-	1	1	100	1	1	100
<i>Klebsiella pneumoniae</i>	3	2	67	5	4	80	5	3	60
Total	118	103	87.2	107	99	92.5	101	89	88.1

Medical Officer's Comment: The MO provided a similar table of the eradication rates of the above isolates at the EOS.

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Table 116.6:
Table of Sponsor-Defined Pathogen Eradication Rates at the EOS (Modified by MO)
(Table includes all relevant sponsor-evaluable uropathogens $\geq 10^5$ at baseline)

Pathogen	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
<i>Escherichia coli</i>	90	73	81	77	64	83	72	54	75
<i>Enterococcus faecalis</i>	5	1	20	2	0	0	-	-	-
<i>Proteus mirabilis</i>	7	5	71	4	4	100	3	2	67
<i>Pseudomonas aeruginosa</i>	1	1	100	1	0	0	-	-	-
<i>Pseudomonas fluorescens</i>	-	-	-	1	1	100	-	-	-
<i>Staphylococcus aureus</i>	1	1	100	-	-	-	3	2	67
<i>Enterobacter aerogenes</i>	1	1	100	-	-	-	1	1	100
<i>Enterobacter cloacae</i>	2	1	50	1	1	100	1	1	100
<i>Klebsiella oxytoca</i>	-	-	-	1	1	100	-	-	-
<i>Klebsiella pneumoniae</i>	3	2	67	5	3	60	5	3	60
Total	110	85	77.2	92	74	80.4	85	63	74.1

Medical Officer's Comment: The MO points out that all of the above pathogen eradication tables apply only to those isolates which could be construed as uropathogens, thus excluding organisms thought to be contaminants.

The MO was unclear as to why the sponsor elected to present eradication rates for the EOT and EOS separately. When queried, the sponsor stated that both timepoints were evaluable as TOCs and thus the EOS tabulations applied only to those patients who followed up at that point. Additionally, changes in numerators and denominators are explained by the ability for a patient to have been assessed at either the EOT or the EOS.

Equivalence was shown between the trovafloxacin 3-day regimen and norfloxacin treatment arm for *Escherichia coli* at the EOT. Additionally, bacteriologically, the 3-day regimen appeared comparable to the other arms for other Gram (-) organisms. There were however, too few isolates to draw any firm conclusions. The FDA Statistical Reviewer, Dr. Jiang confirmed that there was equivalence between the trovafloxacin 3-day arm and the norfloxacin 3-day regimen.

Superinfecting Pathogens and Colonizing Organisms:

(Copied below is the sponsor's text from page 33 of the study report. This information refers to the clinically ITT population (182, 182, 178):

Superinfecting organisms were isolated from 22 subjects (12%) in the trovafloxacin 3-day group (*Escherichia coli* [seven isolates], *Klebsiella pneumoniae* [three isolates], *Staphylococcus haemolyticus* [three isolates], *Enterococcus faecalis* [two isolates], *Proteus mirabilis* [two isolates], and one isolate each of *Acinetobacter* spp., *Enterobacter aerogenes*, *Enterobacter agglomerans*, *Enterobacter cloacae*, *Pseudomonas fluorescens*, *Lecleria adecarboxylata*, and *Citrobacter freundii*), from 16 subjects (9%) in the trovafloxacin 7-day group (*Staphylococcus haemolyticus* [four isolates], *Staphylococcus epidermidis* [three isolates], *Enterococcus faecalis* [three isolates], *Escherichia coli* [two isolates], and one isolate each of *Proteus mirabilis*, *Acinetobacter calcoaceticus* V. *hoeffii*, *Acinetobacter* spp., *Corynebacterium* spp., *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Morganella morganii*, *Providencia* spp., *Pseudomonas putida*, and *Staphylococcus saprophyticus*), and 20 subjects (11%) in the norfloxacin group (*Escherichia coli* [seven isolates], *Enterococcus faecalis* [four isolates], *Staphylococcus haemolyticus* [four isolates],

Staphylococcus epidermidis [four isolates], *Enterobacter cloacae* [two isolates], *Klebsiella oxytoca* [two isolates], *Klebsiella pneumoniae* [two isolates], and one isolate each of *Acinetobacter calcoaceticus v. anitratus*, *Corynebacterium spp.*, *Staphylococcus saprophyticus*, and *Staphylococcus spp.*).

Colonizing organisms were isolated from 36 subjects (20%) in the trovafloxacin 3-day group, 35 subjects (19%) in the trovafloxacin 7-day group, and 37 subjects (21%) in the norfloxacin group.

Medical Officer's Comment: *The most frequently isolated superinfecting pathogen was Escherichia coli followed by Enterococcus faecalis. Interestingly, Group B Streptococcus was the most frequent colonizer. These results seem to be in accord with the overall eradication rates and possibly the fact that the patient population was composed mostly of women.*

Clinical Response:

(Copied from pages 35 and 36 of the study report are the sponsor's analysis and Table E)

Sponsor-defined clinical success rates (cure + improvement) were comparable among the trovafloxacin 3-day group, the trovafloxacin 7-day group, and the norfloxacin group at the end of treatment (97%, 97%, and 92%, respectively).

Sponsor-defined clinical success rates at the end of study were comparable for the trovafloxacin 3-day group and the norfloxacin group at the end of study (86% and 82%, respectively). A higher clinical success rate was noted in the trovafloxacin 7-day group compared to the norfloxacin group at the end of study (91% and 82%, respectively).

Table E. Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study (Clinically Evaluable Subjects)				
	Trovafloxacin 100 mg/day 3 Days (N=144)	Trovafloxacin 100 mg/day 7 Days (N=144)	Norfloxacin 400 mg BID 3 Days (N=125)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	140 (100%)	144 (100%)	125 (100%)	
Success (Cure + Improvement)	136 (97%)	140 (97%)	115 (92%)	
Trova 3 days vs. Trova 7 days				(-3.9, 3.8)
Trova 3 days vs. Norfloxacin				(-0.4, 10.6)
Trova 7 days vs. Norfloxacin				(-0.2, 10.7)
Distribution of Clinical Response:				
Cure	106 (76%)	123 (85%)	98 (78%)	
Improvement	30 (21%)	17 (12%)	17 (14%)	
Failure	4 (3%)	4 (3%)	10 (8%)	
End of Study:				
Number of Subjects Assessed	133 (100%)	127 (100%)	114 (100%)	
Success (Cure + Improvement)	114 (86%)	115 (91%)	93 (82%)	
Trova 3 days vs. Trova 7 days				(-12.7, 3.0)
Trova 3 days vs. Norfloxacin				(-5.1, 13.4)
Trova 7 days vs. Norfloxacin				(0.2, 17.7)
Distribution of Clinical Response:				
Cure	109 (82%)	111 (87%)	91 (80%)	
Improvement	5 (4%)	4 (3%)	2 (2%)	
Failure	4 (3%)	4 (3%)	10 (9%)	
Relapse	15 (11%)	8 (6%)	11 (10%)	

Trova=trovafloxacin; CI=confidence interval
Ref.: Table 5.2.1

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Medical Officer's Comment: *The MO agreed with the sponsor's analysis of clinical response.*

Summary of the Differences between the Investigator and Sponsor-Defined Clinical Response at the EOT and EOS:

The sponsor provided multiple tables both in the study report as well as in the appendices. These were reviewed as well as the CRFs when necessary.

The MO noted the following:

- Overall the sponsor's determination was more conservative.
- In all cases, those patients who received an alternative antimicrobial during follow-up were classified as failures by the sponsor and carried forward.
- The MO can provide a list of these patients, however, in all cases the MO agreed with the sponsor and therefore the data is accepted as presented.

Clinical Response by Baseline Pathogen:

Copied from page 39 of the study report:

Among clinically evaluable subjects with *Escherichia coli* isolated at baseline, sponsor-defined clinical success rates (cure + improvement) at the end of treatment were 97% in the trovafloxacin 3-day group, 98% in the trovafloxacin 7-day group, and 91% in the norfloxacin group.

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in the following table.

Table F. Summary of Clinical Success Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)

	Trovafloxacin 100 mg/day 3 Days	Trovafloxacin 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days	Trovafloxacin 100 mg/day 3 Days	Trovafloxacin 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days
Number and Percentage (%) of Subjects						
Pathogen	End of Treatment			End of Study		
<i>E. coli</i>	111/115 (97%)	108/110 (98%)	88/97 (91%)	98/109 (90%)	90/98 (92%)	71/87 (82%)

^a ≥10 isolates of a given pathogen in any treatment group.
 Several subjects were not evaluated clinically at the end of treatment.
 Ref.: Table 5.4

Medical Officer's Comment: *The MO agreed with the sponsor's analysis.*

Signs and Symptoms:

Overall the percentage of patients with moderate to severe signs and symptoms at baseline was comparable among the 3 groups (dysuria: trovafloxacin 3-day: 76%, trovafloxacin 7-day: 72%, and norfloxacin: 72%, urgency 85%, 81%, and 75% respectively, suprapubic pain: 37%, 41%, and 44% respectively, frequency 86%, 84%, and 78% respectively, flank pain and CVA tenderness 1%: all arms.

In all treatment groups there was improvement from baseline to the EOT and then to the EOS and there were no significant differences between the arms.

Analysis of Sponsor-Defined Patients with a Bacteriologic Response of Persistence and a Clinical Response of Failure/Relapse:

35 trovafloxacin 3-day patients had a bacteriologic response of persistence. Of these, 14 received additional antimicrobial therapy.

For the 7-day trovafloxacin arm, these numbers were 23 and 9 and for the norfloxacin arm: 31 and 16.

The remaining 21 trovafloxacin 3-day, 14 trovafloxacin 7-day, and 15 norfloxacin patients did not receive additional therapy and were classified as clinical cures or improvements at the EOT.

27 of the 35 trovafloxacin 3-day patients with persistence had cultures that showed *Escherichia coli*, *Enterococcus faecalis*, and *Proteus mirabilis*. The respective numbers for the trovafloxacin 7-day arm were 17 *Escherichia coli* and for the norfloxacin arm 21 *Escherichia coli*.

Medical Officer's Comment: *There was no table to accompany this information, a review of these patients revealed that Escherichia coli was the predominant isolate found in all groups which is compatible with this organism being the predominant isolate.*

Of these isolates only 1 Proteus mirabilis from the trovafloxacin 3-day arm and 1 Pseudomonas aeruginosa from the 7-day arm were resistant at baseline with MICs of 8. 1 Enterococcus faecalis from the norfloxacin arm was intermediate to norfloxacin at baseline with an MIC of 8.

Clinical Failures:

(Copied below from page 43 of the study report is the sponsor's analysis of the clinical failures)

Four trovafloxacin 3-day subjects, four trovafloxacin 7-day subjects, and 10 norfloxacin subjects were clinical failures at both the end of treatment and the end of study. All subjects were designated as clinical failures after completing their respective treatment regimens. With the exception of Subject 5681- 0289 in the norfloxacin group, all subjects designated as clinical failures received additional antibiotics for inadequate response.

Of the subjects designated as clinical failures, two of four subjects in the trovafloxacin 3-day group had repeat cultures that showed persistence of *Escherichia coli*, one of four subjects in the trovafloxacin 7-day group had a repeat culture that showed persistence of *Enterococcus faecalis* and *Staphylococcus haemolyticus* and three of ten subjects in the norfloxacin group had repeat cultures that showed persistence of *Escherichia coli*.

Clinical Relapse: Fifteen trovafloxacin 3-day subjects, eight trovafloxacin 7-day subjects, and 11 norfloxacin subjects were designated as clinical relapses at the end of study. Ten of the 15 trovafloxacin 3-day, five of the eight trovafloxacin 7-day, and Nine of the 11 norfloxacin subjects designated as clinical relapses received additional antibiotics for inadequate response.

Of the subjects designated as clinical relapses, seven of 15 subjects in the trovafloxacin 3-day group had repeat cultures that showed persistence of *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Enterococcus faecalis*, or *Citrobacter freundii*, five of eight subjects in the trovafloxacin 7-day group had a repeat culture that showed persistence of *Escherichia coli* or *Klebsiella pneumoniae* and five of 11 subjects in the norfloxacin group had repeat cultures that showed persistent of *Escherichia coli*, *Klebsiella pneumoniae* or *Enterococcus faecalis* at either the end of treatment and/ or end of study. With the exception of two subjects in the trovafloxacin 3-day group and two subjects in the norfloxacin group with pathogen outcomes of eradication, all other subjects with a sponsor- defined subject bacteriological response of relapse had pathogens with outcomes of presumed persistence.

Cross-Tabulation of Clinical Response and Bacteriological Response in Bacteriologically and Clinically Evaluable Patients:

Medical Officer's Comment: *There were inconsistent results, that is clinical success with bacteriologic persistence or clinical failure with bacteriologic eradication in 42 subjects. The sponsor presented this information in the form of 2 tables (5.6.1 and 5.7.1) which are summarized below:*

Specifically, 2 trovafloxacin 3-day patients were clinical failures with bacteriologic eradication, both with Escherichia coli, and 17 patients were clinically cured or improved with bacteriologic persistence. Of these 17, 7 had Escherichia coli, 7 had Enterococcus faecalis (one patient had polymicrobial UTI), and there was 1 Citrobacter freundii, 1 Klebsiella pneumoniae, and 1 Enterobacter cloacae. The 1 patient with 3 organisms also had a Staphylococcus haemolyticus.

On the trovafloxacin 7-day arm, 2 patients were clinical failures with bacteriologic eradication, 1 each with Escherichia coli and Enterococcus faecalis. The remainder were clinical cures with bacteriologic persistence, with 4 Escherichia coli, 1 Klebsiella pneumoniae, 1 Pseudomonas aeruginosa, and 1 Staphylococcus epidermidis

On the norfloxacin arm, 4 patients were clinical failures with bacteriologic eradication, all with Escherichia coli. 9 patients were clinical cures with bacteriologic persistence, 5 with Escherichia coli, 1 Staphylococcus aureus, 2 Enterococcus faecalis, and 1 Klebsiella pneumoniae

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Sponsor's Conclusion:

Copied below are portions of the sponsor's conclusion from pages 51 and 52 of the study report (modified by MO in Times New Roman font):

Administration of trovafloxacin 100 mg once daily for 3 days and administration of trovafloxacin 100 mg once daily for 7 days were shown to be effective for the treatment of uncomplicated urinary tract infections. Among bacteriologically evaluable subjects, pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined subject bacteriological responses at the end of treatment (86% (120/139), trovafloxacin 3 day, 93% (132/142), trovafloxacin 7 day, 88% (109/124), norfloxacin) supported equivalence of trovafloxacin 3-day versus norfloxacin, and trovafloxacin 7-day versus norfloxacin.

Sponsor-defined subject eradication rates at the end of study were comparable among the three treatment groups (74% (95/128), trovafloxacin 3-day, 84% (99/118), trovafloxacin 7-day, 73% (80/109), norfloxacin). Similar results were observed among bacteriological intent-to-treat subjects and subjects with a baseline uropathogen $\geq 10^5$ CFU/ML.

Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates for the most frequently isolated baseline pathogen (*Escherichia coli*) were comparable among the three treatment groups at the end of treatment (92% (105/114), trovafloxacin 3-day, 95% (103/108), trovafloxacin 7-day, 90% (87/97), norfloxacin) and at the end of study (81% (85/105), trovafloxacin 3-day, 83% (74/89), trovafloxacin 7-day, 74% (62/84), norfloxacin). Similar results were observed among bacteriological intent-to-treat subjects and subjects with a baseline uropathogen $\geq 10^5$ CFU/ML.

Among clinically evaluable subjects, sponsor-defined clinical success rates (cure + improvement) at the end of treatment were comparable among the three treatment groups (97% (136/140), trovafloxacin 3-day, 97% (140/144), trovafloxacin 7-day, 92% (115/125), norfloxacin).

Sponsor-defined clinical success rates at the end of study were comparable between the trovafloxacin 3-day group (114/133:86%) and the norfloxacin group (93/114:82%). A higher clinical success rate was noted in the trovafloxacin 7-day group compared to the norfloxacin group at the end of study (115/127 (91%) and 93/114 (82%), respectively). Additionally, these findings were

supported by marked decreases in the presence of clinical signs and symptoms of infection from baseline to the end of treatment and the end of study in all three treatment groups. Similar results were observed among clinical intent-to-treat subjects.

Medical Officer's Comment: *The MO agreed that trovafloxacin 100 mg PO daily for 3 days appeared equivalent to norfloxacin 400 mg PO bid for 3 days in terms of the primary and secondary efficacy variables.*

The sponsor is requesting approval for the 3-day regimen and needs to show equivalence only with the norfloxacin arm of the study.

Interestingly, it may be that neither 3-day arm is as good as the trovafloxacin 7-day arm, however, norfloxacin is an approved agent for this indication at the dose requested.

Medical Officer's Analysis of Efficacy:

The MO elected to accept as the FDA evaluable population, the sponsor's bacteriologically evaluable population with baseline counts of $\geq 10^5$ CFU/mL. Although there was an initial discussion about the lower bound of the EOT "window of analysis", being set early, a review of the data indicated that NO patients on the 3-day arms of this study would have been excluded because of an early evaluation. This was not the case for the 7-day arm, where 65 patients would have been excluded from the analysis if the lower bound was set at day 13. Because the sponsor is requesting approval for the 3-day regimen and only needs to show equivalence with an approved comparator, the MO accepted the sponsor's numbers.

Additionally, the MO performed a random audit of every 7th patient via review of the CRFs and the electronic data set. The MO found NO inconsistencies in data transfer or differences in outcome assessments.

All cases of patients excluded from the analyses for protocol violations, including the use of alternative antimicrobials were also reviewed and the MO found that the sponsor exercised very conservative judgment in the inclusion/exclusion of these patients. All failures were carried forward appropriately.

Of the original 560 patients, 18 were withdrawn prior to randomization. This was uniformly due to withdrawal of consent. Of the 542 remaining patients, 182 were randomized to trovafloxacin 3-day, 182 to trovafloxacin 7-day, and 178 to norfloxacin.

The MO in provided an analysis of the excluded patients on the section pertaining to the sponsor's demographics. The sponsor's bacteriologically evaluable population was 143, 142 and 125 patients per arm respectively, as compared to the MO's, which is 120, 113 and 106 per arm respectively. This difference of 23, 19 and 19 patients is because the Reviewer excluded those patients with colony counts of $\leq 10^5$ CFU/mL.

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**Table 116.7:
Bacteriologically Evaluable Population (as per the MO)**

MO's Bacteriologically Evaluable Population ($\geq 10^5$ CFU/mL)			
Reason for exclusion	Trova 3-day	Trova 7-day	Norflox 3-day
	N=542		
Total Randomized:	N=182	N=182	N=178
No Baseline Pathogen	32	27	44
BSL count $< 10^3$	3	3	4
BSL count $> 10^3$ but $< 10^5$	23	29	19
Withdrawn because of insufficient R/x/ con. AB or no consent prior to EOT	4	10	5
Total Evaluable	120	113	106
No. not evaluated at EOT but at EOS	4	-	1
Total Evaluated at EOT	116	113	105
No. not evaluated at EOS but at EOT	12	15	12
Total Evaluated at EOS	104	98	93

Specifically, patients that were withdrawn were:

Trovafloxacin 3-day (N = 4):

- 50110366: Insufficient r/x, no postbaseline culture
- 50410187: No postbaseline culture, no consent
- 57970619: Clin. Eval but not bact. No culture, consent
- 58010617: Concomitant antimicrobial

Trovafloxacin 7-day (N = 10):

- 50130373: Insufficient R/x, concomitant antimicrobial
- 50050184: Insufficient R/x, concomitant antimicrobial
- 50050300: No postbaseline culture/consent
- 51380013: No postbaseline culture in window
- 54920228: Insufficient R/x, no culture
- 56810154: No postbaseline assessment in window
- 56810160: No postbaseline assessment in window
- 58210741: Insufficient therapy, concomitant antimicrobial
- 57870222: No culture but clinically evaluable
- 57970622: No culture but clinically evaluable

Norfloxacin (N = 5):

- 50050173: Concomitant antimicrobial
- 50410191: Insufficient R/x
- 56360259: Insufficient R/x
- 56810151: Insufficient R/x
- 57878020: No postbaseline assessment in window

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In addition to the above, there were 4 patients from the trovafloxacin 3-day arm who did not have a bacteriological assessment at the EOT although they did have one at the EOS. These patients are unevaluable as per the MO and are listed below:

- 56300064
- 56300211
- 56810159
- 57830159

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On the norfloxacin arm there was 1 patient that was not evaluated at the EOT and therefore excluded: 57830089.

Presented in Table 116.8 are the bacteriologically evaluable patients by center. The MO's clinically evaluable population has been tied to the bacteriologically evaluable.

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Table 116.8:
Bacteriologically Evaluable Population by Center/Sponsor/MO

Center	Total Randomized N = 542 (100%)		Trovafloxacin 100 mg x 3 days		Trovafloxacin 100 mg x 7 days		Norfloxacin 400 mg b. i. d. x 3 days		Total evaluable N = 334 (100%)	
			Sponsor and MO Evaluable N = 116	%	Sponsor and MO Evaluable N = 113	%	Sponsor and MO Evaluable N = 105	%		
5003 *	35	6.4	6	5.1	6	5.3	6	5.7	18	5.3
5005*	54	9.9	11	9.4	13	11.5	11	10.4	35	10.4
5011 *	18	3.3	4	3.4	5	4.4	4	3.8	13	3.8
5013 *	27	4.9	7	6.0	3	2.6	2	1.9	12	3.5
5041 *	27	4.9	4	3.4	5	4.4	3	2.8	12	3.5
5138 *	14	2.5	2	1.7	2	1.7	1	.9	5	1.4
5492 *	48	8.8	10	8.6	10	8.8	8	7.6	28	8.3
5630 *	13	2.3	1	.8	2	1.7	1	.9	4	1.1
5632 *	28	5.1	3	2.5	5	4.4	4	3.8	12	3.5
5633 *	7	1.2	2	1.7	2	1.7	0	-	4	1.1
5635 *	8	1.4	1	.8	2	1.7	0	-	3	.89
5636 *	8	1.4	2	1.7	2	1.7	2	1.9	6	1.7
5637 *	10	1.8	2	1.7	2	1.7	4	3.8	8	2.3
5681 *	54	9.9	16	13.7	16	14.1	17	16.1	49	14.6
5733 *	29	5.3	6	5.1	4	3.5	5	4.7	15	4.4
5783	18	3.3	5	4.3	3	2.6	4	3.8	12	3.5
5784	17	3.1	4	3.4	4	3.5	4	3.8	12	3.5
5785	6	1.1	2	1.7	1	.8	2	1.9	5	1.4
5786	6	1.1	2	1.7	2	1.7	1	.9	5	1.4
5787	19	3.5	3	2.5	4	3.5	5	4.7	12	3.5
5792	2	0.3	-	-	-	-	-	-	-	-
5794	13	2.3	2	1.7	2	1.7	3	2.8	7	2.0
5797	2	0.3	-	-	-	-	-	-	-	-
5798	7	1.2	1	.8	2	1.7	1	.9	4	1.1
5799	5	1.4	2	1.7	2	1.7	1	.9	5	1.4
5801	12	2.2	3	2.5	1	.8	2	1.9	6	1.7
5802	10	1.8	3	2.5	3	2.6	3	2.8	9	2.6
5803	4	0.7	-	-	-	-	-	-	-	-
5804	24	4.4	8	6.8	5	4.4	7	6.6	20	5.9
5821	17	3.1	4	3.4	5	4.4	4	3.8	13	3.8

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None of the randomized and treated patients from centers 5792, 5797, and 5803 met the Reviewer's criteria for evaluability.

Only center 5681 had greater than 10% of the evaluable patients on all 3 arms. The US centers represent approximately 66.5% of the evaluable population.

The demographics of the FDA evaluable population can be seen in the following Table:

**Table 116.9:
Demographic Characteristics of the FDA Evaluable Population:**

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Characteristics	Trova 3-day	Trova 7-day	Norflox 3-day
	N = 116	N = 113	N = 105
Sex (Female)	116	113	105
Age (years) 16 -44	71	77	68
45 - 64	27	15	23
≥ 65	18	21	14
Mean	40.9	39.2	39.9
Race:			
Asian	1	3	0
Black	3	1	3
White	105	99	95
Hispanic	7	10	6
Nat Am.	0	0	1
Body weight (kg) mean	67.4	65.1	69.4

All of the subjects were female and all 3 arms consisted of a comparable population in terms of weight, age, and race.

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EFFICACY:

**Table 116.10:
Table of Bacteriologic Efficacy by Patient (as per the MO):**

Timepoint	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
EOT	116	101	87.1	113	105	92.9	105	94	89.5
EOS	104	77	74	98	81	82.7	93	69	74.2

From Table 116.10, it is apparent that at the MO TOC, (EOT), there was equivalence between the trovafloxacin 3-day arm and the norfloxacin arm with a CI of -11.8% ,6.9% with CCF ($\Delta = 15\%$). The failure rate was 15 patients or 12.9% for the trovafloxacin 3-day arm as compared to 11 patients or 10.5% for the norfloxacin arm. Interestingly, there was also equivalence between the trovafloxacin 7-day and the norfloxacin arms with a CI of -5.1% 11.8% ($\Delta = - 10\%$) with CCF but NOT between the trovafloxacin 3-day and the trovafloxacin 7-day regimens: CI -14.4% 2.7% ($\Delta = - 10\%$) with CCF.

This difference persisted at the EOS where again there was equivalence between the trovafloxacin 3-day and norfloxacin regimens, CI -12.5% 13.5% ($\Delta = - 20\%$) with CCF and the norfloxacin and trovafloxacin 7-day regimens, CI 4.4% 20.8% ($\Delta = - 15\%$) with CCF but not between the trovafloxacin 3-day and 7-day regimens, CI -19.7% 4.4% ($\Delta = - 15\%$) with CCF.

Additional statistical analyses provided by Dr. Nancy Silliman, FDA STL, revealed that if the analyses were adjusted for 2 primary comparisons, then the 97.5% CI was -13.0%, 8.1% ($\Delta = 15\%$). Therefore, the trovafloxacin 3 day regimen remained equivalent to the norfloxacin regimen. If the analysis was adjusted for 3 primary comparisons, the 98.5% CI was -13.7%, 8.8% ($\Delta = 15\%$). Therefore, once again the trovafloxacin 3 day regimen was equivalent to the norfloxacin regimen.

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**Table 116.11:
Bacteriologic Efficacy by Pathogen at EOT:**

Pathogen	Trova 3-day			Trova 7-day			Norfloq 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
<i>Escherichia coli</i>	96	88	92	90	85	93	81	75	93
<i>Enterococcus faecalis</i>	5	1	20	3	2	67	5	3	60
<i>Proteus mirabilis</i>	8	7	88	4	4	100	4	4	100
<i>Enterobacteriaceae</i>	7	4	66	8	7	87.5	9	7	71.4
<i>Pseudomonas aeruginosa</i>	1	1	100	1	0	0	0	0	0
<i>Pseudomonas spp.</i>	-	-	-	1	1	100	-	-	-
<i>Staphylococcus haemolyticus</i>	3	2	66.6	3	2	66.6	1	1	100
<i>Staphylococcus saprophyticus</i>	2	2	100	6	6	100	3	3	100
<i>Staphylococcus aureus</i>	2	2	100	-	-	-	3	2	66.6
Other <i>Staphylococci</i>	2	2	100	-	-	-	1	1	100
<i>Beta-hemolytic Streptococci</i>	-	-	-	-	-	-	1	1	100
Other <i>Streptococci</i>	-	-	-	-	-	-	1	1	100
<i>Morganella morganii</i>	-	-	-	-	-	-	1	1	100
<i>Acinetobacter spp</i>	-	-	-	-	-	-	1	1	100
Total	126	109	86.5	116	107	92.2	111	100	90

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From Table 116.8, it appeared as if the overall eradication rate for all bacterial isolates was 86.5% for trovafloxacin 3-day arm compared to 92.2% for the 7-day arm and 90% for the norfloxacin arm. The CIs for these results were:

- Trovafloxacin 3-day vs. Norfloxacin: -12.6%, 5.4% with CCF, ($\Delta = -10\%$): NOT equivalent;
- Trovafloxacin 7-day vs. Norfloxacin: -6.1%, 10.4% ($\Delta = -10\%$)
- Trovafloxacin 3-day vs. Trovafloxacin 7-day: -14.3%, 2.3% ($\Delta = -10\%$) NOT equivalent;

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Therefore, equivalence was not shown between the 3-day treatment arms versus the bacterial isolates as a whole.

If the coagulase-negative Staphylococci including *Staphylococcus haemolyticus* are excluded (but including *Staphylococcus saprophyticus*) and the Streptococci other than *Enterococcus faecalis* are excluded these rates are:

- Trovafloxacin 3-day vs. Norfloxacin: 105/121 (86.7%) CI -12.2%, 6.3% ($\Delta = -15\%$),
- Trovafloxacin 7-day vs. Norfloxacin: 105/113 (92.9%) CI -5.2%, 11.6% ($\Delta = -10\%$) and
- Trovafloxacin 3-day vs. Trovafloxacin 7-day: 96/107 (89.7%), CI -14.7, 2.4% ($\Delta = -10\%$)

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Therefore there was equivalence for the 3-day regimens only and not between the trovafloxacin 3 and 7 day arms.

The CIs for *Escherichia coli* alone were:

- Trovafloxacin 3-day vs. Norfloxacin: - 10.0%, 8.2% ($\Delta = - 10\%$)
- Trovafloxacin 7-day vs. Norfloxacin: - 6.7%, 10.4% ($\Delta = - 10\%$)
- Trovafloxacin 3-day vs. Trovafloxacin 7-day: - 11.1%, 5.6 % ($\Delta = - 10\%$) NOT EQUIVALENT

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Thus the 3-day regimens were again equivalent but the 7-day regimen was superior to both.

Overall trovafloxacin 100 mg for 3 days was equivalent to norfloxacin 400 mg bid for 3 days both for overall bacteriologic efficacy as well as for *Escherichia coli* eradication.

A by center analysis for both bacteriological efficacy and clinical efficacy is available, however there were no "outlier" centers and additionally, the number of patients per center was too small to detect any significant differences.

Table 116.12:
Clinical Efficacy (Bacteriologically Evaluable Population/as per the MO)

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Timepoint	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
EOT	116	113	97.4	113	110	97.3	105	97	92.4
EOS	107	91	85.0	101	90	89.1	98	81	82.7

From Table 116.12, it is apparent that the trovafloxacin 3-day arm was as effective as the comparator in the treatment of uncomplicated UTI from the standpoint of clinical efficacy, (95% CI : -1.7 %, 11.7 % ($\Delta = - 10\%$) at the EOT/TOC and at the EOS -8.1%, 13.6% ($\Delta = - 10\%$) for the trovafloxacin 3-day vs. norfloxacin arms).

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Table 116.13:
Cross Tabulation of Clinical and Bacteriological Efficacy at the EOT for FDA Evaluable Population:

	Trova 3-day N=116				Trova 7-days N= 113				Norflox 3-day N = 105			
	Bact. Assessment				Bact. Assessment				Bact. Assessment			
	Erad.		Pers		Erad.		Pers		Erad.		Pers	
	N	%	N	%	N	%	N	%	N	%	N	%
Clinical Assessment												
Success	100	86.2	13	11.2	104	92.0	6	5.3	90	85.7	7	6.7
Failure	1	0.9	2	1.7	1	0.9	2	1.8	4	3.8	4	3.8
Total	101	87.1	15	12.9	105	92.9	8	7.1	94	89.5	11	89.5

From Table 116.13, it is evident that there were disparate results between clinical success and bacteriologic eradication in 13 of the 113 clinical successes on the trovafloxacin 3-day arm, 6 of the 110 clinical successes on the trovafloxacin 7-day arm and 7 of the 97 clinical successes on the norfloxacin arm.

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Additionally, there were 1 of 3 trovafloxacin 3-day clinical failures with bacteriologic eradication, 1 of 3 trovafloxacin 7-day patients and 4/8 norfloxacin patients had similar results.

From the line listings provided, the MO identified these subjects and provides below a list per arm with their EOS bacteriologic and clinical responses :

Trovafloxacin 3-day (N = 14):

PID	EOT Bact Resp	EOT CL. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf. Y /N	Reviewer Determination
50030098	Pers.	Cure	Pers.	Relapse	Y	(<i>Klebsiella pneumoniae</i>) Persistence of original <i>Escherichia coli</i> /Bactrim Rx/ <i>Klebsiella pneumoniae</i> NOT a true superinfection N
50110027	Pers.	Cure	Pers.	Not Assessable		<i>Escherichia coli</i> persistent at F/u, no further culture
50130140	Pers.	Cure	Pers.	Cure	N	<i>Escherichia coli</i> Erad/Group D persistent at F/u, cleared without therapy N
50130375	Pers.	Impr.	Pers.	Impr.	N	<i>Escherichia coli</i> cleared/ <i>Klebsiella pneumoniae</i> Persistent Day 12, no R/x, cleared and recurred at Day 42 N
50410188	Pers.	Impr.	Pers.	Impr.	N	<i>Escherichia coli</i> decreased to at F/u but at Day 42: N
56360260	Pers.	Cure	Pers.	Cure	N	<i>Escherichia coli</i> persistent at both F/u visits N
57330206	Pers.	Impr.	Pers.	Relapse	N	<i>Proteus mirabilis</i> Eradicated and at day 42 N
57830840	Pers.	Cure	Erad	Cure	N	<i>Escherichia coli</i> , at F/u and Erad at day 42. N
57980584	Pers.	Cure	Pers.	Not Assessable		Group D at F/u, no EOS culture, N
57990599	Pers.	Impr.	Pers.	Relapse	Y	(<i>Escherichia coli</i>) <i>Enterobacter</i> spp., <i>Klebsiella pneumoniae</i> at initial culture, <i>Enterobacter</i> Pers., cleared with Cipro, <i>Escherichia coli</i> at Day 42, Y
58020573	Pers.	Cure	Erad.	Cure	Y	(<i>Citrobacter</i> fr./ <i>Pseudomonas fluorescens</i>) Original <i>Escherichia coli</i> Erad., all others
58020578	Pers.	Cure	Pers.	Not Assessable	Y	(<i>Klebsiella Pneumoniae</i>) Group D Pers., <i>Klebsiella</i> at F/u, no R/x, no F/u, Y
58210735	Pers.	Impr.	Pers.	Relapse	Y	(<i>Lecleria ad.</i>) <i>Citrobacter</i> 10'5 Erad after Day 12 w/o r/x, Bactrim day 43 for clinical complaints, <i>Lecleria</i> N
54920346	Erad.	Failure	Pers.	Failure	N	<i>Escherichia coli</i> Erad, Bactrim day 13 all cultures (-), N

Trovafloxacin 7-day (N = 7):

50410192	Pers.	Impr.	Pers.	Cure	N	<i>Escherichia coli</i> decreased to at F/u but at Day 42: N
56330032	Pers.	Cure	Pers.	Relapse	N	<i>Klebsiella pneumoniae</i> Pers. Day 12, Cipro R/x, no further cultures, N
56360090	Pers.	Cure		Not Assessable		<i>Pseudomonas aeruginosa</i> Pers., Erythro for tooth abscess
57870798	Pers.	Cure	Pers.	Relapse		<i>Escherichia coli</i> Pers. At F/u, Noroxin R/x, cleared, N
57980585	Pers.	Cure	Pers.	Not Assessable	Y	(<i>Enterococcus faecalis</i> / <i>Staphylococcus haemolyticus</i>) Original pathogens cleared, both Y
58210754	Pers.	Impr.	Erad.	Impr.	Y	(<i>Enterococcus faecalis.</i>) Original <i>Escherichia coli</i> at day 42, <i>Enterococcus</i> N

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54920026 Erad. Failure Pers. Failure N *Enterococcus faecalis, no culture at EOT, Cipro R/x, F/u (-). N*

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Norfloxacin 3 day (N = 11):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp	Sup/inf. Y /N	Reviewer Determination
50050138	Pers.	Cure	Pers.	Relapse	N	<i>Klebsiella pneumoniae</i> Day 12, Cefuroxime cleared, N
50130058	Pers.	Cure	Pers.	Cure	N	Group D, <i>Escherichia coli</i> at day 1, decreased to at EOT, <i>Escherichia coli</i> at EOS, N
50410007	Pers.	Impr.	Pers.	Relapse	N	<i>Escherichia coli</i> Pers., no R/x, N
58020571	Pers.	Cure	Erad	Cure	Y	(<i>Staphylococcus epidermidis</i>) <i>Escherichia coli</i> , Group D decreased at EOT, cleared w/o R/x, <i>Staphylococcus epidermidis</i> N
58020580	Pers.	Cure	Pers.	Relapse	N	Gp. D Pers., CiproR/x, N
58040762	Pers.	Cure	Pers.	Cure	N	<i>Escherichia coli</i> Pers., No R/x, N
58210737	Pers.	Cure	Pers.	Cure	N	<i>Staphylococcus aureus</i> decreased to but <i>Citrobacter</i> no r/x, N
54920077	Erad.	Failure	Erad.	Failure	Y	(<i>Klebsiella pneumoniae</i>) <i>Escherichia coli</i> Erad, Nitrofur. R/x for clinical, <i>Klebsiella pneumoniae</i> at EOS, Y
56810289	Erad.	Failure	Erad.	Failure	N	<i>Escherichia coli</i> Pers, N
57330068	Erad.	Failure	Pers.	Failure	N	<i>Escherichia coli</i> , Bactrim r/x, N
57330302	Erad	Impr.	Erad.	Cure	N	<i>Escherichia coli</i> Erad, N

The MO did not discover any significant trends in the above list. Overall, most clinical failures remained failures at the EOS, with the exception of 1 norfloxacin patient. There was no definitive trend in the persistent/improvement group in terms of their evolution to cures or relapses.

Using the Reviewer's criteria, there were only 2 superinfections found on the trovafloxacin 3-day arm, and 1 on each of the other arms for a total of 4 amongst this population of patients where there were disparate bacteriologic and clinical outcomes.

Overall, the Reviewer agreed with the sponsor's determination of outcome in terms of failure/cure.

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Clinical Relapses:

The following patients were classified as relapses, where applicable, patients from the previous list who are relapses have their PIDs bolded:

Trovafloxacin 3-day (N = 13):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp	Sup/inf. Y /N	Reviewer Determination:
50030098	Pers.	Cure	Pers.	Relapse	Y	(<i>Klebsiella pneumoniae</i>) Persistence of original <i>Escherichia coli</i> /Bactrim Rx/ <i>Klebsiella pn.</i> NOT a true superinfection N
50030119	Erad.	Cure	Pers.	Relapse	N	<i>Staphylococcus saprophyticus</i> Erad, then recurred, Bactrim R/x, N but RECURRENCE
50050424	Erad.	Impr.	Erad.	Relapse	Y	(<i>Klebsiella pneumoniae</i>) <i>Escherichia coli</i> cleared/ <i>Klebsiella pneumoniae</i> at EOS, Y

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50410465	Erad.	Cure.	Erad	Relapse	Y (<i>Escherichia coli</i>)	<i>Proteus mirabilis</i> Erad, <i>Escherichia coli</i> at Day 33, Y
54920195	Erad.	Cure	Pers.	Relapse	N	Group B <i>Streptococcus</i> and <i>Staphylococcus aureus</i> <i>Staphylococcus aureus</i> cleared, Group B decreased at EOT at EOS, N
56360088	Erad.	Cure	Pers.	Relapse	Y (<i>Proteus Mirabilis</i>)	<i>Escherichia coli</i> day 1, <i>Proteus mirabilis</i> Day 4, Cipro, Y
56810052	Erad.	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> Erad, RECURRED , Nitrof. R/x, N
56810203	Erad.	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> , RECURRED , Bactrim R/x, N
56810292	Erad.	Cure	Pers.	Relapse	Y (<i>Escherichia coli</i>)	<i>Proteus mirabilis</i> Erad. <i>Escherichia coli</i> r/x Bactrim, Y
57330206	Pers.	Impr	Pers.	Relapse	N	<i>Proteus mirabilis</i> Eradicated and at day 42 N
57990599	Pers	Impr.	Pers	Relapse	Y (<i>Escherichia coli</i>)	<i>Enterobacter</i> , <i>Klebsiella</i> <i>pneumoniae</i> at initial culture, <i>Enterobacter</i> Pers., cleared with Cipro, <i>Escherichia coli</i> at at Day 42, Y
58040760	Erad.	Cure	Pers.	Relapse	Y (<i>Enterobacter agglomerans/Proteus mirabilis</i>)	<i>Escherichia coli</i> Erad. other orgs isolated Noroxin R/x <i>Enterobacter agglomerans</i> = S, <i>Proteus</i> = NO, Y
58210735	Pers.	Impr.	Pers.	Relapse	Y (<i>Lecleria ad.</i>)	<i>Citrobacter</i> Erad after Day 12 w/o r/x, Bactrim day 43 for clinical complaints, <i>Lecleria</i> N

Trovafloxacin 7-day (N = 8):

50410010	Erad.	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> Erad Day 12, EOS
56330032	Pers..	Cure	Pers.	Relapse	N	<i>Klebsiella pneumoniae</i> Pers. Day 12, Cipro R/x, no further cultures, N
54920029	Erad..	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> Erad, RECURRENCE , Nitrof. R/x, N
54920080	Erad..	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> Erad, no cultures, Nitrof R/x, N
57870798	Pers	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> Pers. at F/u, Noroxin R/x, cleared, N
58040728	Erad..	Impr	Pers.	Relapse	Y (<i>Acinetobacter calcoetaenius/Enterobacter cloacae/Escherichia coli</i>)	<i>Escherichia coli</i> = S only, Noroxin R/x, Y
58040761	Erad..	Cure	Pers.	Relapse	Y (<i>Staphylococcus saprophyticus</i>)	S after original <i>Escherichia coli</i> cleared, Y
58040728	Erad..	Impr	Pers.	Relapse	Y (<i>Escherichia coli.</i>)	<i>Escherichia coli</i> superinf. after original <i>Klebsiella</i> <i>pneumoniae</i> Erad, Y

Norfloxacin 3-day (N=8):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf. Y /N	Reviewer Determination
50050138	Pers.	Cure	Pers.	Relapse	N	<i>Klebsiella pneumoniae</i> Day 12, Cefuroxime cleared, N
50410007	Pers.	Impr.	Pers.	Relapse	N	<i>Escherichia coli</i> Pers. , no R/x, N

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50030107	Erad..	Cure	Pers.	Relapse	N	<i>Staphylococcus saprophyticus</i> Erad but Nitrof. R/x, N
50030109	Erad..	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> R/x with Macrobid, no repeat culture, N
58020580	Pers.	Cure	Pers.	Relapse	N	<i>Enterococcus Pers.</i> , CiproR/x, N
56360087	Erad..	Cure	Pers.	Relapse	N	<i>Enterococcus</i> , no EOT culture, Lomeflox R/x, N
56810153	Erad..	Cure	Pers.	Relapse	N	<i>Escherichia coli</i> , Erad EOT, RECURRENT EOS , N
56810202	Erad..	Cure	Pers.	Relapse	Y	(<i>Klebsiella pneumoniae</i>) <i>Escherichia coli</i> Erad., <i>Klebsiella pneumoniae</i> Day 42, nitrof. R/x, Y

There were no significant trends identified in the patients who were clinical relapses. There were 13 relapses at the EOS on the trovafloxacin 3-day arm (8 in patients who were initially eradication/cures, 1 persistent/cure, 3 persistent/improved, and 1 eradication/improved). The respective numbers for the trovafloxacin 7-day arm were 8 relapses (4 eradication/cures, 2 persistent/cures and 2 eradication/improved) and 8 norfloxacin relapses (5 eradicated/cured, 2 persistent/cured and 1 persistent/improved).

Overall more patients with an EOT status of Eradicated/Improved were found to have superinfections.

These determinations reflect the sponsor's determinations of superinfecting organisms as opposed to the Reviewer's. The sponsor applied stricter criteria than the Reviewer did, and specifically, a superinfecting pathogen was any organism other than the original pathogen found any time after Day 10 in an amount of $\geq 10^3$ CFU/mL. The Reviewer has adhered to DAIDP guidelines and determined as superinfecting pathogens, any organism associated with UTIs in an amount of $\geq 10^5$ CFU/mL after original clearance.

Recurrence, a category not used by the sponsor refers to the culture of $\geq 10^5$ CFU/mL of the original pathogen after documented clearance.

Persistence was also defined differently by the Reviewer. Persistence is defined as the culture of the original pathogen in an amount of $\geq 10^5$ at the EOT whereas the sponsor determined persistence to be the culture of the original pathogen in an amount of $\geq 10^3$ at EOT. The MO elected to accept the sponsor's definition (see introduction of MOR).

Based on the Reviewer's definition, although ALL of the patients constitute relapse or failures, the reviewer determined that there were 6 superinfections on the trovafloxacin 3-day arm as compared to the sponsor's 7 and that 3 of the 13 relapses were RECURRENCES of the original pathogen.

On the trovafloxacin 7-day arm and on the norfloxacin arm, the Reviewer agreed with the sponsor's determination of superinfection in all cases and recategorized 1 patient on each arm to RECURRENCE status. Amongst the organisms that were recurrent one was a *Staphylococcus saprophyticus* on the trovafloxacin 3-day arm, and all others were *Escherichia coli* (2, 1, 1) and all required further therapy.

Bacterial Superinfections:

Trovafloxacin 3-day (N = 17):

- 50030098: EOS clinical relapse with *Klebsiella pneumoniae*/NOT a superinfecting pathogen per MO, $< 10^5$ CFU/mL, Bactrim® R/x.
- 50050424: EOS clinical relapse with *Klebsiella pneumoniae*/MO agreed.
- 50410465: EOS clinical relapse with *Escherichia coli*/MO agreed.

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- 56330033: EOS cure with *Enterococcus faecalis* in urine/MO agreed.
- 56360088: EOS clinical relapse with *Proteus mirabilis*/MO agreed, Cipro® r/x.
- 56810292: EOS clinical relapse with *Escherichia coli*/MO agreed, Bactrim® r/x.
- 56810309: EOS cure with *Enterobacter aerogenes* in urine/MO agreed. No R/x.
- 57870793: EOS cure with *Enterobacter cloacae* in urine/MO agreed. No R/x.
- 57940982: EOS cure with *Staphylococcus haemolyticus* in urine. Not a superinfecting pathogen per Reviewer.
- 57990599: EOS clinical relapse with *Escherichia coli*/MO agreed.
- 58020573: EOS cure with *Citrobacter freundii* and *Pseudomonas fluorescens* in urine. NOT superinfecting pathogens per MO
- 58020578: EOS cure with *Klebsiella pneumoniae* in urine/MO agreed.
- 58040760 EOS clinical relapse with *Enterobacter agglomerans* and *Proteus mirabilis* in urine/*Enterobacter agglomerans* was a superinfecting pathogen per the Reviewer but NOT the *Proteus mirabilis*.
- 58040758: EOS cure with *Staphylococcus haemolyticus* in urine. Not a superinfecting pathogen per Reviewer.
- 58040765: EOS cure with *Staphylococcus haemolyticus* in urine. Not a superinfection per Reviewer but *Acinetobacter* in urine was a superinfecting pathogen.
- 58210735: EOS cure with *Lecleria adecarboxylata* in urine. NOT a superinfecting pathogen per MO.
- 58210753: EOS clinical relapse with *Acinetobacter* spp. MO agreed, but no R/x mentioned.

On the trovafloxacin 3-day arm, there were 17 patients with superinfecting organisms (20) as per the sponsor, however as per the Reviewer, there were 12 superinfecting organisms and 12 patients. Of these, only 3 received therapy at this timepoint. There were no identifiable trends in types of organisms isolated.

Trovafloxacin 7 day (N = 13):

- 50050132: EOS cure with *Providencia* spp. in urine. MO disagreed
- 51380231: EOS cure with *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* in urine. Not superinfecting pathogens per Reviewer
- 56300216: EOS cure with *Proteus mirabilis* in urine. Not superinfecting pathogen per MO
- 57330305: EOS cure with *Staphylococcus haemolyticus* and *Enterococcus faecalis* in urine. Not superinfecting pathogens per MO
- 57980585: EOS cure with *Staphylococcus haemolyticus* and *Enterococcus faecalis* in urine. MO agreed

- 58020574: EOS cure with *Staphylococcus epidermidis* in urine/Not a superinfecting pathogen per Reviewer.
- 58020576: EOS cure with *Staphylococcus epidermidis* in urine. Not a superinfecting pathogen per Reviewer.
- 58040728: EOS clinical relapse with *Escherichia coli*, *Enterobacter cloacae* and *Acinetobacter* spp. Only *Escherichia coli* was a superinfecting pathogen per the Reviewer . Noroxin® R/x.
- 58040726: EOS cure with *Acinetobacter* spp. in urine. Superinfecting pathogen per Reviewer, > 10⁵
- 58040761: EOS clinical relapse with *Staphylococcus saprophyticus*. Superinfecting pathogen per Reviewer
- 58040763: EOS cure with *Pseudomonas putida*. in urine. Superinfecting pathogen per Reviewer
- 58040768: EOS clinical relapse with *Morganella morganii*. Not a superinfecting pathogen per Reviewer.
- 58210754: EOS cure with *Enterococcus faecalis* in urine. Not a superinfecting pathogen per MO

On the trovafloxacin 7-day arm, there were 13 patients with 18 superinfecting bacterial isolates as per the sponsor. As per the Reviewer, there were 5 patients with 6 superinfecting organisms. Only 1 patient received additional therapy at this timepoint.

Norfloxacin (N = 7):

- 54920077: EOS cure with *Klebsiella pneumoniae* in urine. MO agreed.
- 56810202: EOS clinical relapse with *Klebsiella pneumoniae*. MO agreed. Bactrim® R/x.
- 56810321: EOS cure with *Acinetobacter* spp. in urine. MO agreed.
- 57980588: EOS cure with *Enterococcus faecalis* in urine. Not a superinfecting pathogen per MO (< 10⁴ CFU/mL).
- 58020571: EOS cure with *Staphylococcus epidermidis* in urine. Not a superinfecting pathogen per Reviewer.
- 58040725: EOS cure with *Enterobacter cloacae*, *Klebsiella oxytoca*, and *Staphylococcus haemolyticus*. None of the organisms were superinfecting pathogens per the Reviewer
- 58040731: EOS cure with *Escherichia coli* in urine. Superinfecting pathogen per Reviewer

On the norfloxacin arm the sponsor found 7 patients with 9 superinfecting organisms. The Reviewer agreed with 4 patients and 4 organisms. Only 1 received therapy at this timepoint.

Safety Review:

There were no deaths in this trial and none of the patients discontinued therapy because of an abnormal laboratory value. There were also no patients who temporarily discontinued therapy because of an adverse event.

1/182 (2%) of the trovafloxacin 3-day subjects, 4/182 (2%) of the trovafloxacin 7-day subjects and 4/178 (2%) of the norfloxacin subjects discontinued therapy because of an AE and are presented below: (One patient from each of the above treatment arms discontinued from the study because of an AE.)

Trovafloxacin 3-day (N = 3):

- 50030117: Discontinued after 1 dose because of dizziness, dry heaves, headache, hives, cough, lightheadedness, nausea, tingling, and wheezing.
- 50110366: Discontinued after 2 doses because of dizziness and nausea, did not complete study.
- 54920285: Discontinued after 3 days because of nausea, ringing in ears, and a sensation of skin crawling. Had already completed course of therapy.

Trovafloxacin 7-day (N = 4):

- 50050184: Discontinued treatment because of stomach pain and vertigo after 1 dose
- 50130300: Discontinued after 5 days because of chest pain, palpitations, and tremors not related to the study drug and did not complete the study.
- 56350006: Discontinued after 5 days because of an intestinal virus not related to the study drug and did not complete the study.
- 58210741: Discontinued after 1 dose because of erysipelas in the right leg not related to the study drug and pyrosis which was related.

Norfloxacin (N = 4):

- 50050136: Discontinued after 3 days because of headaches.
- 50410191: Discontinued after first dose because pill lodged in throat.
- 50410248: Discontinued after 1 dose because of a maculopapular rash.
- 56360259: Discontinued after 2 days because of head "swimming."

One patient on each of the trovafloxacin arms had "serious" AEs (< 1%):

- 50130057: anxiety attack requiring hospitalization, the dose was continued unchanged and the attack resolved.
- 56300064: in the post-treatment period this patient suffered a fractured sternum and was hospitalized.

There were 9 (5%) severe AEs reported on the trovafloxacin 3-day regimen, 9 (5%) on the trovafloxacin 7-day regimen, and 3 (2%) on the norfloxacin regimen. The severe AEs that were treatment related were:
Trovafloxacin 3-day:

- 4 episodes of severe headache.
- 2 episodes of nausea.
- 1 fungal infection.

Trovafloxacin 7-day:

- 1 episode of dizziness.
- 3 episodes of headache.
- 1 episode of vertigo.
- 1 episode of thirst.

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Norfloxacin:
None of the severe events were treatment-related.

Within the trovafloxacin 3-day group, the most common severe AEs were headache and nausea.

Within the trovafloxacin 7-day group headache was also the most common AE.

Within the norfloxacin group aggravated allergy, somnolence, and generalized edema were reported most frequently.

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Copied from the Esub and modified by the MO are the sponsor's Tables 6.2, Summary of AEs by Body System: All Causality and Table 6.3, Summary of AE's by Body System, Treatment-Related.

**Table 116.14:
Adverse Events by Body System, All Causality.**

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	Trovafloracin 3-day	Trovafloracin 7-day	Norfloxacin
NUMBER OF SUBJECTS:			
Evaluable for Adverse Events	182 (100%)	182 (100%)	178 (100%)
Subjects With At Least One Event	69 (38%)	61 (34%)	60 (34%)
Subjects Discontinued due to Adverse Event	3 (2%)	4 (2%)	4 (2%)
ADVERSE EVENTS BY BODY SYSTEM:			
Appl./ Inj./ Incision/ Insertion Site	0	1 (<1%)	0
Autonomic Nervous	2 (1%)	1 (<1%)	3 (2%)
Cardiovascular	0	2 (1%)	0
Centr. & Periph. Nerv.	35 (19%)	37 (20%)	23 (13%)
Gastrointestinal	28 (15%)	16 (9%)	21 (12%)
General	13 (7%)	8 (4%)	18 (10%)
Metabolic/ Nutritional	0	1 (<1%)	0
Musculoskeletal	2 (1%)	1 (<1%)	0
Neoplasms	0	0	1 (<1%)
Other Adverse Events	1 (<1%)	0	3 (2%)
Psychiatric	5 (3%)	3 (2%)	3 (2%)
Reproductive	10 (5%)	8 (4%)	5 (3%)
Respiratory	4 (2%)	5 (3%)	2 (1%)
Skin/ Appendages	5 (3%)	4 (2%)	3 (2%)
Special Senses	1 (<1%)	0	1 (<1%)
Urinary System	1 (<1%)	1 (<1%)	1 (<1%)

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**Table 116.15:
Adverse Events by Body System: Treatment-Related.**

	Trova 3-day		Trova 7-day		Norfloxacin	
Evaluable for Adverse Events	182	(100%)	182	(100%)	178	(100%)
Subjects With At Least One Event	42	(23%)	44	(24%)	36	(20%)
Subjects Discontinued due to Adverse Event	3	(2%)	3	(2%)	4	(2%)
ADVERSE EVENTS BY BODY SYSTEM						
Autonomic Nervous	1	(< 1%)	1	(< 1%)	3	(2%)
Cardiovascular	0		2	(1%)	0	
Centr. & Periph. Nerv.	25	(14%)	27	(15%)	13	(7%)
Gastrointestinal	18	(10%)	11	(6%)	18	(10%)
General	5	(3%)	2	(1%)	6	(3%)
Metabolic/ Nutritional	0		1	(< 1%)	0	
Psychiatric	4	(2%)	2	(1%)	2	(1%)
Reproductive	3	(2%)	6	(3%)	2	(1%)
Respiratory	1	(< 1%)	0		0	
Skin/ Appendages	4	(2%)	3	(2%)	2	(1%)
Special Senses	1	(< 1%)	0		0	

The most frequently affected body systems were the CNS and the autonomic nervous systems with 14%, 15%, and 7% of the AEs per arm respectively. This was followed by the gastrointestinal tract with 10%, 6%, and 10%, respectively. These results are similar to those seen in study 103.

**Table 116.16:
Most Common Treatment-Related AEs (All Randomized Patients)**

Nervous System	Trovafloracin 3-day N= 182		Trovafloracin 7-day N = 182		Norfloxacin N = 178	
	25	(14%)	27	(15%)	13	(7%)
Headache	22	12	20	11	15	8
Dizziness	18	10	18	10	8	4
GI System	18	10	11	6	18	10
Nausea	20	11	7	4	12	7
Abdominal Pain	-	-	1	< 1	2	1
Diarrhea	2	1	1	< 1	2	1

*PATIENTS MADE HAVE HAD MORE THAN 1 CONCURRENT AE.

Other frequently reported AEs included:

Paresthesias: 2 (1%) of the trovafloxacin 3-day patients.

Flatulence: 2 (1%) of the trovafloxacin 7-day patients.

Fatigue: 3 (2%) of the trovafloxacin 3-day, 2 (1%) of the trovafloxacin 7-day patients, and 4 (2%) of the norfloxacin patients.

Dreaming abnormalities and psychiatric disturbances: 4 (2%) of the trovafloxacin 3-day, 2 (1%) of the trovafloxacin 7-day, and 2(1%) of the norfloxacin patients.

Vaginitis: 3 (3%) trovafloxacin 3-day, and 6 (3%) of the trovafloxacin 7-day patients.

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Rash and skin: 4 (2%), 3 (2%), and 2 (1%) per arm ,respectively.

Clinical Laboratory Abnormalities:

Only 17 subjects on the trovafloxacin 3-day arm and 8 on the norfloxacin arm of this study were evaluable for laboratory abnormalities, due to protocol design. There were 154 evaluable patients on the trovafloxacin 7-day arm.

Of these subjects, 3 trovafloxacin 3-day, 18 trovafloxacin 7-day, and 1 norfloxacin patients had clinically relevant abnormalities.

No subject in any group had significant abnormalities of creatinine, total bilirubin, hemoglobin, or hematocrit.

One patient receiving trovafloxacin 3-day developed an elevated SGOT (#50050179: baseline SGOT _____ and SGPT at baseline _____). This patient had a history of psoriasis and had recently been treated with methotrexate and indomethacin, to which the sponsor attributes the abnormalities.

Subject #54920074, on the trovafloxacin 7-day arm, had increased LFTs at baseline (SGOT _____ and SGPT _____), which increased to 152 and 151, respectively. These values subsequently decreased slightly, on day 39 to 145 and 149, respectively.

Other than these events, no other laboratory abnormalities were deemed to be significant by the MO.

Reviewer's Conclusion:

The MO concluded that trovafloxacin 100 mg PO daily for 3 days is as effective as norfloxacin 400 mg PO bid for 3 days in the treatment of uncomplicated UTI in women with a baseline colony count of CFU/mL *Escherichia coli*. No conclusions could be drawn as to trovafloxacin's effectiveness against other uropathogens.

Among the FDA bacteriologically evaluable subjects at the EOT (TOC), the MO found a bacteriological eradication rate of 101/116 (87.1%) for trovafloxacin 3-day vs. 94/105 (89.5%) for norfloxacin. This was equivalent when a 95% CI was applied. There was also equivalence between the trovafloxacin 7-day arm 105/113(92.9%) and the norfloxacin arm 94/105 (89.5%) but not between the 2 trovafloxacin arms where the 7-day regimen was superior.

At the EOS, the rates decreased to 77/104(74%) trovafloxacin 3-day vs. 69/93 (74.2%) norfloxacin, which were equivalent although, neither 3-day regimen was able to demonstrate equivalence with the trovafloxacin 7-day arm 81/98 (82.7%).

Bacteriologic efficacy analyses by pathogen revealed statistical equivalence between the trovafloxacin 3-day and norfloxacin arms for *Escherichia coli* (88/96 (92%) vs. 75/81 (93%). Equivalence was not demonstrated between the trovafloxacin 3 and 7-day arms (88/96 (92%) vs. 85/90 (93%) in this analysis.

The FDA clinically-evaluable population was the same as the bacteriologically evaluable and there was equivalence between all 3 arms at EOT and EOS (EOT: 113/116 (97.4%) 3-day; 110/113 (97.3%) 7-day; 97/105 (92.4%) norfloxacin; EOS: 91/107 (85%) 3-day; 90/101 (89.1%) 7-day; 81/98 (82.7%) norfloxacin).

The MO analyzed all failures, relapses, recurrences, and superinfections and although the MO determined that there were fewer superinfections on all arms as compared to the sponsor, no real difference between the arms was noted.

The MO's results are similar to the sponsor's results both in terms of all overall efficacy as well as in the separate analyses.

In terms of safety, the MO determined that the most frequently reported AEs were from the CNS and the peripheral nervous systems. This was consistent with the AE profile seen in study 103 with > 15% of the patients complaining of dizziness and headache. In this trial, there was also a large number of patients who complained of nausea.

There were 2 trovafloxacin patients with minor elevations of SGOT or SGPT. This was also seen in study 103.

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Reviewer's Overall Conclusion for the Indication of Uncomplicated UTI:

**Table 116.17
Overview of Efficacy Results/Uncomplicated UTI studies (as per the MO)**

Study #	154- 103	154 - 116
Location	US	US and Europe
Type	Phase II, Double-blind	Phase III, Double-blind
Comparator/Duration	Trovafloxacin 100 bid x 7d Trovafloxacin 100 qd x 7d Ciprofloxacin 250 bid x 7d	Trovafloxacin 100 qd x 3d Trovafloxacin 100 qd x 7d Norfloxacin 400 bid x 3d
# Enrolled	221	560
# MO Evaluable (BT)/EOT	22, 22, and 29	116, 113, and 105
# MO Evaluable (Clinically)/EOT	22, 22, and 29	116, 113, and 105
Bacteriologic Efficacy/Patient EOT/EOS	21/22 (95.5%) 15/21 (75%) 19/22 (86.4%) 18/21 (85.7%) 27/29 (93.1%) 22/27 (81.5%)	101/116 (87.1%) 77/104 (74%) 105/113 (92.9%) 81/98 (82.7%) 94/105 (89.5%) 69/93 (74.2%)
Bacteriologic Efficacy by Pathogen/EOT	21/22 (95.4%) 20/23 (86.9%) 28/30 (89.2%)	109/126 (86.5%) 107/116 (92.2%) 100/111 (90%)
Clinical Efficacy by Patient/EOT	21/22 (95.5%) 16/18 (88.9%) 21/22 (95.5%) 17/19 (89.5%) 28/29 (96.6%) 22/26 (84.6%)	113/116 (97.4%) 91/107 (85%) 110/113 (97.3%) 90/101 (89.1%) 97/105 (92.4%) 81/98 (82.7%)
Eradication EOT <i>Escherichia coli</i>	19/19 (100%) 17/18 (94.4%) 21/21 (100%)	88/96 (92%) 85/90 (93%) 75/81 (93%)
Conclusion	Underpowered and Phase II. Trovafloxacin 100 qd appeared numerically comparable to ciprofloxacin for 7 days.	Trovafloxacin 3 days equivalent to norfloxacin 3 days. Trovafloxacin 7 days was superior to trovafloxacin 3 days but equivalent to norfloxacin 3 days for BT efficacy at EOT. Neither 3 day was equivalent to 7 day at EOS. Same results by pathogen. Clinical efficacy revealed equivalence between all 3 arms.
Adverse Events all causality	CNS 26 (36%) 21 (28%) 18 (24%)	35 (19%) 37 (20%) 23 (13%)

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Overall, trovafloxacin appeared safe and effective in the treatment of uncomplicated urinary tract infections caused by *Escherichia coli*, predominantly in women, and the sponsor's request for this indication should be approved at a dose of 100 mg PO daily for 3 days.

The sponsor submitted 2 clinical trials in support of this indication. The first study, 154-103, was a Phase II trial that compared 7 days of trovafloxacin 100 mg/day, trovafloxacin 100 mg/bid and ciprofloxacin 250 mg/bid for 7 days. Although 221 patients were enrolled, the MO determined that only 22, 22, and 29 patients per arm respectively, were evaluable. The MO differed from the sponsor in the inclusion of patients with colony counts $\leq 10^5$ CFU/mL and as to the timing of the TOC analysis. The MO considered evaluable only those patients with colony counts of $\geq 10^5$ CFU/mL and the TOC visit had to be at least 5 days after the completion of therapy.

Statistically significant results could not be obtained from this underpowered study. The MO found an overall bacteriologic eradication rate at the EOT of 21/22 (95.5%), 19/22 (86.4%), and 27/29 (93.1%) per arm respectively.

Bacteriologic efficacy by pathogen for the most commonly isolated baseline pathogen, *Escherichia coli* was 19/19 (100%), 17/18 (94.4%), and 21/21 (100%) per arm respectively.

Clinical efficacy at EOT was also comparable for all 3 arms, with cure rates of 21/22 (95.5%), 21/22 (95.5%), and 28/29 (96.6%) per arm respectively.

The second study, 154-116, was considered pivotal by both the sponsor and the MO. It was a Phase III trial comparing trovafloxacin 100 mg/qd for 3 days (the proposed dose), with trovafloxacin 100 mg/qd for 7 days, and norfloxacin 400 mg/bid for 3 days. Norfloxacin is currently approved for uncomplicated UTI at the dose utilized in this trial.

The MO concluded that trovafloxacin 100 mg PO daily for 3 days was as effective as norfloxacin 400 mg PO bid for 3 days in the treatment of uncomplicated UTI in women with a baseline colony count of $\geq 10^5$ CFU/mL *Escherichia coli*. No conclusions could be drawn as to the effectiveness against other organisms.

Among the FDA bacteriologically evaluable subjects at the EOT (TOC), the MO found a bacteriological efficacy rate of 101/116 (87.1%) for trovafloxacin 3-day vs. 94/105 (89.5%) for norfloxacin. This was statistically-equivalent when a 95% CI was applied. There was also equivalence between the trovafloxacin 7-day arm 105/113 (92.9%) and the norfloxacin arm 94/105 (89.5%) but not between the 2 trovafloxacin arms where the 7-day regimen was superior.

At the EOS, the rates decreased to 77/104 (74%) trovafloxacin 3-day vs. 69/93 (74.2%) norfloxacin, which were equivalent although, neither 3-day regimen was equivalent to the trovafloxacin 7-day arm 81/98 (82.7%).

Bacteriologic efficacy analyses by pathogen revealed equivalence between the trovafloxacin 3-day and norfloxacin arms for *Escherichia coli* (88/96 (92%) vs. 75/81 (93%). Equivalence was not demonstrated between the trovafloxacin 3 and 7-day arms (88/96 (92%) vs. 85/90 (93%) in this analysis.

Equivalence was found in terms of clinical cure between all 3 arms at EOT and EOS (EOT: 113/116 (97.4%) 3-day; 110/113 (97.3%) 7-day; 97/105 (92.4%) norfloxacin; EOS: 91/107 (85%) 3-day; 90/101 (89.1%) 7-day; 81/98 (82.7%) norfloxacin).

The MO's results are similar to the sponsor's results both in terms of all overall efficacy as well as in the separate analyses.

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In terms of safety (study 116), the MO determined that the most frequently reported AEs were from the CNS and the peripheral nervous systems. This was consistent with the AE profile seen in study 103 with > 15% of the patients complaining of dizziness and headache. In this trial, there was also a large number of patients who complained of nausea.

**Recommended Regulatory Action:
Indications and Usage:**

The following statement can be added to the labeling:

APPROVED FOR LABELING
BY [unclear]

/S/

[Handwritten signature]

Regina Alivisatos, MD
Medical Officer, DSPIDPs

- Orig. NDA #20-759
- Orig. NDA #20-760
- HFD-590
- HFD-590/Div. Dir./MGoldberger /S/
- HFD-590/Dep. Dir./RAlbrecht
- HFD-590/MTL/BLeissa /S/12/18/97
- HFD-590/MO/RAlivisatos
- HFD-590/CSO/PFogarty
- HFD-725/Biostat/Silliman
- HFD-344/Thomas

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INFORMATION**

Bacterial Prostatitis:

The proposed indication as it will appear in the labeling, if approved is:

Bacterial Prostatitis caused by *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, or coagulase-negative staphylococci.

The proposed dose is 200 mg PO daily for 28 days.

In support of this indication, the sponsor submitted one double-blind, comparative trial of the efficacy and safety of trovafloxacin at the proposed dose compared to ofloxacin 300 mg PO BID for 6 weeks (42 days).

The MO located other documents within the electronic submission related to the pharmacokinetics and microbiological properties of trovafloxacin. These are summarized in the MOR.

Oral Antimicrobial Agents Currently Approved for this Indication:

Ofloxacin: (*Escherichia coli*)

Norfloxacin: (*Escherichia coli*)

Carbenicillin: (*Escherichia coli*, *Enterococcus faecalis*, *Proteus mirabilis*, and *Enterobacter* spp.)

Ciprofloxacin: (*Escherichia coli* and *Proteus mirabilis*; chronic bacterial prostatitis)

Abbreviations used in this section:

Ofloxacin = Floxin®, Oflox

UTI = urinary tract infection

VB1 = voided bladder specimen 1, (first 5 - 10 ml of voided urine = urethral specimen)

VB2 = voided bladder specimen 2, midstream urine

VB3 = voided bladder specimen 3, the urine voided after prostatic massage

EPS = prostatic secretions expressed by massage

V1 = visit one or baseline visit on study day 1

V2 = visit 2, window = study days 3 - 5

V3 = visit 3, study day 18 - 22

V4 = visit 4, EOT visit for the trovafloxacin-treated patients, study days 33 - 37, window = days 25 - 42

V5 = visit 5, EOT visit for the ofloxacin patients and the second follow-up visit for the trovafloxacin patients, study days 47 - 51, window = study days 43 - 59

V6 = visit 6, EOS visit for all patients, study days 63 - 84, window = study days 60 - 90

EOT = End of Therapy

EOS = End of Study

TOC = Test of Cure

AE = Adverse Event

PTC = Points to Consider

Background:

The term prostatitis is a clinical term, used to describe a large group of adult men with a variety of complaints from the lower urogenital tract. Classification of these patients can be made into 4 subgroups: acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, and prostatic pain. This subdivision is based on careful bacteriologic assessment of sequential urine cultures obtained during urination (technique of Meares and Stamey). Specifically, VB1, VB2, and VB3 are the sequential urines obtained in addition to the expressed prostatic secretion culture (EPS). The diagnosis of bacterial prostatitis requires that the colony count in the VB3 specimen or the EPS exceed that in VB1, or VB2 by 10-fold. In patients with chronic prostatitis, there are only small numbers of bacteria in the prostate and often this technique is not helpful in establishing a pathogen.

The syndromes of acute and chronic bacterial prostatitis are distinct. Additionally, acute prostatitis does not usually lead to chronic disease and chronic disease is not usually preceded by acute disease.

Acute bacterial prostatitis is an acute localized infectious process, characterized by the development of local heat, tenderness, and fever. Other symptoms of disease include chills, perineal pain, back pain, dysuria, increased frequency, and urgency. The prostate gland is warm, swollen, and tender to palpation. Gram stain specimens of EPS reveal polymorphonuclear leukocytes and bacteria.

Chronic disease usually produces fewer symptoms to none at all, related to the prostate, which serves as a nidus of a low-grade infection. Patients with chronic disease often have symptoms such as low back pain, perineal pressure, low-grade fever, or difficulty urinating during an acute phase but often can be asymptomatic. Chronic bacterial prostatitis, however, is the most common cause of relapsing UTI in men. Rectal examination is not notable during the chronic phase in these patients. This entity is very difficult to cure because of poor penetration of most antimicrobials into the noninflamed prostate and additionally the nidus of the infectious process may be small calculi. Relapses occur frequently.

From the standpoint of bacterial etiology, most cases of acute prostatitis are caused by Gram (-) enteric organisms. In the past, *Neisseria gonorrhoeae* was common but now is seen less frequently. Chronic disease is most commonly caused by *Escherichia coli*, but also by *Klebsiella* spp., *Enterobacter* spp., *Proteus mirabilis* and enterococci. Coagulase-negative staphylococci such as *Staphylococcus epidermidis* as well as *Staphylococcus aureus* and diptheroids are often isolated in EPS specimens but there is debate as to their role as true pathogens as opposed to their presence as urethral commensals.

In terms of therapy, current recommendations suggest that only lipid-soluble and basic compounds are capable of entering the acidic environment of the prostate and exerting a therapeutic effect. Trimethoprim and the fluoroquinolones diffuse into the prostate tissue in high concentrations. Acute disease usually responds well to antimicrobial therapy and following a favorable initial clinical response, therapy should be continued for 4 – 6 weeks. Chronic disease, as stated above, is difficult to cure and often requires surgical intervention. Prior to this however, antimicrobial therapy is used and duration of treatment can be anywhere from 1 – 3 months. Cure rates approximate 33% in these patients. If therapy is unsuccessful, the management approach suggested is either the treatment of acute exacerbations in a traditional manner or the use of chronic suppressive therapy using low daily doses of the aforementioned antimicrobials.

Mandell, Douglas and Bennett's principles and Practice of Infectious Diseases, Fourth edition, pages 680, 681, 1080, 1081.

Other sources that enabled the MO to ascertain current thought as to the bacterial etiology of prostatitis included:

Urinary Tract Infections, Molecular Physiology and Clinical Management, HLT Mobly and John Warren, MD, 1996, page 39: "Acute prostatitis is generally associated with UTI and is caused most commonly by Gram (-) bacilli (*Escherichia coli*, *Klebsiella* spp., and *Proteus* spp., among others). Acute prostatitis is associated with increased number of WBCs per high-power field in prostatic fluid. Gram-positive cocci, including *Enterococcus* spp. and *Staphylococcus aureus* are much less frequently associated with acute prostatitis. Prostatitis due to *Staphylococcus aureus* is often the consequence of catheter use. Infection of the prostate may also occur with *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma* spp. or rarely trichomonads.

Chronic prostatitis can be associated with either relapsing UTI or the persistence of a pathogen within the prostate gland."

Current IDSA Guidelines (Clinical Infectious Diseases, Vol. 15, supplement 1, Nov. 1992, pages S219 – S224), state that "Acute uncomplicated UTI in men, analogous to that occurring in women, is quite uncommon. It should be assumed that any UTI in a man > 40 years of age, is associated with bacterial invasion of the prostate and/or kidney."

"The differentiation in most men between bacterial prostatitis and bacterial UTI is artificial and inaccurate. This distinction should be eliminated for the purposes of clinical trials and all UTIs in men should be regarded as complicated."

"Some men have persistent symptomatic or asymptomatic infection of the prostate even after eradication of bladder bacteruria. This persistence is frequently the cause of recurrent infection with the same microorganism."

In terms of trial design, the IDSA suggests that patients be characterized as having acute disease if they had been free of symptoms of UTI for > 6 months and as having chronic UTI if they have had symptomatic infection with the same organism at least once in the 6 months before enrollment. The schedule of visits is the same in all complicated UTIs including prostatitis. An entry visit followed by V1 at 3 -5 days after the start of therapy, followed by a TOC visit 5 -9 days after therapy is completed are suggested. A second follow-up visit, 4 - 6 weeks after completion of therapy is recommended and should encompass at least 50% of the evaluable patients. It is expected, that in acute disease, > 90% of patients will have improvement at V1 and that > 75% will have microbiological suppression and clinical improvement at the EOT, (5- 9 days post R/x visit). If > 50 % of patients are seen at the 4 -6 week follow-up visit, it is expected that > 50% of these patients will continue to have clinical improvement and microbiological suppression (that is a final outcome of cure).

The current Guidance for Evaluability Criteria of the DAIDP has not recently addressed the issue of bacterial prostatitis. The only available guidance is from the DAIDP's Points to Consider document, which states that for acute prostatitis "one statistically adequate and well controlled multicenter trial establishing equivalence or superiority to an approved product is suggested. In this infection, an evaluable patient should be both clinically and microbiologically evaluable."

"It is assumed that the compound would have also established effectiveness in complicated UTI and that the majority of pathogens are similar. Clearly some potential pathogens such as species of *Chlamydia*, should be evaluated on their responses in this study."

Based on the above, the MO concluded that bacterial prostatitis, although apparently a well-defined clinical entity, has not been dealt with separately by IDSA. Additionally, there is no concurrence between the currently available guidance documents and the medical literature as to the true bacterial etiology of this disease. The current submission as well as previously reviewed NDAs, cited below, have not adequately defined acute and chronic disease, thus all populations studied, appear to have included patients with both acute and chronic disease.

NDA 19-735/Ofloxacin for bacterial prostatitis:

This review resulted in the approval of ofloxacin for the treatment of bacterial prostatitis due to *Escherichia coli*. As per the Division Director's review, the study submitted (in accordance with the PTC Guidance document), utilized the following as minimal evaluability criteria:

- clinical signs and symptoms of prostatitis pretreatment
- expressed prostatic secretion culture positive for a recognized pathogen, prior to the initiation of treatment
- treatment with the drug product for approximately 6 weeks unless a clinical failure
- EPS culture obtained 5 - 9 days after stopping therapy (for those patients treated for approximately 6 weeks; clinical failures not cultured post-treatment, or cultured while still on therapy were considered presumed bacterial persistences)
- clinical signs and symptoms assessed at 5 - 9 days post-therapy and approximately 4 - 6 weeks post-therapy
- no concurrent antimicrobials during the treatment period or follow-up time period (if given, patients were judged to be clinical failures)

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Ofloxacin had a clinical cure rate of 79% at long-term follow-up compared to a 53% clinical cure rate for carbenicillin. Cure plus improvement resulted in an overall cure rate of 86% for the ofloxacin-treated patients and 78% for the carbenicillin-treated patients at the EOT. The eradication rates at the first post-therapy visit were 75% for ofloxacin versus 67% for carbenicillin. There was a 0% and 11% reinfection rate per arm, respectively.

All patients on the ofloxacin arm of the study had an infection with a single organism. The most commonly isolated pathogen was *Escherichia coli* (15/33), followed by *Proteus mirabilis* (4/33), and *Pseudomonas aeruginosa* (4/33). The respective numbers for the carbenicillin patients were 14/33, 5/33, and 1/33. *Enterococcus faecalis* was also seen in 4/33 of the carbenicillin patients and none of the ofloxacin patients. Coagulase-negative staphylococci were considered evaluable in 1/33 isolates on each arm.

The MO determined that the overall trial design of this study was very similar to that reviewed in this NDA. However, although coagulase-negative staphylococci were not excluded, they represented an extremely small percentage of the "pathogens." No differentiation was made in regards to chronicity of disease.

MOR NDA 19-384/S-020/Norfloxacin:

The sponsor submitted 2 studies comparing the efficacy and safety of norfloxacin to carbenicillin. One study was domestic and the other foreign. At the request of the reviewing MO, the sponsor also submitted data demonstrating adequate penetration into prostatic tissue as well as tissue levels. Overall trial design was similar to that described for the ofloxacin NDA with the exception that the late post-therapy follow-up was performed 9 - 12 weeks after the EOT.

One of the per protocol exclusion criteria in these studies was that patients were excluded if they had an organism isolated that had "a high probability of being a urethral colonizer," including *Staphylococcus epidermidis*, diphtheroids, and nonenterococcal streptococci. Eradication rates were higher overall for norfloxacin-treated patients (14/15) as compared to carbenicillin-treated patients (12/15). Recurrence rates were higher for the carbenicillin-treated patients. *Escherichia coli* was the most commonly isolated pathogen (11/15) norfloxacin, (8/15) carbenicillin. The remainder of the isolates were Gram (-) organisms. These results applied to the US study only.

In the foreign trial there were 49 and 26 evaluable patients per arm, respectively. Information was provided at the request of the MO as to the number of previous episodes of prostatitis the patients had had. 32/48 evaluable norfloxacin and 22/26 evaluable carbenicillin patients had had one or more episodes in the past. The status of the remaining patients was unknown. The MO determined, based on this information, that most of the patients had chronic prostatitis as opposed to acute disease. Clinical cure rates (including improved patients) were 48/48 and 25/26 per arm, respectively.

Eradication rates were 40/50 and 14/26 per arm, respectively. Relapse rates were comparable. The pathogen most commonly isolated was *Escherichia coli* (21/50 norfloxacin isolates compared to 6/26 carbenicillin isolates). Gram (-) organisms accounted for the remainder of the evaluable pathogens. *Staphylococcus aureus* was isolated in 6 norfloxacin and 10 carbenicillin patients but was not considered evaluable. Pooled efficacy data revealed a clinical cure rate of 66/67 (98.5%) norfloxacin versus 38/40 (95%) carbenicillin. Bacteriologic efficacy was 57/68 (83.8%) norfloxacin versus 26/41 (63.4%) carbenicillin. There were 3 relapses on the norfloxacin arm and 5 of the carbenicillin arm.

Despite the chronicity of the infections studied, the MO recommended and norfloxacin was approved for the treatment of "prostatitis due to *Escherichia coli*."

Overall trial design was similar to that in the current submission. However, non-enterococcal Gram (+) isolates were not considered evaluable. Additionally, the protocol allowed the investigator to provide the number of previous episodes that occurred in the last 6 months, thus allowing the ROM to analyze the patients for acute and chronic disease.

MOR NDA 19-537/SE1-021/Ciprofloxacin:

Although the applicant submitted this supplement in order to obtain the indication of prostatitis, the RMO requested that the indication be changed to "chronic bacterial prostatitis." The 2 pivotal trials were conducted in the US and Germany and included treatment for 28 days

Follow-up evaluations were performed at 3 days, 3 months, and 6 months after treatment. Evaluable pathogens were either Gram (-) rods or *Enterococcus faecalis* only. *Escherichia coli* was the most common pathogen (56/104 evaluable isolates), followed by *Proteus mirabilis* (12 evaluable isolates). No Gram (+) organisms with the exception of enterococci and *Enterococcus faecalis* (8/10 evaluable pathogens), were considered evaluable. Bacterial eradication rate for ciprofloxacin was 72/89 (80.8%) versus 16/23 (69.5%) TMP-SMX versus 17/20 (85%) carbenicillin. Specific pathogens: *Escherichia coli*: 49/56 (87.5%) and *Proteus mirabilis*: 12/12 (100%).

Although trial design differed as opposed to that of the current NDA, ciprofloxacin was briefly reviewed in order to demonstrate the change in the requested indication. Ciprofloxacin was ultimately approved for chronic bacterial prostatitis caused by Escherichia coli and Proteus mirabilis. The RMO did not provide the numbers of previous infections per patient in the MOR and therefore this reviewer could not ascertain the basis for the characterization of the studied population as one of chronic prostatitis.

Literature Review:

The MO was unable to find many recent, (last 10 years), references pertaining to the bacterial etiology of prostatitis. The following were noted:

- Ten years experience with chronic prostatitis in Africa; Magocha et al; East Afr. J. of Med; 1996 March; 73 (3) 176-8.
73 men were prospectively evaluated. 58 had prostatitis of a non-bacterial etiology. 11 (73.3%) of those patients with an isolate were found to have *Escherichia coli*.
- Bacterial infection in prostatic prostatic; Lowentritt et al; Dept. of Urology, Tulane, Journal of Urology 1995, October 154 (14) 1378-81.
22 patients and 16 controls. 9 patients had positive cultures from prostatic secretions.

Coagulase-negative staphylococci were the most common isolate (68%). The authors concluded that these organisms appear to play an increasing role in the bacterial etiology of chronic bacterial prostatitis.

- Bacteriology of patients with chronic bacterial prostatitis: Fernandez-Milian et al: Programs and Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 33 (0). 1993

A group of 156 men with symptoms of chronic bacterial prostatitis were evaluated using the 4 glass segmental urine test. 142 patients had cultures from all 4 segmented urines. 51 patients (36%) were culture-positive with a total of 62 bacterial strains. The organisms most frequently recovered were coagulase-negative staphylococci (15/62), *Escherichia coli* (6/62), enterococci (3/62), 2 each *Morganella*, *Pseudomonas*, *Staphylococcus aureus*, *Citrobacter*, and *Proteus*. 1 strain of *Enterobacter* was recovered.

- Coagulase-negative *Staphylococcus* in Chronic Prostatitis; Nickel J.C. et al, University of Calgary, Canada, Journal of Urology 1992, February, Vol. 147, 398 –401.

3 patients with a clinical history of prostatitis with coagulase-negative staphylococci in EPS were studied after failing antimicrobial therapy. Biopsies were performed in addition to cultures and the authors concluded that "Coagulase-negative staphylococci may be implicated in the pathogenesis of chronic bacterial prostatitis." They suggested that the biofilm surrounding these bacteria keeps them from being eradicated by antibiotics.

- Kunin Calvin M.: Urinary Tract Infections, Detection, Prevention, and Management. Fifth edition, 1997.

"Acute bacterial prostatitis is a suppurative process characterized by fever, chills, leucocytosis, and acute perineal and low back pain. In more severe cases there may be bacteremia, shock, and DIC. Blood cultures are often positive with the same microorganism found in the urine. *Escherichia coli* and other uropathogens are considered to be the etiologic agents."

"Chronic bacterial prostatitis may be asymptomatic or characterized by a sensation of perineal fullness, low back pain, dysuria, and pyuria. Fever is less common. The hallmark of this process is the presence of the same microorganism with each recurrent episode of UTI. This is the most important cause of recurrent UTI in the adult male and difficult to eradicate because of the presence of prostatic calculi. The microorganisms are the same uropathogens as found in UTIs. Coagulase-negative staphylococci, alpha-hemolytic streptococci, and diphtheroids are part of the normal flora of the male urethra and only rarely cause infections."

"Prostodynia is a noninflammatory condition of unknown origin, encountered most often in young men and characterized by a sense of fullness or pressure in the perineum, testicles and low back. The EPS secretions are sterile."

MO Conclusion: From the information provided above, the MO determined that the sponsor provided a well-designed clinical trial in order to assess the efficacy of trovafloxacin in the treatment of bacterial prostatitis. However, the MO elected not to accept the sponsor's evaluability criteria (listed in the protocol review), as applied in the data analysis because they are inconsistent with the Points-to-Consider guidelines, the medical literature, and IDSA. The evaluability criteria that the MO imposed are:

- Strict adherence to the lower limit of the window of evaluation at the EOT visit, which is also, the TOC visit. As per protocol this was at 5 – 9 days post-therapy. The sponsor widened out this window to a range of study days 25 – 42 (from study days 33 – 37) for the trovafloxacin-treated patients and to study days 43 – 59 (from study days 47 – 51) for the ofloxacin-treated patients. Because of the pharmacokinetics of trovafloxacin and its long half-life of 11 hours, the MO did not consider as an evaluable cure, any patient who was seen before study day 33 (or day +5 post-therapy) for the trovafloxacin-treated patients or study day 47 (day +5 post-therapy) for the ofloxacin-treated patients.

Initially, the MO imposed no such restrictions on the upper limit of the window or at any side of the final (V6) visit. However, after reviewing the sponsor's evaluability criteria and prior to reviewing the data, the MO in conjunction with the MTL, Dr. Brad Leissa, determined that the sponsor in setting up the evaluability windows did not provide for an equal comparison between the 2 arms. Specifically, the trovafloxacin TOC or V4 was set at 25 - 42 days post-therapy which would be anywhere from 3 days before the EOT (28 days) to 14 days or 2 weeks after. The analogous timepoint for the ofloxacin-treated patients (V5) was set at study days 43 - 59 or anytime 1 day post-therapy up to 17 days post-therapy. The sponsor set V6 at study days 60 - 90 for both groups, which represents +5 - +8 weeks post-therapy for the trovafloxacin-treated patients and +3 - +6 weeks post-therapy for the ofloxacin-treated patients. Because this analysis was performed prior to unblinding, it became apparent, that potentially an unfair comparison was being made and that the trovafloxacin-treated patients would technically have had 2 timepoints at which they could have been called a recurrence. However, the same was not true for the ofloxacin-treated patients, where a patient could have only been called a recurrence at V6.

The MO elected to modify the windows for the MOR of the data in the following manner:

V4: Trovafloxacin TOC: Days 33 - 53 (+5 - +25)
 V5: Ofloxacin TOC: Days 47 - 67 (+5 - +25)
 V6: Recurrence assessment: Trovafloxacin: Study days 54 - (+) 4 weeks (= approximately 6 - 10 weeks post-therapy or days + 26 - + 84)
 Ofloxacin: study days 68 - (+) 4 weeks (= approximately 3 - 7 weeks post-therapy or days + 26 - 90).

The MO determined that this modification would ensure a fair comparison and that although staggered it allowed for a clearer assessment of clinical efficacy (cures, failures, or recurrences) and bacteriologic efficacy (eradication, persistence, partial eradication, and presumed persistence).

The MO points out that all evaluable failures were carried forward and that in the sponsor's analysis, the increased range of the window, (against protocol requirements), was effected by the sponsor, post-study and prior to unblinding, in order to capture an increased number of patients.

- The MO did not clearly determine from the literature review or the review of previous NDAs the appropriateness of accepting Gram (+), coagulase (-) organisms as true pathogens in this disease. The MO communicated this to the sponsor on June 19, 1996 in a Telecon. The MTL, Dr. Leissa was present. During the discussion, the MO requested that the sponsor provide information that would justify the inclusion of Gram (+) cocci, other than enterococci, in the group of evaluable pathogens. Additionally, it was requested that the sponsor also provide information pertaining to the acceptability of mixed specimens of this type of organism. The MO stated that she was willing to consider as evaluable only those coagulase-negative staphylococci that were sole pathogens and that meet the other requirements imposed by the sponsor, that is that in order for an organism to be classified as a pathogen in bacterial prostatitis, it is required that the colony count in the VB3 specimen or the EPS exceed by 10-fold that in VB1 or VB2. A consultant's opinion would also have been acceptable if their opinion could be backed up by literary sources. The MO recognized that trovafloxacin, if approved for this organism, has the potential for use in patients where it does not represent a true pathogen but a contaminant.
- The MO was not able to classify the patients into those with acute, chronic, and acute exacerbations of chronic disease. The MO concluded from the literature review that these are indeed different clinical entities but that the bacteriology is similar as is the duration of antimicrobial therapy. Certainly, the relapse rate is expected to be higher for those patients with chronic recurring disease, who may require surgical removal of calculi or other procedures. The sponsor did not provide the investigators with the ability to differentiate these patients in the CRF. Nor was any information provided on the number of recurrences in the last 6 months, as was done in the norfloxacin review. The sponsor did provide the duration since the onset of the primary diagnosis for each patient. The mean duration for the 108 sponsor-evaluable trovafloxacin patients was 73.4 days with a range of 1 - 1042 days, and

42.3 days for the 111 ofloxacin-treated, sponsor-evaluable patients with a range of 1 - 437 days. No real conclusions could be drawn from this information because, as per Dr. Johnson on June 13, 1997, the investigators reported 2 different things in this section, either the duration of the current episode or the duration of the underlying disease. Based on this information, the MO concluded that this study is compromised of a mixed population of patients who most likely were suffering from "acute exacerbation" of chronic prostatitis. The MO points out that true "acute prostatitis" is characterized by toxicity including high fever, and frequent bacteremias necessitating hospitalization and intravenous antimicrobial therapy. EPS can often aggravate this state and many physicians, based on current standard of care, are reluctant to perform this exam on patients. It is therefore relatively unlikely that many patients in this study had true acute disease.

Additionally, the bacteriology associated with this submission was more consistent with that of chronic prostatitis as opposed to acute prostatitis. Consideration should be given to the granting of the indication as "acute exacerbation of chronic prostatitis" or as "chronic prostatitis."

- The MO requested that in the reanalysis of the data, the sponsor adhere strictly to IDSA and Divisional policy in terms of the verification of the bacterial etiology of prostatitis by colony counts. In other words the MO required adherence to the protocol, that in order for a pathogen to be considered evaluable, it had to be present in an amount 10-fold than that which was present in VB1 and VB2. The sponsor did not adhere to this in their analysis but instead, elected to use the standard of "greater than" as opposed to 10-fold.

Toxicity Issues:

The initial IND associated with this NDA was submitted in 7/92. The RMO expressed concern over increased LFTs found in 2/8 dogs studied (increased serum LFTs at 2 months and histologic findings at 6 months). The MO re-reviewed this study (93-783-16) in the MOR of Supplemental Preclinical information, submitted on April 1, 1994. 8 dogs received 50mg/kg of the study drug daily for 6 months. The abnormalities were associated with findings consistent with hepatic necrosis on the microscopic exam. The lesions consisted of centrilobular hepatocellular vacuolar degeneration and necrosis of moderate degree in a male dog and marked in a female. The associated LFT abnormalities were from 2 to 16 times those of the control animals. The RMO provided a comparison of animal and human drug exposure and stated that if this comparison was performed on a mg/m² basis, the conversion factor from dogs to humans is 1/2 (NCI). Using this factor, the human dose that is equivalent to the dog dose is 25 mg/kg/day, for 180 days or if a 60 kg person were used, the daily comparative dose would be 1500 mg. This was compared to the 200 mg daily dose that was ultimately used in the prostatitis study. The MO concluded that there was a safety factor of at least 5 with regards to daily dosage and an additional factor of 12 if duration was considered.

The RMO also provided a comparison of serum blood levels and concluded that a human dose of 300 - 600 mg/day would correspond to the dosage in dogs that had caused hepatotoxicity. This would mean that the safety factor was much lower as only 1 to 2 times the proposed dosage caused problems in dogs. The RMO requested that clinical studies be limited to 14 days duration.

This study (94-783-23), was performed and 4/16 dogs were found to have increased LFTs (primarily ALT), which returned to baseline after treatment discontinuation on days 67 to 89. There was microscopic correlation, that is findings of hepatocellular necrosis and periportal infiltration in 3 of the animals. The histologic changes were all found to be reversible at necropsy. This was at a 50 mg/kg dose for 6 months. The prostatitis study was allowed to proceed after this data was provided but limited to 4 weeks for the trovafloxacin-treated patients. Additionally, the RMO revised the protocol to provide for laboratory reevaluations at day 21 of the study and weekly thereafter.

In addition to the above, the sponsor also performed a phase I study, #154-007, which was an open study, comparing safety, tolerance, and pharmacokinetics in patients with chronic hepatic insufficiency and normal subjects. No abnormalities of significance, attributable to the trovafloxacin were found in patients with Class A impairment at the 100 mg dose daily for 7 days and permission was given to the sponsor to

study patients with class B impairment at a 200 mg daily dose for 7 days. Weight adjusted mean values of AUC than in normal subjects at both dose levels. On multiple dosing, weight adjusting gave the class B subjects the highest dose-adjusted AUC (20.6 mcg-hr/mL), followed by the class A subjects (15.2 mcg-hr/mL). The values for the Class B and A controls were 12.6 mcg-hr/mL and 10.3 mcg-hr/mL, respectively.

The MO provided the above information as background material. This information was of import because of its implications on the duration of therapy and how the protocol was ultimately designed.

Safety issues that developed during this study were reviewed in the safety section of this review.

Microbiology:

In support of the effectiveness of trovafloxacin against the requested pathogens, the sponsor submitted table G.39.1 from the microbiology section of the electronic submission. This table, entitled "Trovfloxacin MICs at Baseline versus Clinical Response and Pathogen Outcome at the EOT for Subjects Treated with Trovfloxacin in Prostatitis Studies," showed the MICs of the pathogens isolated versus trovafloxacin. These are listed below for the requested organisms:

Escherichia coli: $\leq .03$ mcg/mL - $\leq .06$ mcg/mL
Enterococcus faecalis: .12 - .25 mcg/mL
Staphylococcus epidermidis: $\leq .03$ - 8 mcg/mL
Staphylococcus haemolyticus: $\leq .03$ - 4 mcg/mL

Pharmacokinetics:

The sponsor provided a study entitled, "An Open Randomized Study in Patients to Determine the Penetration of Trovfloxacin into Prostatic Tissue Following Multiple Dosing with Trovfloxacin (200 mg QD)"/ protocol 154-041. The pharmacokinetics reviewer reviewed this study, however, for the purposes of this review, it was also mentioned here.

This was an open, randomized study to determine trovafloxacin concentrations in prostatic tissue relative to serum at corresponding timepoints. Thirty-two (32) male subjects scheduled to undergo elective trans-urethral resection of the prostate, ranging in age and in weight entered and completed the study. Subjects received trovafloxacin 200 mg daily, beginning at least 3 days before their scheduled surgery. If the surgery was delayed, an additional (fourth) dose could have been administered. Subjects had their scheduled surgery within one of the following time intervals: 2 to 6 hr, >6 to 12 hr, or >12 to 30 hr after the last dose of trovafloxacin. Two samples of prostate tissue were collected during surgery. At the same time that the first tissue sample was taken, a venous blood sample was also taken for the purpose of determining serum trovafloxacin levels.

Trovfloxacin concentrations in serum and prostatic tissue were generally greater than 1 μ g/mL and 1 μ g/g, respectively, at 3 to 10 hours post-dose. This was many times higher than the MIC 90 of trovafloxacin *in vitro* against *Escherichia coli* (0.06 μ g/mL). The mean tissue concentrations were 0.96 ± 0.63 mcg/mL, the mean serum concentrations were 1.0 ± 0.6 mcg/mL. Both prostatic tissue and serum trovafloxacin concentrations peaked rapidly and then declined in parallel. Trovfloxacin penetrated well into prostatic tissue, with a mean prostatic tissue/ serum concentration ratio of 1.0 ± 0.3 .

The sponsor did not provide information about tissue or serum concentrations beyond 30 hours after the last dose, however, the MO determined previously that it was appropriate to set the lower limit of the first post-therapy evaluability window, at 5 days post-therapy in order to ensure that there was no residual drug in concentrations that would inhibit bacterial growth.

Study 154-119

TITLE: A Randomized, Multicenter, Double-blind, Double-dummy, Comparative trial of Trovafloxacin and Ofloxacin for the Treatment of Bacterial Prostatitis.

List of Principal Investigators:

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	5179	Melvin Russell, MD
	5225	Robert Grajewski, MD
	5254	Walter Gaman, MD
	5630	Ronald Castellanos, MD
	5631	Stacy Childs, MD
	5634	Steven Bull, MD
	5638	Scott Cinel, MD
	5642	Stanley Brosman, MD
	5645	Clair Cox, MD
	5647	Robert Feldman, MD
	5648	Michael Milroy, MD
	5655	George Schuster, MD
	5657	Christopher Steidle, MD
	5661	Norman Zinner, MD
	5662	Donald Gleason, MD
	5666	John Tuttle, MD
	5667	W. Lamar Weems, MD
	5668	W. Glen Wells, MD
	5669	Jay Young, MD
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	5836	Peter Knapp, MD
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	5847	Joseph Macaluso, Jr., MD
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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	6145	William Smith, MD
	6146	Barton Wachs, MD
	6314	Melvin Duckett, MD
	6315	Danny Keiller, MD
	6316	Fredrick Snoy, MD
	6318	Dwight Beckstrom, MD
	6335	Vernon Urich, MD
	6336	Harold Fuselier, Jr., MD
	6371	Marc Gittelman, MD
	6372	Scott Slavis, MD
	6373	Mitchell Wiatrak, MD

Study dates: July 17, 1995 - May 30, 1996

Objective: The primary objective of this study was to compare the safety and efficacy of trovafloxacin and ofloxacin as treatment for bacterial prostatitis.

Study Design: This was a randomized, multicenter, double-blind, double-dummy, comparative trial of trovafloxacin (200 mg daily), administered orally for 28 days versus ofloxacin (300 mg twice daily), administered orally for 42 days.

Protocol Overview:

Copied below from the electronic submission, appendix A of the study report is the sponsor’s schedule of visits and procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

STUDY DAYS

	Screening Day -5	Baseline Day 1	On Therapy			EOT ^a Day 42	Post-Therapy	
			Visit 2 (3-5) ^b Day 4	Visit 3 (18-22) Day 20	Visit 4 (33-37) Day 35	Visit 5 (47-51) Day 49	Visit 6 Day 63-84	
Treatment		X	_____				X	
Compliance Checks			X	X	X		X	
Informed Consent	X							
Demographic Information	X							
Targeted Physical Examination	X							
Concomitant Medication	X		X	X	X		X	X
Vital signs	X		X	X	X		X	X
Assessments								
Clinical	X		X	X	X		X	X
Laboratory								
1. Hematology	X		X	X	X		X	(X) ^c
2. Serum Chemistry	X		X	X	X		X	(X) ^c
3. Urinalysis	X		X	X	X		X	(X) ^c
4. Fractionated Urine Cultures ^d	X				X		X	X
5. Urine Culture			X	X				
Adverse Events	X		X	X	X		X	

^a End of therapy (double-blind dosing)

^b Window for visit

^c To be done only if there is/are significant abnormality(ies) at visit 5

^d VB₁-Initial 5-10 mL of urinary stream

VB₂-Clean-catch midstream urine Specimen

EPS-Expressed prostatic secretions by digital massage after midstream urine Specimen

VB₃-First 5-10 mL of urinary stream immediately after prostatic massage

As noted from this schedule, within 5 days of starting study drug (screening visit), all subjects were to have a presumptive diagnosis of bacterial prostatitis characterized by one or more signs and symptoms from each of the following two groups:

- APPROX THIS WAY
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- Disturbances of urination, including frequency, urgency, dysuria, and/or lower urinary tract obstruction.
 - Perineal or low back pain, fevers chills, and/or a tender, tense prostate on palpation.

If the screened patients met the above criteria, as well as the inclusion and exclusion criteria, they were considered eligible for evaluation. At this visit they also underwent collection of demographic information, medical history, targeted physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature). Hematology, serum chemistry, and urinalysis determinations were performed for safety testing. The investigator confirmed the diagnosis of bacterial prostatitis by quantitative bacteriological cultures (processed by the local laboratory), of the following fractionated urine and prostatic secretion specimens obtained within 5 days before initiation of therapy:

- Voided bladder 1 (VB₁) - Initial 5-10 mL of urine specimen.
- Voided bladder 2 (VB₂) - Clean-catch midstream urine specimen.
- Expressed prostatic secretions (EPS) - Secretions expressed from prostate by digital massage after midstream urine specimen.
- Voided bladder 3 (VB₃) - First 5-10 mL of urine stream immediately after prostatic massage.

The diagnosis of bacterial prostatitis was confirmed by one of the following criteria:

- The colony count of a pathogen in VB₃ exceeded that in VB₁ or VB₂
- The colony count of a pathogen in EPS exceeded that in VB₁ or VB₂

If a patient did not have a confirmed diagnosis of bacterial prostatitis, based on the isolation of a baseline pathogen, they were discontinued from the trial by the investigator. If, however, a patient had a pathogen resistant to study drugs, they were not discontinued from the study drug unless there was failure to improve clinically. If this occurred, the patient was considered an "evaluable failure." In this case, the concomitant medication used as the alternative therapy was reported and the patient was considered evaluable for safety.

At the baseline visit (Visit 1, Day 1, V1) the patients who met all of the above criteria, were randomized to receive treatment. No other assessments were required at this visit, which was to take place as soon as the pathogen was known.

Efficacy evaluations were performed at visits 2 (V2, Day 4) and 3 (V3, Day 20). The evaluations included clinical assessment of signs and symptoms of bacterial prostatitis, as well as any new signs or symptoms since the previous visit. A routine urine culture was obtained from a clean-catch midstream urine specimen and processed by the central laboratory (SciCor). The results of this culture had no implications upon therapy unless the investigator felt that the subject's clinical condition warranted such a change. Other assessments performed at these visits included recording of vital signs, concomitant medication, study drug dosing, adverse events volunteered by the subject or observed by the investigator, and laboratory (hematology, serum chemistry, and urinalysis) evaluations.

At Visit 4 (Days 25-42; EOT for trovafloxacin, V4), an efficacy evaluation, which included clinical assessment of signs and symptoms of bacterial prostatitis, as well as any new signs or symptoms since the third visit was obtained. The investigator made a global clinical assessment, compared to the screening assessment. Quantitative bacteriological culture, as outlined above, was repeated. If expressed prostatic secretion (EPS) was not obtained at this time, bacteriological efficacy was based on urine cultures from VB₁, VB₂, and VB₃. In addition to the efficacy evaluation, other assessments included recording of vital

signs, concomitant medication, study drug dosing, adverse events volunteered by the subject or observed by the investigator, and laboratory (hematology, serum chemistry, and urinalysis) evaluations.

At Visit 5 (Days 43-59, EOT for ofloxacin, V5), an efficacy evaluation was performed in the same manner for the ofloxacin-treated patients.

The final visit or Visit 6 (Days 60-84 EOS, V6) was included for recurrent infections in those subjects cured or improved at visit 5 or visit 4. At this visit, an efficacy evaluation, which included clinical assessment of signs and symptoms of bacterial prostatitis, as well as any new signs or symptoms since the fifth visit was obtained. A global clinical assessment was made, and as in visit 5, quantitative bacteriological cultures were repeated. In addition to the efficacy evaluation, other assessments included recording of vital signs and concomitant medication. Laboratory evaluations performed at previous visits were repeated at this visit only if clinically significant results were detected at V5.

Medical Officer's Comment: *The MO underlined the word "exceeded" in the description of the fractionated urine culture methodology and points out that, although the sponsor utilized this parameter, the protocol as well as all current references and guidelines, clearly state, that the diagnosis of prostatitis is confirmed when the colony count of the organism isolated in the EPS or VB3 specimen is 10-fold that in VB1 or VB2. Therefore, the MO adhered to this parameter in the MO's analysis.*

As stated in the introduction, the MO requested modifications of the windows of evaluability and strict adherence to the lower boundaries of V4 and V5.

Compliance:

This study was conducted in compliance with local or central Institutional Review Board (IRB) and informed consent regulations.

Protocol Amendments:

This protocol was not amended.

Concomitant Medications:

The investigator documented all concomitant medication usage at each visit. This included any therapeutic interventions. No other antimicrobials were allowed. If another antimicrobial was used, the patient was classified as a treatment failure.

Discontinuation of Therapy:

The investigator discontinued therapy if the patient showed no signs of improvement, clinical worsening or if significant laboratory abnormalities developed. If a patient was discontinued for one of these reasons, a final efficacy assessment was performed at the time of discontinuation. A final safety assessment was performed at visit 5. If the discontinuation occurred because of an adverse event, clinical and microbiological efficacy evaluations were performed at all scheduled visits through visit 6.

Study Population:

As per the original protocol, 300 patients were to be enrolled in this trial, in order to obtain 150 evaluable subjects or 75 per arm. Each study site was to attempt to enroll 5 patients.

Inclusion and Exclusion Criteria:

(Copied from pages 6 and 7 of the original protocol)

Inclusion criteria

1. Outpatient men.
2. At least 18 years of age.
3. Presumptive clinical diagnosis of bacterial prostatitis, based on the presence of one or more signs and symptoms from each of the following two groups:
 - a. Disturbances of urination, including frequency, urgency, dysuria, and/or lower urinary tract obstruction.
 - b. Pains (perineal or low back), fever, chills, and/or a tender, tense prostate on palpation.The clinical diagnosis must be supported by bacteriological confirmation (i.e., a quantitative culture of isolated pathogenic organisms).
4. Written informed consent must be obtained.

Medical Officer's Comment: *These criteria represent standard diagnostic criteria for a prostatitis diagnosis. The sponsor ensured that this study remained a clinical/microbiological study by obtaining bacteriologic confirmation prior to the institution of therapy.*

However, these criteria also allowed for the enrollment of a sub-acute or chronic population rather than an acute (see introduction).

Exclusion criteria

1. Severity of infection requiring parental antimicrobial therapy, (e.g. acute bacterial prostatitis).
2. Known hypersensitivity to any quinolone antibiotic.
3. Inpatients.
4. Non-bacterial prostatitis.
5. Presence of permanent transurethral catheter or history of cystostomy or nephrostomy.
6. History of transurethral resection of the prostate within six months of study enrollment
7. Known or suspected prostatic cancer.
8. Benign prostatic hypertrophy in the absence of findings of bacterial prostatitis.
9. Presence of any other infection at enrollment that may require treatment with an antibiotic other than the study drug.
10. Treatment with any systemic antibiotic for 24 hours or longer within seven days prior to entry into the study, unless there is documented evidence of resistance or clinical failure.
11. Treatment with another investigational drug within 30 days prior to entry into the study.
12. Evidence of significant gastrointestinal or other conditions which may affect drug absorption.
13. Evidence or history of clinically significant hematologic, renal (i.e., serum creatinine greater than 2.0 mg/dL or creatinine clearance $\leq$ 50 mL/min), or immunologic compromise (i.e., neutropenia [total white blood cell count $<$ 2500 mm³ or absolute neutrophil count $<$ 1000 mm³]; or known AIDS).
14. History of epilepsy or seizures.
15. Prior enrollment in this protocol.
16. Subjects who for any reason, in the opinion of the investigator, may not be expected to comply with the requirements of the protocol.

Medical Officer's Comment: Although most of the exclusion criteria were standard, the sponsor specifically excluded patients with a "true" acute" prostatitis (see discussion at the beginning of the MOR).

Randomization and Blinding:

The investigator sequentially assigned study numbers to the subjects as they were determined to be eligible for treatment. The study number was entered onto the subject's case report form and the subject received study medication with the corresponding number.

Dosage Form and Administration:

(Copied from the study report)

Study medication was in the form of tablets, packaged in blister cards, and capsules, packaged in bottles, using a double-dummy technique to maintain blinding. The study drug administration schedule provided one of the following two doses of study drug, dependent upon the randomization assignment:

Trovafloxacin: 200 mg (2 tablets) daily as a single dose for 28 days

Ofloxacin: 300 mg (1 capsule) bid for 42 days

In order to maintain blinding, subjects were given the medication as outlined in the following table:

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloxacin	2- tablets x 100 mg for 28 days	1-placebo for ofloxacin for 42 days
	1-placebo for ofloxacin for 42 days	
Ofloxacin	2-placebos for trovafloxacin for 28 days	1-ofloxacin x 300 mg for 42 days
	1-ofloxacin x 300 mg for 42 days	

The blister card and bottle with the randomization number corresponding to that assigned to the subject were given to the subject on visit 1 (day 1). Subjects were instructed to begin study drug medication with the morning dose (even if it was not morning), and to complete a full day of medication on day 1. Following day 1, through day 28 of the treatment period, the subject was directed to take two tablets and one capsule in the morning and one capsule 12 hours later. From day 29 through day 42, the subject was to take one capsule in the morning and one capsule 12 hours later.

The subjects were informed that compliance with taking all tablets as instructed was imperative and the investigator reviewed the following with each subject:

- Blister card and bottle labeling, clearly indicating those to be used for morning administration and evening administration
- Morning and evening dosing should be approximately 12 hours apart

- Mineral supplements, vitamins with iron or zinc, or calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing
- Study medication was not to be taken within (before or after) two hours of meals

Indices of Compliance:

Subjects were informed that compliance with taking all tablets and capsules as instructed was imperative and were asked to bring all unused medication or empty packs to visits 2 and 3, and again to visits 4 and 5. All doses taken were to be recorded in the case report form.

Microbiologic Methods:

The central laboratory performed susceptibility testing for all bacterial isolates by disk diffusion and MICs. The criteria for determining susceptibility were copied from page 11 of the original protocol, below:

CRITERIA	Trovafoxacin		Ofloxacin	
	Zone Size (mm) 5 µg disc	MIC (µg/mL)	Zone Size (mm) 5µgdisc	MIC (µg/mL)
SUSCEPTIBLE	≥ 15	≤ 2	≥ 16	≤ 2
INTERMEDIATE	11-14	4	13-15	4
RESISTANT	≤ 10	≥ 8	≤ 12	≥ 8

Clinical Response:

Clinical response was determined by the sponsor and evaluated at Visits 4, (Days 25-42; end of treatment for trovafloxacin), and 5, (Days 43-59; end of treatment for ofloxacin), or, at the time of discontinuation from the study. This determination was primarily based upon the investigators' global assessment of the clinical presentation of the subject at the evaluation timepoint compared to the screening assessment. Subjects were assessed for signs and symptoms of bacterial prostatitis, as detailed below, and these assessments were recorded on the CRF (Copied from page 21 of the study report):

- Urinary frequency and urgency, dysuria, lower urinary tract obstruction, perineal pain, low back pain, fever >99°F (past 24 hours), chills, and prostate tenderness were to be assessed at Screening and Baseline (Visit 1) and at every clinic visit thereafter by the investigator and noted as present, absent, or not done.

The investigator classified the clinical response of the subject as cure (complete resolution of signs and symptoms of bacterial prostatitis), improved (incomplete resolution of any of the signs and symptoms of bacterial prostatitis, but no requirement for additional antibiotics), or failure (no apparent response or progression of signs and symptoms of bacterial prostatitis).

The presence or absence of recurrence was based on clinical findings at Visit 6. As stated by the sponsor:

"Only subjects cured or improved at Visit 5 were to be assessed at this visit. Their clinical response at Visit 6 was classified as success (cure or improvement at Visit 5, with no recurrence of signs or symptoms of bacterial prostatitis) or recurrence."

Medical Officer's Comment: *The MO agreed with the overall design of this trial and determined that it was consistent with those found in previously reviewed antimicrobials for the indication of prostatitis. The MO queried the sponsor as to the date of the TOC and was informed that this timepoint was at the EOT evaluation or V4 for the trovafloxacin-treated patients and V5 for the ofloxacin-treated patients. In order to maintain the blind, however, the trovafloxacin-treated patients, had an assessment at V5, concurrently with the ofloxacin-treated patients TOC (5-9 days post-therapy for the ofloxacin group and 19 – 23 days post-therapy for the trovafloxacin arm). Therefore, the trovafloxacin-treated patients had an extra evaluation at V5 and then all patients who were cured or improved, were reevaluated for recurrence at V6 (35 – 56 days post-therapy for the trovafloxacin-treated patients and 21 – 42 days post-therapy for the ofloxacin-treated patients). The MO reminds the reader that the primary endpoint in this study was clinical. The MO outlined the MO evaluable windows in the introduction.*

Bacteriological Response

Bacteriological response was determined by the sponsor and determined from the culture results at Visits 4 (Days 25-42; end of treatment for trovafloxacin), 5 (Days 43-59; end of treatment for ofloxacin), 6 (Day 60-84; end of study), or at the time of discontinuation from the study. Eradication of the baseline pathogen defined bacteriological efficacy. Bacteriological response for each subject was classified by the sponsor as eradication (complete or partial), complete persistence, or superinfection.

The presence or absence of recurrence was based on bacteriological findings at Visit 6. Only subjects with complete or partial eradication at Visit 5 were assessed at this visit. Bacteriological response at Visit 6 was classified as success (complete or partial eradication of pathogens at Visit 5 with no recurrence of the eradicated pathogen at Visit 6) or recurrence.

Quantitative bacterial cultures were repeated at V4 and V5; the central laboratory processed these cultures. If expressed prostatic secretions (EPS) were not obtainable at that time, bacteriological efficacy was based on urine cultures from VB₁, VB₂ and VB₃.

Medical Officer's Comment: *As noted above, the sponsor and not the investigator made the determination of bacteriologic response, the opposite of what occurred with clinical response. The sponsor also made the ultimate determination of overall response.*

Only patients who were cured or improved were seen at V6 and the sponsor stated that "all failures were carried forward from earlier timepoints".

Safety Assessments:

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality, and was monitored up to Visit 5.

All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the CRF. Following resolution of the adverse event or at the end of the study, the investigator's judgment of causality of the adverse event was recorded.

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the Pfizer-appointed monitor immediately by telephone. Serious adverse events were monitored throughout the study and for 30 days after the last dose of study drug. All deaths were immediately reported, regardless of elapsed time between last dose in a clinical trial and the death, and thus extended beyond the 30-day post-study timepoint. In case of death, a summary of available autopsy findings was submitted as soon as possible to the Pfizer-appointed monitor.

Medical Officer's Comment: *The MO queried the sponsor as to the adverse event monitoring. The MO was unclear if an adverse event documented in the period after V5 was recorded on the CRF. The*

sponsor's text implied that this was not the case and that only those events that had occurred prior and up to V5 were recorded and followed-up. The sponsor confirmed this statement because "V6 was so far out that it would have been unlikely for any adverse event which could have occurred in this period to have been drug-related".

Clinical Laboratory Tests:

Hematology, serum chemistry, and urinalysis evaluations were performed at screening (Day -5); no laboratory assessments were performed at baseline (Day 1). Hematology, serum chemistry, and urinalysis evaluations were performed at Visits 2 (Day 4), 3 (Day 20), 4 (Day 25-42), and 5 (Day 43-59). Additional laboratory safety tests were only to be obtained at Visit 6 (Days 60-84) if clinically indicated, or if a clinically significant abnormality was present at Visit 5.

Study Monitoring

The study was monitored routinely through site visits by the sponsor or by CROs (Contract Research Organizations), under the supervision of the sponsor.

Data Analysis (as per the sponsor):

(Copied from the study report)

"The data analysis plan outlined in the protocol included an assessment of clinical and bacteriological response between the two groups at specific timepoints during the study (Visits 4, 5 and end of study). However, due to the differing dosing durations, it was thought that comparisons between the treatment arms at the same visit could artificially favor the comparator agent due to its longer treatment duration (i.e., Visit 4 was one week post-therapy for trovafloxacin and during therapy for ofloxacin). Therefore, additional analyses were performed to assess response in relation to dosing. These new analyses assessed clinical and bacteriological response one week post-therapy (Visit 4 for trovafloxacin subjects and Visit 5 for ofloxacin subjects) and clinical response was again assessed three to six weeks post-therapy (last nonmissing observation between Days 46 and 70 for trovafloxacin and end of study visit for ofloxacin)."

***Medical Officer's Comment:** The above statement reflected the manner in which the sponsor ultimately evaluated the data. This schema provided for a staggered analysis. These decisions were made by the sponsor prior to unblinding the data thus ensuring a fair and reasonable comparison.*

At this point, the MO again points out that although the windows of evaluation for V4, V5, and V6 were outlined above, the sponsor, prior to unblinding, widened these out "in order to capture as many patients as possible."

Specifically, V4, as per the protocol was to be performed at study days 33 – 35 but was performed at study days 25 – 42. This implies that although this visit was initially scheduled at 5 – 9 days post-therapy for the trovafloxacin-treated patients, that it could have been done within 3-4 days post-therapy and extending up to 2 weeks post-therapy.

For those patients evaluated at V5, this window was extended to study days 43 – 59 or from 5 – 9 (days 47 – 51) days post-therapy to 1 – 17 days post-therapy.

These changes were not made during the study or prior to breaking the blind.

The MO requested clarification and was informed that "in order to be evaluable for a cure"; the minimum amount of treatment necessary was 21 days.

As determined by the MO and based upon the pharmacokinetic profile of trovafloxacin, the MO's lower boundary for V4 and V5 was maintained at 5 – 9 days post-therapy for both treatment groups and the MO proposed different evaluability windows (see above) for each timepoint.

Subject Subsets:

The sponsor presented results for the following subsets (copied from page 24 of the study report):

All Randomized Subjects

The all randomized subjects subset included all subjects who were randomized to a treatment group, regardless of whether or not a particular subject received any study medication.

All Treated Subjects

The all treated subjects subset included all subjects who received one or more doses of active double-blind study medication. This subset was used for all safety tables.

Clinical Intent-to-Treat Subjects

The clinical intent-to-treat subjects subset included those subjects in the all randomized subjects subset who had a confirmed diagnosis of bacterial prostatitis. Some subjects in this subset may have never received study medication.

Clinically Evaluable Subjects

The clinically evaluable subjects subset included all subjects in the clinical intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied.

Bacteriological Intent-to-Treat Subjects

The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one baseline pathogen. Some subjects in this subset may never have received any study medication.

Bacteriologically Evaluable Subjects

The bacteriologically evaluable subjects subset included all subjects in the clinically evaluable subjects subset with at least one baseline pathogen, unless one or more of the criteria for non-evaluability applied.

Medical Officer's Comment: *As in previously reviewed trials, the sponsor provided extensive analyses of the data for multiple subgroups. The MO presented only the efficacy analyses for the clinically and bacteriologically evaluable populations. As noted previously, these populations are by protocol the same, although, in the study, the sponsor presents a clinically-evaluable population and a subpopulation of bacteriologically-evaluable patients..*

Both the sponsor and the MO presented safety analyses for ALL treated subjects.

Clinical Evaluability Criteria:

As per the sponsor, if any of the following were present, the subject was considered non-evaluable for clinical efficacy (copied from page 25 of the study report):

1. **Insufficient Therapy:** A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before completing 21 days of active double-blind therapy was not evaluable.

Medical Officer's Comment: *The MO agreed with this criterion with the prerequisite, that ALL failures diagnosed as such at V2 (days 3-5 on therapy), were carried forward. Therefore an evaluable failure could have received as little as 3 to 5 days of therapy, whereas, an evaluable cure must have received a minimum of 21 days of therapy.*

2. Prior Antibiotic Usage: A subject was not evaluable if the subject had been treated with any systemic antibiotic for 24 hours or longer within 7 days prior to enrollment and without documented evidence of resistance or clinical failure.

Medical Officer's Comment: *The MO agreed with this criterion. The practical application was to ensure the enrollment of patients with true pathogens.*

3. Concomitant Antibiotics Given for Intercurrent Illness: A subject who was prescribed a concomitant antibiotic (at any time before the one week post-therapy assessment in the new analyses; at any time before the Visit 5 assessment per the protocol) that was potentially effective against the condition under study was not evaluable if the concomitant antibiotic was given for an adverse event or intercurrent illness. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the clinically evaluable subjects subset. For the purpose of subject evaluability, prior antibiotic use that ended on Day 1 was not considered to be concomitant.

Medical Officer's Comment: *This statement allowed for the exclusion of patients who failed therapy and who were given another antimicrobial prior to their follow-up visit. This would primarily have affected the trovafloxacin-treated patients. The MO queried the sponsor as to how often this occurred. The sponsor replied that ALL evaluable failures were carried forward and that it was extremely unlikely that this situation occurred. The MO determined that since the potential existed, ALL patients who received concomitant antimicrobials and who were excluded, would require a detailed review.*

4. Intercurrent Illness: A subject who developed an intercurrent illness whose clinical course confounded the evaluation of the subject's clinical response was not evaluable. The Pfizer Clinical Group determined intercurrent illnesses that caused a subject to be not evaluable for this reason.

Medical Officer's Comment: *The MO queried the sponsor as to the meaning of this statement. The sponsor replied that this situation was not applicable in this indication. The MO determined that ALL patients excluded from the analyses for this reason would require detailed review.*

5. No Post-Baseline Clinical Assessments: A subject with no post-baseline investigator clinical assessments was not evaluable unless given an antibiotic for insufficient response any time during the study, up to and including the last day of the analysis window in the new analyses; end-of-study analysis window per the protocol.

Medical Officer's Comment: *The MO agreed with this criterion.*

6. No Post-Baseline Assessment in the Evaluable Analysis Window: In order to be evaluable a subject must have had an assessment in evaluable timepoint windows one week post-therapy for the new analyses; Visit 5 per the protocol, unless
 - the investigator's clinical response was a failure at the previous visit for ofloxacin subjects in the new analyses; failure at the previous visit per the protocol, or
 - the subject was given an antibiotic for insufficient response before or during the one week post-therapy window in the new analyses; Visit 5 window per the protocol.

Medical Officer's Comment: *The sponsor refers only to V5 in this statement but verified to the reviewer that V4 was considered the TOC for the trovafloxacin-treated patients and V5 for the ofloxacin-treated patients. The MO agreed with this criterion with the addition of the lower boundary as previously stated and, for the MO's analysis the change in the analysis windows (see above). Please note that the sponsor did not update the study report to reflect the staggered TOC analysis in all of the following paragraphs but that the MO confirmed that this was what was implied.*

Per protocol, a subject was included in the analysis at the end of study assessment if the subject was:

- clinically evaluable at the Visit 5 assessment, and
- was not given any antibiotics for intercurrent illness before the assessment at the end of study visit, and
- had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study, up to and including the last day of the end of study analysis window, or the subject was a clinical failure at Visit 4 or 5.

A subject was included in the new analyses three to six weeks post-therapy based on the protocol-defined evaluability for Visit 5 and at the end of study assessment:

Criteria for Bacteriological Evaluability:

As per the sponsor, if any of the following were present, the subject was considered non-evaluable for bacteriological efficacy (copied from pages 26 – 27 of the study report):

1. No Baseline Pathogen: No baseline causative pathogen was isolated.
2. Baseline Culture Outside Baseline Visit Window: The baseline culture was done more than 5 calendar days before the first dose of double-blind study medication.
3. No Post-Baseline Cultures: Post-baseline cultures were not obtained, unless:
 - subject was given an antibiotic for insufficient response, at any time up to and including the last day of the one week post-therapy analysis window in the new analyses; Visit 5 analysis window per the protocol, or
 - the investigator's clinical response was recorded in the appropriate window (presumed eradication and presumed persistence are defined by clinical response when post-baseline cultures are missing), or
 - there was a prior clinical failure.

Per protocol, bacteriologically evaluable subjects were excluded from the analysis at the end of study visit if:

- they were excluded from the clinical analysis at the end of study visit, or
- they did not have a culture result or clinical response in the appropriate window, unless given an antibiotic for inadequate response or the subject was a clinical failure at Visit 4 or 5.

In the new analyses, bacteriological response was not performed three to six weeks post-therapy.

Medical Officer's Comment: *The MO agreed with sponsor's criteria of bacteriologic evaluability and points out that all failures were carried forward. However, from these statements, it became apparent that although this was a clinical/microbiological study in that a patient had to have a "pathogen" in order to be considered evaluable, the ultimate outcome for that pathogen was determined by clinical response if follow-up cultures were not obtained.*

The sponsor's final statement confirms that the bacteriologic TOC was performed at V4 and V5 per arm and that V6 was performed merely in order to assess for recurrences.

Primary and Secondary Endpoints for Efficacy:

The sponsor provided the text for both their initial analysis as well as for that which was developed later, that is that of a staggered analysis. Therefore, although V4 is not mentioned, the primary efficacy endpoint was sponsor-defined clinical response at V4 for the trovafloxacin-treated patients and V5 for the ofloxacin-treated patients.

Copied below, from page 28 of the study report are the secondary efficacy endpoints:

Sponsor-defined subject clinical response three to six weeks post-therapy in the new analyses; Visit 4 and end-of-study per the protocol.

Investigator-defined subject clinical response one week post-therapy in the new analyses; Visits 4, 5, and end-of-study per the protocol.

Sponsor-defined subject bacteriological response one week post-therapy in the new analyses; Visits 4, 5, and end-of-study per the protocol.

Sponsor-defined organism outcome one week post-therapy in the new analyses; Visits 4, 5, and end-of-study per the protocol.

Medical Officer's Comment: *The MO agreed with these endpoints (although they were not strictly adhered to in the sponsor's analysis), and their definitions as provided below:*

Sponsor-Defined Subject Clinical Response:

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the global evaluations made by the investigator at Visits 4 and 5 and the end of study visit. The occurrence of any of the following conditions were to supersede the investigator's assessment.

1. Failure: If the investigator-defined subject clinical response was failure at any visit, then the sponsor-defined subject clinical response was failure at all subsequent assessments.
2. Failure: If a subject was given a concomitant antibiotic for insufficient clinical response during double-blind therapy plus one day then the sponsor-defined subject clinical response was failure at the end of treatment and all subsequent assessments. If a subject was given a concomitant antibiotic for insufficient clinical response at any time before the assessment plus one day the sponsor-defined clinical response was failure at that assessment and all subsequent assessments. If a subject did not have an assessment in a particular window and was given an antibiotic for insufficient response in that assessment window then the sponsor-defined clinical response was failure at that timepoint and all subsequent assessments.
3. Failure: If a subject had no post-baseline assessment, then the sponsor-defined clinical response was failure at all visits (Intent-to-Treat Analysis only).
4. Recurrence:

If a subject was a clinical cure or improvement at Visit 5 and was assessed by the investigator to be a failure at the end of study, then that subject was classified as a clinical recurrence at the end of study.

If a subject was a clinical cure or improvement at Visit 5, but required additional antibiotic therapy for the primary disease before the end of study, then the subject was classified as a clinical recurrence at the end of study.

For the analysis of the clinical intent-to-treat subject subset, a “last observation carried forward” strategy was used for subjects who were lost to follow-up before the end of study. If, for any reason, no clinical assessment was made at Visit 4, but an assessment was made at Visit 5, then the Visit 4 assessment was treated as missing data.

CI_s (95%) for differences in clinical success (cure + improvement) rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.

Medical Officer's Comment: *The MO agreed with the sponsor's proposed definitions and points out that ultimate clinical assessments of cure were made by the investigators but that the sponsor's determination superseded that of the investigators' in the cases of failures that were not carried forward.*

Sponsor-Defined Subject Bacteriological Outcome (copied from page 29 of the study report):

The sponsor-defined subject bacteriological assessment was defined as follows:

1. Complete Eradication: Eradication of all initial pathogens.
2. Partial Eradication: Eradication of at least one, but not all initial pathogens.
3. Complete Persistence: Persistence of all initial pathogens.
4. Recurrent Infection: Appearance of one or more of the initial baseline pathogens, eradicated at Visit 5, but with recurrence of the eradicated pathogen(s) at the end of study.

CI_s (95%) for differences in subject bacteriological eradication (complete + partial) rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.

Medical Officer's Comment: *Once again the sponsor did not refer to V4 in the above statement. The MO agreed with these definitions but repeats that only Gram (-) isolates or Enterococcus faecalis were considered evaluable pathogens. All coagulase (-) gram (+) isolates were considered evaluable only if they were the sole organism isolated and met the aforementioned criteria.*

Sponsor-Defined Pathogen Outcome (copied from pages 29 –31 of the study report):

For both evaluable and intent-to-treat subjects, the sponsor classified each baseline organism as a pathogen or as a non-pathogen. Each baseline pathogen was assigned a sponsor-defined pathogen outcome. Multiple baseline pathogens identified in culture samples from the same subject were assigned separate outcomes. Baseline pathogens were assigned a separate outcome at Visits 4 and 5 and the end of study.

1. Eradication: Baseline pathogen was absent from a culture from VB₃ and EPS. Or, absent only from EPS or VB₃ if the baseline pathogen was identified in EPS or VB₃ only, respectively. If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this negative culture, the eradication was carried forward to all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up, the eradication was carried forward to subsequent implied visits. (clinical failure but bacteriologic eradication)

Presumed Eradication: No culture results (i.e., not done), and subject was clinically cured or improved.

Persistence: Baseline organism is present in EPS. Or, the baseline organism was present in VB₃ if the baseline pathogen was identified in VB₃. If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this positive culture, the persistence was carried forward to all subsequent visits, regardless of subsequent culture results. (Clinical failure and bacteriologic persistence). If the subject was lost to follow-up, persistence was carried forward to subsequent implied visits.

2. Presumed Persistence:

Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day as, or within 3 days after, a positive or negative culture, in the absence of prior microbiological data in the same evaluable analysis window resulted in a sponsor-defined pathogen outcome of presumed persistence at that visit and all subsequent implied visits, regardless of subsequent culture results. If the subject was lost to follow-up then the presumed persistence was carried forward to subsequent implied visits. Absence of microbiological data was defined as either no visit in the window or culture not done (results from VB₃ or EPS were missing) at all visits in the window.

Culture was not done (results from VB₃ or EPS were missing) and the sponsor-defined subject clinical response was failure.

The baseline pathogens of subjects who were lost to follow-up (i.e., no visit) at Visits 4, 5 or the end of study were assigned the outcome presumed persistence if the organism was persistent at any previous visit.

3. Recurrence: The original baseline pathogen was present at end of study after a previous post-baseline culture was negative at Visit 5 (applicable at end of study only).

In addition, organisms not present at baseline were classified as follows:

1. Superinfection: A pathogen, other than one identified at baseline, that was identified at any post-baseline time in culture material obtained from the site of infection and associated with emergence or worsening of clinical evidence of infection.
2. Colonization: Any organism, other than one identified at baseline, that was identified at any post-baseline time in culture material obtained from the site of infection and not associated with signs or symptoms of active infection.

CI_s (95%) for differences in pathogen eradication rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.

Medical Officer's Comment: *Although the MO agreed with the general proposal/definitions of the sponsor, the MO was unclear as the meaning of the underlined statements and requested clarification from the sponsor on June 17, 1997. The sponsor responded that the intent of the statements was to reflect the timing of when a response was carried forward. The MO has added the potential responses in Times New Roman font.*

If a patient was a clinical cure with documented bacteriologic eradication and was given an antibiotic for insufficient response within 3 days of a visit, they were classified as a clinical failure with bacteriologic eradication since this would have been the last culture obtained. If this occurred 4 days after the visit then the patient was classified as a clinical cure with bacteriologic failure or recurrence depending on the timepoint.

At this point the MO determined that a change in the evaluable windows was necessary (See above). The MO presented the sponsor's analysis as is and for the MOR (utilizing the MO-defined timepoints) determined that:

- *If a trovafloxacin patient was seen twice within the context of V4 with the initial assessment being a clinical cure and the second, a clinical failure, then the failure would be the assigned assessment for this patient. In this case a V6 visit to assess for recurrence was not necessary.*
- *If a trovafloxacin-treated patient was a clinical cure at V4, then a determination for relapse/recurrence was made at V6*
- *If an ofloxacin-treated patient was a clinical cure at V5, then a determination of relapse/recurrence was made at V6.*
- *If an ofloxacin-treated patient was seen twice within V5, initially as a cure and then as a failure, the assessment for V5 was failure and the patient was not re-evaluated for recurrence at V6.*
- *Pathogens were assessed for eradication, presumed eradication, persistence, presumed persistence, recurrence, superinfection, and colonization as defined by the sponsor within the context of the MO's windows of evaluability and the MO's criteria of acceptable pathogens.*
- *The MO accepted, after review of the patient profiles and verification of the accuracy of the data, the sponsor's determination of clinical and bacteriologic efficacy. Overall, the sponsor's determinations were more conservative than those of the investigators'.*

Based on the above, the MO requested, on June 18, 1997, that the sponsor provide a reanalysis of the data utilizing the MO's evaluability criteria.

Demographics:

As per the sponsor, 660 subjects signed consent. 385 subjects were withdrawn prior to randomization because they did not meet entry criteria. Thus 142 subjects were randomized, to receive trovafloxacin and 135 to receive ofloxacin. All 142 randomized trovafloxacin patients received treatment as compared to 133 of the randomized ofloxacin patients. 2 randomized subjects from the ofloxacin arm did not receive therapy (see below).

Of the treated groups, 128 trovafloxacin patients and 123 ofloxacin patients completed the study and 105 trovafloxacin and 118 ofloxacin completed treatment. 37 trovafloxacin patients or 26% as compared to 15 or 11% of the ofloxacin patients were withdrawn during treatment. An additional 7 (5%) patients on the trovafloxacin arm and 2 (2%) patients on the ofloxacin arm were withdrawn during follow-up, thus 98 (69%) trovafloxacin and 116 (87%) ofloxacin patients completed the study and treatment. 7 (5%) trovafloxacin and 8 (6%) ofloxacin patients were withdrawn from treatment and from the study.

The MO recreated the Sponsor's Table of the Disposition of Enrolled subjects (119.1)

Table 119.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafoxacin		Ofloxacin	
		N	%	N	%
Subjects with Signed Consent	660				
Withdrawn Prior to Randomization	385				
Randomized		142	100	135	100
Randomized, But Not Treated		0	0	2	
All Treated Subjects		142	100	133	100
Withdrawn During Treatment		37	26	15	11
Completed Treatment		105	74	118	89
Withdrawn During Follow- up		7	5	2	2
Completed Study		128	90	123	92
Completed Treatment and Study		98	69	116	87
Withdrawn During Treatment and Study		7	5	8	6

Copied and modified below is the Sponsor's Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

Table 119.2
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor, Modified by MO)

Center	Total Randomized N = 277 (100%)		Trovaflaxacin				Ofloxacin			
			Randomized N = 142 100%		Treated N = 142 100%		Randomized N = 135 100%		Treated N = 133 100%	
5005	18	6.4	9	6.3	9	6.3	9	6.6	9	6.7
5014	8	2.8	4	2.8	4	2.8	4	2.9	4	3.0
5630	12	4.3	6	4.2	6	4.2	6	4.4	6	4.5
5631	3	1.0	1	0.7	1	0.7	2	1.4	2	1.5
5642	8	2.8	4	2.8	4	2.8	4	2.9	4	3.0
5645	7	2.5	3	2.1	3	2.1	4	2.9	4	3.0
5647	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0
5648	6	2.1	4	2.8	4	2.8	2	1.4	2	1.5
5655	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5657	11	3.9	6	4.2	6	4.2	5	3.7	5	3.7
5661	14	5.0	7	4.9	7	4.9	7	5.1	7	5.2
5662	1	0.4	1	0.7	1	0.7	0	0	0	0
5666	32	11.5	16	11.2	16	11.2	16	11.8	16	12.0
5667	4	1.4	2	1.4	2	1.4	2	1.4	2	1.5
5668	3	1.0	2	1.4	2	1.4	1	0.7	1	0.7
5669	17	6.1	9	6.3	9	6.3	8	5.9	8	6.0
5827	1	0.4	1	0.7	1	0.7	0	0	0	0
5836	7	2.5	4	2.8	4	2.8	3	2.2	3	2.2
5846	7	2.5	4	2.8	4	2.8	3	2.2	3	2.2
6029	5	1.8	3	2.1	3	2.1	2	1.4	2	1.5
6031	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0
6032	1	0.4	0	0	0	0	1	0.7	1	0.7
6035	1	0.4	0	0	0	0	1	0.7	1	0.7
6036	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0
6037	4	1.4	2	1.4	2	1.4	2	1.4	1	0.7
6082	3	1.0	2	1.4	2	1.4	1	0.7	1	0.7
6083	1	0.4	0	0	0	0	1	0.7	1	0.7
6085	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
6086	6	2.1	4	2.8	4	2.8	2	1.4	2	1.5
6102	3	1.0	1	0.7	1	0.7	2	1.4	2	1.5
6103	6	2.1	3	2.1	3	2.1	3	2.2	3	2.2
6104	3	1.0	2	1.4	2	1.4	1	0.7	1	0.7
6105	14	5.0	7	4.9	7	4.9	7	5.1	7	5.2
6128	3	1.0	1	0.7	1	0.7	2	1.4	2	1.5
6129	2	0.7	0	0	0	0	2	1.4	2	1.5
6130	6	2.1	3	2.1	3	2.1	3	2.2	3	2.2
6146	1	0.4	1	0.7	1	0.7	0	0	0	0
6314	8	2.8	4	2.8	4	2.8	4	2.9	3	2.2
6315	1	0.4	1	0.7	1	0.7	0	0	0	0
6316	5	1.8	2	1.4	2	1.4	3	2.2	3	2.2
6318	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
6335	2	0.7	0	0	0	0	2	1.4	2	1.5
6371	1	0.4	0	0	0	0	1	0.7	1	0.7
6373	9	3.2	5	3.5	5	3.5	4	2.9	4	3.0

Medical Officer's Comment: From Table 119.2 it appears as if the patients were randomized equally between treatment arms and centers. Center 5666 (Dr. John Tuttle/US) had the greatest number of patients overall, comprising approximately 11- 12% of the patients per arm. Centers 6031, 6032, 6083, 6129, 6335, and 6371 had no patients on trovafloxacin. Centers 5662, 5827, 6146, and 6135 had no patients on ofloxacin.

Copied and modified below is the sponsor's table of all randomized patients and the study evaluation groups:

Table 119.3
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

Table A. Summary of Subject Disposition				
	Trovafloxacin		Ofloxacin	
	Number and Percentage (%) of Subjects			
Randomized Subjects	142		135	
Randomized, Not Treated	0		2	
All Treated Subjects	142	(100%)	133	(100%)
Withdrawn from Treatment ^a	37	(26%)	15	(11%)
Completed Treatment	105	(74%)	118	(89%)
Withdrawn from Study	14	(10%)	10	(8%)
Withdrawn during Treatment	7	(5%)	8	(6%)
Withdrawn during Follow-Up	7	(5%)	2	(2%)
Completed Study	128	(90%)	123	(92%)
Completed Treatment and Study	98	(69%)	116	(87%)
Evaluated for Efficacy (Original Analyses)				
Clinical Intent-to-Treat	141	(>99%)	135	(100%)
Clinically Evaluable at Visits 4 and 5	108	(76%)	111	(82%)
Clinically Evaluable at End of Study	100	(70%)	103	(76%)
Bacteriological Intent-to-Treat	136	(96%)	128	(95%)
Bacteriologically Evaluable at Visits 4 and 5	92	(65%)	98	(73%)
Bacteriologically Evaluable at End of Study	86	(61%)	92	(68%)
Evaluated for Efficacy (Additional Analyses)				
Clinical Intent-to-Treat one week post-therapy	134	(94%)	129	(97%)
Clinically Evaluable one week post-therapy	113	(80%)	111	(83%)
Clinical Intent-to-Treat three to six weeks post-therapy	132	(93%)	135	(100%)
Clinically Evaluable three to six weeks post-therapy	107	(75%)	103	(77%)
Bacteriological Intent-to-Treat one week post-therapy	128	(90%)	118	(89%)
Bacteriologically Evaluable one week post-therapy	98	(69%)	98	(74%)
Assessed for Safety				
Adverse Events	142	(100%)	133	(99%)
Laboratory Tests	140	(99%)	132	(99%)

^a Of the subjects withdrawn from treatment, 30 trovafloxacin and seven ofloxacin completed study.
Ref.: Tables 1.1 and 1.2

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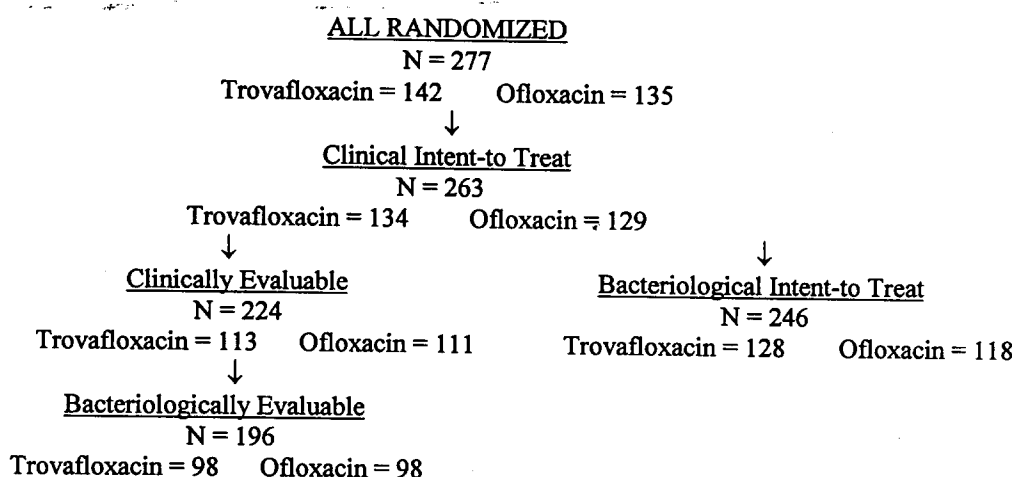
Medical Officer's Comment: Please note that although the sponsor states that 142 patients were randomized to trovafloxacin, only 141 were included in their ITT and evaluable analyses. One patient, # 56420197, was randomized but then found to have been inappropriately diagnosed and excluded. This patient had prostatodynia as opposed to prostatitis and received 5 days of therapy before discontinuing therapy because of dizziness.. The sponsor's tables and percentages in this section of the study report did not reflect this patient's exclusion.

The 2 ofloxacin patients who were randomized but not treated were #60370104 (27 yo, withdrew consent prior to R/x), and #63140359 (21 YO, lost to follow-up after randomization but prior to R/x, patient had *Staphylococcus aureus* in amounts that would not have met MO or sponsor evaluability criteria).

In addition, the sponsor provided 2 separate efficacy analyses. The second analysis was performed to assess response in relation to time off therapy as opposed to the initial analysis where the trovafloxacin patients were evaluated at both V4 and V5. The reviewer agreed with the revised approach and presented this analysis. The sponsor's evaluable population in table 119.3 is the "Evaluated for Efficacy (Additional analysis) population."

All further numerical references are based on these figures.

Medical Officer's Comment: The MO chose to provide a simplification of this table below:



From this diagram, the reader can appreciate that the bacteriologically-evaluable population was a subset of the clinically-evaluable population and the bacteriological ITT population, which were both subsets of the clinical ITT population. There were a total of 37/142 (26%) trovafloxacin-treated patients who discontinued therapy as compared to 15/133 (11%) ofloxacin-treated patients.

Of the 37 trovafloxacin patients, 26/142 (26%) discontinued for reasons associated with the study drug including:

- Adverse event: 20/142 (14%)
- Insufficient response or failure 2/142 (1%)
- Laboratory abnormality: 4/142 (3%)

The additional 11/142 (8%) of trovafloxacin-treated patients who discontinued therapy, were classified as discontinuations unrelated to the study drug and included:

- Adverse event: 5/142 (4%)
- Laboratory abnormality 1/142 (< 1%)
- Lost to follow-up: 1/142 (<1%)
- Other: 1/142 (<1%)
- Protocol violation: 2/142 (1%)

- Withdrew consent 1/142 (<1%)

Of the 15/133 (11%) ofloxacin patients, 10/133 (8%) discontinued for reasons associated with the study drug including:

- Adverse event: 8/133 (6%)
- Insufficient response or failure 2/133 (2%)
- Laboratory abnormality: 0

The additional 5/133 (4%) of ofloxacin-treated patients who discontinued therapy, were classified as discontinuations unrelated to the study drug and included:

- Adverse event: 1/133 (<1%)
- Did not meet randomization criteria: 1/133 (<1%)
- Laboratory abnormality: 0
- Lost to follow-up: 1/133 (<1%)
- Other: 0
- Protocol Violation: 1/133 (<1%)
- Withdrew consent 1/133 (<1%)

Of these 37 and 15 patients per arm, respectively, 14/142 (10%) of the trovafloxacin patients and 10/133 (8%) of the ofloxacin patients were discontinued from the study. 7 of the trovafloxacin patients were withdrawn during treatment and 7 during follow-up as compared to 8 and 2 ofloxacin patients.

As noted by the MO, not all patients who were discontinued from either treatment or study or both were either clinically or bacteriologically unevaluable. The MO has reviewed the sponsor's tables 4.3.1 and 4.3.2 which were compromised of line listings and divided up the patients in the following manner:

Trovafloxacin:

Discontinued from treatment and clinically and bacteriologically unevaluable (n = 27):

- #50050441: 58 YO discontinued after 26 days because of a toothache. The patient was placed on Pen VK®. The patient had *Enterococcus faecalis* and *Escherichia coli* in appropriate amounts and would have been an evaluable cure. The exclusion was based on the sponsor's rule to exclude all patients who received another antimicrobial unless they were a failure. Reviewer agreed.
- #50140085: 70 YO discontinued after 1 day because of dizziness. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.
- #50140086: 69 YO discontinued after 2 days because of dizziness. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.
- #56470228: 62 YO discontinued after 13 days because of dizziness and rash. Reviewer agreed. This patient had eradication of a *Staphylococcus aureus* but did not receive the minimum duration of 21 days to be an evaluable cure.
- #56480206: 63 YO discontinued after 6 days because of a viral syndrome. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56480409: 31 YO discontinued after 10 days because of a rash. Reviewer agreed. Patient did not have meet reviewer criteria of bacteriologic evaluability.
- #56480210: 34 YO discontinued after 8 days because of an error with randomization. Reviewer agreed, patient did not meet reviewer criteria of bacteriologic evaluability.

- #56550185: 81 YO discontinued after 4 days because of headache. Repeat culture was not done and no further R/x was given. Reviewer agreed.
- #56570037: 47 YO discontinued on day 18 because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56610060: 73 YO discontinued after 1 day because of headache. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #56610404: 71 YO discontinued after 1 day because a lymphoma was diagnosed. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #56660147: 41 YO discontinued after 2 days because of headache. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #56660220: 50 YO discontinued after 14 days because of GI distress. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56660257: 73 YO discontinued after 23 days because of constipation. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56690234: 82 YO discontinued after 17 days because of GI distress. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60290118: 47 YO discontinued after 8 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60360161: 42 YO discontinued after 2 days because of flushing. Reviewer agreed. Patient did not receive the minimum duration necessary to be evaluable.
- #60360397: 42 YO discontinued after 9 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60850142: 59 YO discontinued after 4 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60860293: 56 YO discontinued after 2 days Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61030082: 35 YO discontinued after 3 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61030084: 50 YO discontinued after 3 days Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61050393: 70 YO discontinued after 3 days because of dizziness. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #63140191: 53 YO lost to follow-up after 28 days. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #63140360: 39 YO discontinued after 15 days. Protocol violation, D/x: nonbacterial prostatitis. Reviewer agreed.

- #63730284: 54 YO discontinued after 12 days because of blurry vision. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61460177: 66 YO discontinued after 28 days because of a protocol violation (patient stopped capsules). *Escherichia coli* isolated in equivalent amounts in EPS, VB1, and VB2 specimens.
- Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

Discontinued from treatment but clinically and bacteriologically evaluable (n = 9):

- #50050008: 43 YO discontinued after 28 days because of insufficient response. Evaluable failure.
- #50140269: 73 YO discontinued after 28 days because of insufficient response. Evaluable failure
- #56570341: 59 YO discontinued after 28 days because of diarrhea. Evaluable cure per sponsor but patient does not meet reviewer criteria of evaluability.
- #56670045: 71 YO discontinued after 28 days because of lab abnormalities. Evaluable cure.
- #56690233: 94 YO discontinued after 28 days because of lab abnormalities. Evaluable cure per sponsor but patient did not meet reviewer criteria of evaluability.
- #60370101: 59 YO discontinued after 28 days because of lab abnormalities. Evaluable improvement per sponsor but patient did not meet reviewer criteria of evaluability.
- #61050034: 67 YO discontinued after 28 days because of lab abnormalities. Evaluable cure per sponsor but patient did not meet reviewer criteria of evaluability.
- #61050035: 44 YO discontinued after 28 days because of lab abnormalities. Evaluable cure.
- #61050267: 72 YO discontinued after 28 days because of a rash. Evaluable cure.

One additional patient #56660378 (not included in list), completed therapy but was clinically and bacteriologically unevaluable because he received erythromycin from day 19 – 30 for a sinus infection. The Reviewer agreed with this determination and additionally, this patient did not have meet the reviewer's criteria of bacteriologic evaluability.

Similar categories for the ofloxacin arm are:

Ofloxacin (N= 15):

Discontinued from treatment and clinically and bacteriologically unevaluable (n = 13)

- #50050301: 70 YO withdrew consent after 20 days of therapy, no follow-up cultures, and mixed specimen. Reviewer agreed that patient was not evaluable as per sponsor criteria.
- #56310066: 63 YO discontinued after 10 days because of a rash. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #56480208: 43 YO discontinued after 2 days because of headache. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.
- #56550186: 73 YO discontinued after 2 days because of diarrhea. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.
- #56570314: 55 YO discontinued after 7 days because of insomnia. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

- #56610403: 46 YO discontinued after 4 days because of cramps. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #58360138: 65 YO discontinued after 7 days because of abdominal pain. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #60310223: 43 YO discontinued after 1 day because of flushing. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.
- #60850141: 66 YO discontinued after 31 days because of an URI. Patient did not meet reviewer criteria of evaluability. The sponsor excluded him because he received Biaxin® for 10 days.
- #61030081: 53 YO discontinued after 3 days because of blurry vision. Reviewer agreed. Patient did not receive minimum duration necessary to be evaluable.
- #61040029: 57 YO discontinued after 11 days because of a protocol violation. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61290090: 80 YO discontinued after 3 days because of randomization violation. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #63140358: 29 YO lost to follow-up after 27 days. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

Discontinued from treatment but clinically and bacteriologically evaluable (n = 2):

- #60290120: Insufficient response after 38 days of therapy, evaluable failure carried forward.
- #63730283: Insufficient response after 4 weeks of therapy, evaluable failure carried forward.

In addition to the 27 trovafloxacin-treated patients and the 13 ofloxacin-treated patients listed above, the sponsor appeared to have excluded an additional 16 trovafloxacin and 22 ofloxacin patients from the bacteriologically-evaluable populations. 1 additional trovafloxacin and 9 ofloxacin patients were also clinically unevaluable.

The Reviewer was unable to identify the patients excluded from the analyses based on the information provided in the sponsor's line listings and tables 4.3.1 and 4.3.2., and requested that the sponsor provide the PIDs on June 24, 1997. Provided by the sponsor on June 26, 1997, via FAX, were 16 pages of additional line listings which revealed the following:

Trovafloxacin: Clinically evaluable but bacteriologically unevaluable (N=15):

- #56300020
- #56300413
- #56300414
- #58460128
- #61040030
- #56690298
- #58270181
- #58360140
- #58460426
- #63140192
- #63140357

- #63150229
- #63160203
- #63730335
- #63730437

Ofloxacin: Clinically evaluable but bacteriologically unevaluable (N = 13):

- #56300354
- #56420199
- #56480207
- #56610434
- #56610446
- #56670046
- #56690370
- #60290119
- #60320069
- #60830165
- #63140189
- #63160202
- #63160204

Ofloxacin: Excluded from clinical ITT and all further analyses (N= 6):

- #50050304: 22 YO excluded after 42 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #56300353: 62 YO excluded after 42 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #56420062: 81 YO excluded after 51 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #56660322: 48 YO excluded after 43 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #58460427: 30 YO excluded after 42 days of R/x. Did not meet sponsor or reviewer criteria of evaluability.
- #61020074: 47 YO excluded after a full course because he did not meet sponsor or reviewer criteria of evaluability.

Additional ofloxacin patients excluded from analyses, both clinical and bacteriological, found from line listings by reviewer (N= 3):

- #56690236: 67 YO excluded after 43 days of therapy because he received a 10 day course of Amoxicillin for a sore throat. Reviewer agreed. Patient did not have meet reviewer criteria of bacteriologic evaluability.
- #56690299: 40 YO excluded after a full course because he received 1 day of intravenous ceftriaxone peri-operatively. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.
- #61050036: 42 YO excluded after a full course of R/x because he received 24 hours of achromycin for surgical prophylaxis. Reviewer agreed. Patient did not meet reviewer criteria of bacteriologic evaluability.

Medical Officer's Comment: For the trovafloxacin arm, the MO in subtracting the 27 clinically and bacteriologically unevaluable patients in addition to the one additional patient found in the line listings that was clinically and bacteriologically unevaluable, was able to obtain the sponsor's clinically-evaluable population. Further subtraction of the 15 bacteriologically unevaluable patients ($113 - 15 = 98$), gave the sponsor's bacteriologically-evaluable population.

For the ofloxacin-treated patients, the MO subtracted the 2 patients who were randomized but not treated from 135 to reach 133. From these patients, an additional 6 were excluded from the clinical ITT population, and thus all further analyses, leaving 127. From 127, the 16 clinically and bacteriologically unevaluable patients were subtracted, leaving 111, the sponsor's clinically-evaluable population. If the 13 bacteriologically unevaluable only patients were subtracted from this, 98 patients or the sponsor's bacteriologically-evaluable population remained.

Baseline Characteristics:

All-treated subjects were male, mean age of 52 for the trovafloxacin patients and 51.7 for the ofloxacin patients. The median duration since the onset of symptoms was 25 days for the trovafloxacin patients and 22.5 days for the ofloxacin. There were no marked differences between the populations in terms of underlying disease.

Medical Officer's Comment: As stated in the introduction, the investigators were confused as to the meaning of the "duration of illness." Responses included the duration of the present episode while others provided the duration of the underlying diagnosis of prostatitis, thus rendering it impossible based on this parameter alone, to delineate whether the populations analyzed had acute prostatitis or acute exacerbations of chronic prostatitis.

Concomitant Medications:

The majority of treated patients in both groups received concomitant medications during therapy (77% trovafloxacin and 73% ofloxacin). The most commonly used medications were anti-hypertensives and drugs for the treatment of arthritic conditions.

Concomitant Antimicrobials:

35 trovafloxacin and 14 ofloxacin patients received antimicrobials for the following reasons:

- Inadequate response: 10 trovafloxacin and 3 ofloxacin (all carried forward as evaluable failures)
- Discontinued early due to adverse events: 14 trovafloxacin and 4 ofloxacin
- Other or no reason: 11 trovafloxacin and 7 ofloxacin.

These patients were not listed again as they were already included in the listings of unevaluable patients. The MO agreed with the sponsor's determinations. Patients discontinued for other reasons were usually suffering from an unrelated infection, such as a URI. These patients received antimicrobials, which would not have been expected to have an effect on a prostatitis, and would have been evaluable cures if they had not been excluded.

Protocol Deviations:

There were 2 deviations on the ofloxacin arm.

- #56470225 had a cracked capsule. The site was unblinded but the subject remained blinded.
- #61040029 unblinded himself and the site by cracking a capsule to see which drug he was receiving.

Sponsor’s Efficacy Analysis:

Sponsor-Defined Clinical Response:

Table 119.4

Sponsor-Defined Clinical Response/Clinically Evaluable Population at One-week Post-therapy:
(Modified from Sponsor Table 5.1.1a)

	Trovafloxacin	Ofloxacin	p value*	95% CI	
Total Number of Subjects	116	111			
One week post R/x analysis V4 versus V5					
Number of Assessed Subjects	113 (100%)	111 (100%)			
Cure	28 (25%)	42 (38%)	0.020		
Improvement	73 (65%)	54 (49%)			
Failure	12 (11%)	15 (14%)			
Success (Cure + Improvement)	101 (89%)	96 (86%)	0.448	(-5.6%	11.4%)

* p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer’s Comment: At the EOT (sponsor’s TOC), the two arms appeared equivalent ($\Delta = 15$). Ofloxacin was numerically superior to trovafloxacin in terms of overall cure versus improvement only, at this timepoint. The MO applied a 95% CI with continuity correction factor to this analysis and found the following: -6.5%, 2.3% ($\Delta = 15$). The MO agreed with the sponsor’s determination of equivalence as it applied to the sponsor’s evaluable population for the primary efficacy variable.

Table 119.5

Sponsor-Defined Clinical Response/Clinically Evaluable Population at V6: (Modified from Sponsor Table 5.1.1b)

	Trovafloxacin	Ofloxacin	p value*	95% CI	
Total Number of Subjects	107	111			
Three to Six week post R/x analysis (V6)					
Number of Assessed Subjects	107 (100%)	103 (100%)			
Cure	54 (50%)	71 (69%)	< .001		
Improvement	20 (19%)	0 (0%)			
Failure	33 (31%)	32 (31%)			
Success (Cure + Improvement)	74 (69%)	71 (69%)	0.864	(-12.3%	12.7%)

* p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer’s Comment: At the V6 assessment or the late follow-up, which included only those patients who were cured or improved at V4 and V5, the 2 agents appeared equivalent ($\Delta = 20$). Interestingly, once again ofloxacin was numerically superior to trovafloxacin in terms of complete cure versus improvement only. The MO applied a 95% CI with continuity correction factor to this analysis and found the following: -13.2%, 13.6% ($\Delta = 20$). The MO agreed with the sponsor’s determination of equivalence as it applied to the sponsor’s evaluable population.

The following results were seen in the ITT analyses: success at EOT: 85% (114/134) trovafloxacin-treated patients versus 79% (102/129) ofloxacin-treated patients (95% CI -3.3%, 15.3% ($\Delta = 15$). Thus indicating equivalence between the 2 regimens. In this analysis the apparent numerical superiority of ofloxacin was again apparent in terms of cure (ofloxacin 46/129 (36%), trovafloxacin 33/114 (25%), versus improvement (ofloxacin 56/129 (43%) versus trovafloxacin 81/114 (60%). There were 20/114 (15%) failures on the trovafloxacin arm as compared to 27/129 (21%) on the ofloxacin arm.

At V6, the overall success rate was 89/132 (67%) trovafloxacin versus 89/135 (66%) ofloxacin (95% CI

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-9.8%, 12.8% ($\Delta = 20$). These results mirrored those of the evaluable population, with 46/135 (34%) failures and 3/135 (2%) improvements on the ofloxacin arm compared to 43/132 (33%) failures and 24/132 (18%) improvements on the trovafloxacin arm.

The sponsor and the investigators differed in their determination of response in 6 trovafloxacin patients and 18 ofloxacin patients at V6. There were no differences between them at V4 for the trovafloxacin patients and 3 differences for the ofloxacin patients at V5. In all cases, these were patients who were carried forward by the sponsor as failures as opposed to improvements by the investigator.

Because the Points-to-Consider guidance document provides that the prostatitis indication be studied as a clinical/microbiological study, that is that patients must be both clinically and microbiologically evaluable in order to be assessed, the MO provided the sponsor's analysis for this subgroup of patients below:

Table 119.6

**Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT:
(Modified from Sponsor Table 5.1.3a)**

	Trovafloxacin	Ofloxacin	p value*	95% CI	
Total Number of Subjects	100	98			
One week post R/x analysis (V4, V5)					
Number of Assessed Subjects	98 (100%)	98 (100%)			
Cure	26 (27%)	38 (39%)	0.491		
Improvement	62 (63%)	47 (48%)			
Failure	10 (10%)	13 (13%)			
Success (Cure + Improvement)	88 (90%)	85 (87%)	0.043	(- 5.9%	12.1%)

* p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer's Comment: This analysis essentially mirrored the previous analyses and supported the claim of equivalence of the 2 regimens. No V6 analysis was provided for this subgroup. The MO applied a 95% CI with continuity correction factor to this analysis and found the following: -7.0%, 13.0% ($\Delta = 10$). The MO agreed with the sponsor's determination of equivalence as it applied to the sponsor's evaluable population.

Bacteriological Response:

Sponsor-Defined Bacteriologic Response for Bacteriologically Evaluable Subjects at EOT can be seen in Sponsor's Table 5.3.1a, copied and modified by the MO:

Table 119.7

**Sponsor-Defined Bacteriological Response/Bacteriologically Evaluable Population
(Modified from Sponsor Table 5.3.1a)**

	Trovafloxacin	Ofloxacin	p-value*	95% CI	
Total Number of Subjects	100	98			
One week post R/x (V4 versus V5)					
Number of Assessed Subjects	98 (100%)	98 (100%)			
Complete Eradication	77 (77%)	80 (82%)	0.172	(- 12.0%	-1.8%)
Partial Eradication	12 (23%)	14 (14%)			
Complete Persistence	9	4 (4%)			
Eradication (Complete and Partial)	89 (91%)	94 (96%)	0.072		

* p-value = Cochran-Mantel-Haenszel Test includes adjusting for center effect.

Medical Officer's Comment: The complete eradication rate was numerically superior for the ofloxacin arm. The 95% CI with continuity correction factor performed by the MO was -13.05%, 2.85% ($\Delta = 10$), indicating that trovafloxacin was not equivalent to ofloxacin for this subpopulation.

Below is the sponsor-defined pathogen eradication rate at one week post-therapy for all bacteriologically evaluable subjects. The sponsor stated that (copied from page 44 of the study report):

"Among bacteriologically evaluable subjects, both treatment regimens were 100% effective in eradicating Coagulase-negative *staphylococcus* one week post-therapy. Pathogen eradication rates for other frequently isolated pathogens, including *Escherichia coli* (trovafloxacin: 95%, 19/20; ofloxacin: 100% 18/18), *Enterococcus faecalis* (trovafloxacin: 82%, 14/17; ofloxacin: 83% 15/18), *Staphylococcus haemolyticus* (trovafloxacin: 74%, 14/19; ofloxacin: 86% 18/21), and *Staphylococcus epidermidis* (trovafloxacin: 73%, 24/33; ofloxacin: 65%, 22/34), were comparable between trovafloxacin- and ofloxacin-treated subjects. Pathogen eradication rates for other frequently isolated baseline pathogens were generally similar between the two treatment groups."

The MO created a table of all baseline pathogens and their eradication rates below.

Table 119.8

Sponsor-Defined Pathogen Eradication Rates/ All Bacteriologically Evaluable Patients at EOT (As per the sponsor)

Pathogen	Trovafloxacin		Ofloxacin	
	n/N	%	n/N	%
<i>Escherichia coli</i>	13/ 14	(93%)	18/ 18	(100%)
<i>Enterococcus spp.</i>	12/ 12	(100%)	18/ 18	(100%)
<i>Enterococcus faecalis</i>	14/ 17	(82%)	15/ 18	(83%)
<i>Enterobacter spp.</i>	1/ 1	(100%)	3/ 3	(100%)
<i>Pseudomonas aeruginosa</i>	1/ 2	(50%)	1/ 2	(50%)
<i>Enterobacter aerogenes</i>	4/ 4	(100%)	1/ 1	(100%)
<i>Proteus mirabilis</i>	1/ 1	(100%)	1/ 1	(100%)
<i>Enterobacter cloace</i>	1/ 1	(100%)	3/ 3	(100%)
<i>Klebsiella pneumoniae</i>	4/ 6	(67%)	1/ 1	(100%)
<i>Pseudomonas spp.</i>	1/ 1	(100%)	-	-
<i>Pseudomonas maltophilia</i>	1/ 1	(100%)	-	-
<i>Proteus spp.</i>	1/ 1	(100%)	-	-
<i>Staphylococcus saprophyticus</i>	2/ 2	(100%)	2/ 2	(100%)
<i>Acinetobacter baumannii</i>	1/ 1	(100%)	-	-
<i>Acinetobacter calcoaceticus</i>	1/ 1	(100%)	-	-
<i>Acinetobacter anitratus</i>	1/ 1	(100%)	-	-
<i>Acinetobacter lwoffii</i>	1/ 1	(100%)	-	-
<i>Citrobacter spp.</i>	-	-	1/ 1	(100%)
<i>Citrobacter amalonaticus</i>	1/ 1	(100%)	-	-
<i>Citrobacter diversus</i>	1/ 1	(100%)	1/ 1	(100%)
<i>Citrobacter freundii</i>	2/ 2	(100%)	1/ 1	(100%)
<i>Serratia liquefaciens</i>	1/ 1	(100%)	-	-
<i>Staphylococcus spp.</i>	11/ 11	(100%)	8/ 8	(100%)
<i>Staphylococcus aureus</i>	4/ 4	(100%)	2/ 2	(100%)
<i>Staphylococcus epidermidis</i>	24/ 33	(73%)	22/ 34	(65%)
<i>Staphylococcus haemolyticus</i>	14/ 19	(74%)	18/ 21	(86%)
<i>Staphylococcus hominis</i>	4/ 4	(100%)	6/ 6	(100%)
<i>Staphylococcus simulans</i>	2/ 2	(100%)	3/ 3	(100%)
Coagulase (-) staphylococci	28/ 28	(100%)	33/ 33	(100%)
<i>Streptococcus spp.</i>	3/ 3	(100%)	3/ 3	(100%)
<i>Streptococcus agalactiae</i>	5/ 6	(83%)	4/ 4	(100%)
<i>Streptococcus anginosus</i>	3/ 3	(100%)	2/ 2	(100%)
<i>Streptococcus bovis</i>	-	-	1/ 1	(100%)
<i>Streptococcus mitis</i>	5/ 6	(100%)	6/ 6	(100%)
<i>Streptococcus salivarius</i>	1/ 1	(100%)	2/ 2	(100%)
<i>Streptococcus sanguis I</i>	1/ 1	(100%)	-	-
<i>Streptococcus sanguis II</i>	3/ 3	(100%)	2/ 2	(100%)
<i>Beta streptococcus Group B</i>	-	-	1/ 1	(100%)
<i>Beta hemolytic streptococcus Gp B</i>	-	-	1/ 1	(100%)
TOTAL	174/ 197	(88.3%)	174/ 194	(89.6%)

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Medical Officer's Comment: *Trovafloxacin and ofloxacin were comparable in terms of overall bacterial eradication rates. The sponsor did not provide a total eradication rate and this number was derived from the line listings.*

Of note, was the large number of Gram (+) pathogens (non- enterococcal) in the sponsor's analysis as compared to what is generally expected from a population of patients with prostatitis. As discussed in the introduction, the validity of including these organisms in the analysis was questionable.

The MO's initial impression that the patient population was more consistent with a population of patients with chronic disease as opposed to acute prostatitis could be considered validated by the bacteriology of this submission if one is prepared to accept the argument that these organisms are indeed responsible for acute exacerbations of chronic prostatitis. As stated previously, the sponsor did not apply a strict definition of acute versus chronic prostatitis and has been unable to provide the data which would enable a differentiation of patients based on diagnostic criteria alone. Additionally, although the protocol specified that in order for an isolate to be considered an evaluable pathogen, it had to be present in the EPS or VB3 specimen in an amount at least 10-fold that isolated in VB1 or VB2, this was not done and a rule of "greater than" was applied. The MO was unable to ascertain if these organisms represented urethral commensals or true pathogens based on the information as currently provided. This issue was dealt with in the MO's analysis, wherein the MO's evaluability criteria were applied.

The sponsor provided a 95% CI for Enterococcus faecalis of -26.0%, 24.0%. The MO did not provide a CI for any isolate as the numbers were too small for the results to have had any validity.

Superinfecting Pathogens:

The sponsor stated that (copied from page 45 of the study report):

Thirteen (13) superinfecting pathogens were isolated from 25 subjects (18%) in the trovafloxacin group, and 10 superinfecting pathogens were isolated from 24 subjects (18%) in the ofloxacin group. The most common superinfecting pathogens isolated from subjects in the trovafloxacin group were *Staphylococcus epidermidis* (8 subjects), *Enterococcus faecalis* (5 subjects) and *Staphylococcus haemolyticus* (5 subjects); the most common superinfecting pathogens isolated from subjects in the ofloxacin group were *Enterococcus faecalis* (9 subjects) and *Staphylococcus epidermidis* (9 subjects).

Medical Officer's Comment: *The MO reviewed the sponsor's table 5.7 of superinfecting pathogens and found the following:*

For trovafloxacin-treated subjects the most common superinfecting pathogens were Escherichia coli (2), Enterococcus faecalis (5), Pseudomonas aeruginosa (1), Klebsiella pneumoniae (1), Staphylococcus spp. (1), Staphylococcus epidermidis (8), Staphylococcus haemolyticus (5), Staphylococcus hominis (1), Streptococcus spp. (2), Streptococcus agalactiae (2), Streptococcus anginosus (3), Streptococcus mitis (3), and Streptococcus salivarius (1).

The respective numbers for the ofloxacin arm were 0, 9, 0, 0, 3, 9, 3, 4, 0, 2, 0, 2, and 1. In addition there was 1 Stomatococcus spp. and 1 Serratia marcescens

No conclusions could be drawn from this information other than that both treatment groups had a large number of Gram (+) isolates which met the sponsor's definition of superinfecting pathogens.

Bacteriological ITT Subjects:

The sponsor stated that (copied from page 45 of the study report):

"Sponsor-defined bacteriological eradication rates (complete + partial) one week post-therapy were comparable between the treatment groups for bacteriological intent-to-treat subjects (trovafloxacin: 91%, 117/128; ofloxacin: 94%, 111/118 [CI: -9.1, 3.8])."

"Among bacteriological intent-to-treat subjects, eradication rates of frequently isolated pathogens were generally similar between the treatment groups."

Medical Officer's Comment: *The MO elected not to present the sponsor's full analysis and tables for the ITT population. The results were very similar to those of the evaluable population and the pathogens again included a large number of possible contaminants as opposed to true pathogens.*

Subjects with a Sponsor-Defined Clinical Response of Failure and/or a Bacteriological Response of Persistence One Week Post-Therapy and Subjects with a Sponsor-Defined Clinical Response of Recurrence Three to Six Weeks Post-Therapy (sponsor's analysis, modified by MO in Times New Roman):

Clinical Failure:

Twelve (12) evaluable trovafloxacin subjects and 15 evaluable ofloxacin subjects were clinical failures one week post-therapy. Two (2) of the 12 clinical failures in the trovafloxacin group, (#50140269, #5005008), and two of the 15 clinical failures in the ofloxacin group, (#60290120, #63730283), were discontinued from treatment due to insufficient response after being treated for 28 days (both trovafloxacin subjects), and 38 or 27 days (two ofloxacin subjects). No subject in either treatment group was hospitalized due to worsening of condition. Of the subjects who were clinical failures one week post-therapy, four (4) of the 12 trovafloxacin subjects, (same as above and #56420061, #56680050), and two of the 15 ofloxacin subjects, (same as above), received additional antibiotics for insufficient response.

Of the subjects designated as clinical failures one week post-therapy, one subject in the trovafloxacin group had repeat cultures that showed persistence of *Staphylococcus epidermidis*, one subject showed persistence of *Enterococcus faecalis* and one subject had presumed persistence of *Escherichia coli*. Six of 15 subjects in the ofloxacin group had repeat cultures that showed persistence of *Staphylococcus epidermidis*, *Enterococcus faecalis* and/or *Streptococcus anginosus* one week post-therapy.

Clinical Recurrence. Seven (7) trovafloxacin subjects and four ofloxacin subjects were clinical recurrences at three to six weeks post-therapy; none was discontinued from treatment due to insufficient response. Of the subjects who were clinical recurrences, two (2) of the 7 trovafloxacin subjects and none of the 4 ofloxacin subjects received additional antibiotics for insufficient response.

Of the subjects designated as clinical recurrences at the end of study, two of seven subjects in the trovafloxacin group had repeat cultures that showed persistence of *Enterococcus faecalis*, one subject showed persistence of *Klebsiella pneumoniae*, and one subject had recurrence of *Staphylococcus epidermidis*. Six of 15 subjects in the ofloxacin group had repeat cultures that showed persistence of *Staphylococcus epidermidis*, *Enterococcus faecalis* and/or *Streptococcus anginosus* one week post-therapy.

Subject Bacteriological Response and Pathogen Outcome of Persistence: Nine (9) trovafloxacin and four (4) ofloxacin bacteriologically evaluable subjects had sponsor-defined subject bacteriological responses of complete persistence one week post-therapy.

Eight (8) of the nine trovafloxacin subjects with a sponsor-defined subject bacteriological response of complete persistence had repeat cultures that showed persistence of *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus haemolyticus*, *Staphylococcus epidermidis* and/or *Streptococcus mitis* one week post-therapy. The remaining trovafloxacin subject with a

sponsor-defined subject bacteriological response of complete persistence had a pathogen outcome of presumed persistence for baseline isolate *Escherichia coli* one week post-therapy.

All four ofloxacin subjects with a sponsor-defined subject bacteriological response of complete persistence had repeat cultures that showed persistence of baseline isolates *Staphylococcus epidermidis* and/or *Enterococcus faecalis* one week post-therapy.

Of the subjects with an unfavorable clinical or bacteriological response, who had baseline pathogens with susceptibility testing performed both prior to and following treatment, one subject in the trovafloxacin group had baseline isolates of *Staphylococcus epidermidis* that were susceptible to trovafloxacin (MIC = ≤ 2) at baseline and were resistant to trovafloxacin (MIC = ≥ 8) at the end of study, and two subjects in the ofloxacin group had baseline isolates of *Staphylococcus epidermidis* that were susceptible to ofloxacin (MIC = ≤ 2) at baseline and became resistant to ofloxacin (MIC = ≥ 8) by the end of study.

Cross Tabulation of Sponsor-Defined Clinical Response and Sponsor-Defined Bacteriological Response and Pathogen Outcome:

As per the sponsor, there was an inconsistent response at the 1 week post-therapy (TOC) analysis in 15 trovafloxacin and 8 ofloxacin patients. On the trovafloxacin arm there were 7 patients who were clinical failures with bacteriological eradication and 8 were clinical cures with bacteriological persistence. The respective numbers on the ofloxacin arm were 7 and 1. A review of the line listings and table 5.9.1a revealed that these inconsistencies were associated with the following pathogens (patients had more than 1 baseline pathogen):

Trovafloxacin:

Enterococcus spp.: 2 clinical failures with eradication.
Enterococcus faecalis: 2 clinical cures with persistence and 2 clinical failures with eradication.
Pseudomonas aeruginosa: 1 clinical cure with bacteriological persistence and one clinical failure with eradication.
Staphylococcus saprophyticus: 1 clinical failure with eradication.
Citrobacter freundii: 1 clinical failure with eradication.
Staphylococcus spp: 1 clinical failure with eradication.
Klebsiella pneumoniae: 2 clinical cures with persistence and 2 clinical failures with eradication.
Staphylococcus aureus: 1 clinical failure with eradication.
Staphylococcus epidermidis: 1 clinical failure with eradication and 8 clinical cures with persistence.
Staphylococcus haemolyticus: 3 clinical failures with eradication and 5 clinical cures with persistence.
 Coagulase-negative *staphylococci*: 3 clinical failure with eradication.
Streptococcus spp.: 1 clinical failure with eradication.
Streptococcus agalactiae: 1 clinical cure with persistence.
Streptococcus mitis: 2 clinical failures with eradication and 1 clinical cure with persistence.

Ofloxacin:

Escherichia coli: 1 clinical failure with eradication.
Enterococcus faecalis: 1 clinical cure with persistence and 2 failures with eradication.
Enterococcus spp.: 1 clinical failure with eradication.
Pseudomonas aeruginosa: 1 clinical cure with bacteriological persistence.
Staphylococcus spp.: 2 clinical failure with eradication.
Enterobacter spp: 1 clinical failure with eradication.
Klebsiella pneumoniae: 2 clinical failures with eradication.
Staphylococcus epidermidis: 2 clinical failures with eradication and 8 clinical cures with persistence.
Staphylococcus haemolyticus: 2 clinical failures with eradication and 3 clinical cures with persistence.
 Coagulase-negative *staphylococci*: 2 clinical failures with eradication.
Staphylococcus hominis: 1 clinical failure with eradication.

Streptococcus agalactiae: 2 clinical failures with eradication.

Streptococcus mitis: 1 clinical failure with eradication.

Sponsor's Conclusion: (Copied from the Esub and modified by the MO (in Times New Roman font), to reflect the numerators and denominators):

One hundred forty-two (142) subjects were randomized to receive trovafloxacin and 135 subjects were randomized to receive ofloxacin. The two treatment groups were generally comparable with respect to demographic characteristics at baseline, medical history, and prior and concomitant medications.

Among clinically evaluable and clinical intent-to-treat subjects, comparisons (95% CIs) of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatment regimens one week post-therapy (101/113 (89%) trovafloxacin clinically evaluable versus 96/111 (86%) ofloxacin clinically evaluable), suggesting that the additional two weeks of ofloxacin therapy was of no clinical benefit.

Among bacteriologically evaluable and bacteriological intent-to-treat subjects, sponsor-defined subject bacteriological eradication rates (complete + partial) one week post-therapy were comparable between the treatment groups (89/98 (91%) trovafloxacin bacteriologically evaluable versus 94/98 (96%) ofloxacin bacteriologically evaluable).

Among bacteriologically evaluable subjects, both treatment regimens were 100% effective in eradicating Coagulase-negative *Staphylococcus* one week post-therapy (28/28 trovafloxacin versus 33/33 ofloxacin). Pathogen eradication rates for other frequently isolated pathogens, including *Escherichia coli* (13/14 (93%) trovafloxacin versus 18/18 (100%) ofloxacin), *Enterococcus faecalis* (14/17 (82%) trovafloxacin versus 15/18 (83%) ofloxacin), *Staphylococcus haemolyticus* (14/19 (74%) trovafloxacin versus 18/21 (86%) ofloxacin), and *Staphylococcus epidermidis* (24/33 (73%) trovafloxacin versus 22/34 (65%) ofloxacin) were comparable between the two treatment groups.

Medical Officer's Comment: *The MO agreed with the sponsor's conclusion that trovafloxacin appeared to be numerically comparable to ofloxacin in terms of clinical success and bacteriologic eradication rates as it pertained to the sponsor's evaluable population. The MO also agreed with the sponsor's claim of equivalence with regards to Escherichia coli and Enterococcus faecalis. The MO, however, did not agree with the sponsor's claim in regards to the coagulase-negative staphylococci. The MO recognized the eradication of these organisms but was unclear as to their significance as pathogens.*

Medical Officer's Efficacy Analysis:

On July 11, 1997, the sponsor faxed partial tables and listings for the MO evaluable population, in accordance with the evaluability criteria discussed above.

**Table 119.9
Evaluable Population (as per the MO)**

MO's Evaluable Population		
Reason for exclusion	Trovafloxacin	Ofloxacin
	N= 277	
Total Randomized	142	135
Number Treated	142	133
Excluded from Clinical Analysis by Sponsor (Table 119. 3)	29	22
Excluded from Bacteriological analysis by Sponsor	44	35
Clinically Evaluable by Sponsor	113	111
Bacteriologically Evaluable by Sponsor	98	98
Additional Patients Excluded by MO	30	40
Total MO Evaluable at EOT/TOC	68 (67)*	58

*no. in parentheses refers to final evaluable no. of patients as determined by the MO subsequent to the drafting of table 119.9. This second determination was made based on a second review of 2 patients with initial cultures that revealed mixed microbial flora and who were determined to be "partial cures" by the applicant. However, for purposes of consistency between the tables, both totals of evaluable trovafloxacin patients have been provided in table 119.9 and 119.14.

The MO's population was significantly smaller than that of the sponsor (68 trovafloxacin and 58 ofloxacin patients at the TOC/V4: trovafloxacin, and V5: ofloxacin). The MO excluded an additional 30 patients from the sponsor's trovafloxacin bacteriologically evaluable population and 40 from the ofloxacin. Additionally, those sponsor clinically evaluable patients, who were not evaluable bacteriologically, were not evaluable as per the MO. The MO's population was both clinically and microbiologically evaluable. A by-center breakdown is presented below:

Table 119.10
Evaluable Population by Center/Sponsor/MO

Center	Total Randomized N = 277 (100%)		Trovafoxacin				Ofloxacin			
			Sponsor Evaluable N = 142		MO Evaluable N = 68		Sponsor Evaluable N = 133		MO Evaluable N = 58	
			100%	100%	100%	100%	100%	100%	100%	100%
5005	18	6.4	9	6.3	7	10.3	9	6.7	6	10.3
5014	8	2.8	4	2.8	2	2.9	4	3.0	4	6.9
5630	12	4.3	6	4.2	2	2.9	6	4.5	4	6.9
5631	3	1.0	1	0.7	1	1.5	2	1.5	0	-
5642	8	2.8	4	2.8	1	1.5	4	3.0	2	3.4
5645	7	2.5	3	2.1	2	2.9	4	3.0	4	6.9
5647	9	3.2	5	3.5	1	1.5	4	3.0	1	1.7
5648	6	2.1	4	2.8	0	-	2	1.5	0	-
5655	2	0.7	1	0.7	0	-	1	0.7	0	-
5657	11	3.9	6	4.2	2	2.9	5	3.7	1	1.7
5661	14	5.0	7	4.9	4	5.9	7	5.2	2	3.4
5662	1	0.4	1	0.7	1	1.5	0	0	0	-
5666	32	11.5	16	11.2	9	13.2	16	12.0	9	15.5
5667	4	1.4	2	1.4	2	2.9	2	1.5	1	1.7
5668	3	1.0	2	1.4	2	2.9	1	0.7	0	-
5669	17	6.1	9	6.3	5	7.4	8	6.0	3	5.2
5827	1	0.4	1	0.7	0	-	0	0	0	-
5836	7	2.5	4	2.8	3	4.4	3	2.2	1	1.7
5846	7	2.5	4	2.8	2	2.9	3	2.2	1	1.7
6029	5	1.8	3	2.1	2	2.9	2	1.5	1	1.7
6031	9	3.2	5	3.5	2	2.9	4	3.0	1	1.7
6032	1	0.4	0	0	0	-	1	0.7	0	-
6035	1	0.4	0	0	0	-	1	0.7	0	-
6036	9	3.2	5	3.5	0	-	4	3.0	2	3.4
6037	4	1.4	2	1.4	2	2.9	1	0.7	1	1.7
6082	3	1.0	2	1.4	1	1.5	1	0.7	1	1.7
6083	1	0.4	0	0	0	-	1	0.7	0	-
6085	2	0.7	1	0.7	0	-	1	0.7	0	-
6086	6	2.1	4	2.8	1	1.5	2	1.5	2	3.4
6102	3	1.0	1	0.7	0	-	2	1.5	0	-
6103	6	2.1	3	2.1	1	1.5	3	2.2	0	-
6104	3	1.0	2	1.4	0	-	1	0.7	0	-
6105	14	5.0	7	4.9	6	8.8	7	5.2	4	6.9
6128	3	1.0	1	0.7	1	1.5	2	1.5	1	1.7
6129	2	0.7	0	0	0	-	2	1.5	0	-
6130	6	2.1	3	2.1	3	4.4	3	2.2	1	1.7
6146	1	0.4	1	0.7	0	-	0	0	0	-
6314	8	2.8	4	2.8	1	1.5	3	2.2	1	1.7
6315	1	0.4	1	0.7	0	-	0	0	0	-
6316	5	1.8	2	1.4	0	-	3	2.2	0	-
6318	2	0.7	1	0.7	1	1.5	1	0.7	0	-
6335	2	0.7	0	0	0	-	2	1.5	1	1.7
6371	1	0.4	0	0	0	-	1	0.7	1	1.7
6373	9	3.2	5	3.5	1	1.5	4	3.0	2	3.4

As in the sponsor's population, the majority of patients came from center #5666.

The demographic characteristics of the MO evaluable population can be seen in Table 119.11.

Table 119.11
Demographic Characteristics of the FDA Evaluable Population:

Characteristics	Trovafloracin		Ofloxacin	
	N = 68		N = 58	
Age (years) 16 -44	21		24	
45 - 64	32		26	
≥ 65	15		8	
Mean	52.3		49.4	
Race: Asian	1		0	
Black	5		6	
White	60		50	
Hispanic	2		2	
Nat Am.	0		0	
Body weight (kg) mean	86		87.4	

The patients on both arms were comparable in terms of age, weight, and race.

EFFICACY:

Table 119.12
Bacteriologic Efficacy by Patient (as per the MO)

Timepoint	Trovafloracin			Ofloxacin		
	N	No. Erad.	%	N	No. Erad.	%
EOT	68	57	83.8	58	52	89.6
EOS	54	38	70.4	35	28	80.0

This table applied to complete eradication of the baseline pathogen only. A 95% CI with continuity correction factor (EOT), was: Trovafloracin versus Ofloxacin: -19.1%, 7.5 % ($\Delta = 15$). Thus, equivalence was not established. The sponsor also supplied a table for complete and partial eradication of the baseline pathogens (EOT), where the respective eradication rates were: trovafloracin 58/68 (85.3%) versus ofloxacin 53/58 (91.3%), 95% CI with continuity correction factor: -18.8%, 6.6%, ($\Delta = 10$). Equivalence was again not established although, the numerical differences were very small.

At the EOS, the 95% CI with continuity correction factor was - 30%, 10.7% ($\Delta = 20$). Once again, equivalence was not established. The sponsor also provided an analysis of bacteriologic response at the EOS , which included complete and partial eradication. In that analysis, the trovafloracin eradication rate was 40/54 (74.1%), versus 29/35 (82.9%) ofloxacin. The 95% CI with continuity correction factor was - 28.2%, 10.6% ($\Delta = 20$). Thus equivalence was not established.

A by-pathogen analysis is presented below:

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Table 119.13
Bacteriologic Efficacy by Pathogen at EOT: (All MO Evaluable Patients)

Pathogen	Trovafoxacin			Ofloxacin		
	N	No. Erad	%	N	No. Erad	%
<i>Escherichia coli</i>	13	12	92.3	16	16	100
<i>Enterococcus faecalis</i>	14	11	78.6	14	11	78.6
<i>Enterococcus spp.</i>	2	2	100	-	-	-
<i>Klebsiella pneumoniae</i>	6	4	66.7	1	1	100
<i>Proteus mirabilis</i>	1	1	100	1	1	100
<i>Enterobacter aerogenes</i>	4	4	100	-	-	-
<i>Enterobacter cloace</i>	1	1	100	3	3	100
<i>Citrobacter diversus</i>	-	-	-	1	1	100
<i>Pseudomonas aeruginosa</i>	2	1	50	2	1	50
<i>Pseudomonas maltophilia</i>	1	1	100	-	-	-
<i>Staphylococcus aureus</i>	1	1	100	1	1	100
<i>Staphylococcus epidermidis</i>	10	8	80	6	5	83.3
<i>Staphylococcus saprophyticus</i>	2	2	100	2	2	100
<i>Staphylococcus haemolyticus</i>	6	4	66.7	8	8	100
<i>Staphylococcus hominis</i>	2	2	100	2	2	100
<i>Staphylococcus simulans</i>	1	1	100	-	-	-
<i>Staphylococcus spp.</i>	2	2	100	-	-	-
<i>Streptococcus anginosus</i>	-	-	-	1	0	0
<i>Streptococcus bovis</i>	-	-	-	1	1	100
<i>Streptococcus mitis</i>	-	-	-	1	1	100
<i>Streptococcus salivarius</i>	1	1	100	-	-	-
<i>Streptococcus sanguis I</i>	1	1	100	-	-	-
<i>Streptococcus sanguis II</i>	1	1	100	1	1	100
<i>Streptococcus spp.</i>	-	-	-	1	1	100
Total	71	60	84.5	62	56	90.3

A CI was not performed for this analysis as a patient could have had more than one bacterial isolate.

For *Escherichia coli* and *Enterococcus faecalis*, the additive eradication rates were: 23/27 (85.1%) trovafoxacin versus 27/30 (90%) ofloxacin. A CI was not applied but the 2 agents appeared numerically comparable for these traditional pathogens. The MO's evaluability criteria excluded most of the Coagulase-negative staphylococcal isolates. However, the MO would contest the sponsor's claim of superiority of trovafoxacin versus ofloxacin for these organisms. As no approvals have been granted previously for coagulase-negative staphylococci, the MO does not recommend approval for trovafoxacin either as not only is the number of isolates too small to be granted an indication but superiority could not be established.

Table 119.14
Clinical Efficacy (MO Bacteriologically Evaluable Population)

Timepoint	Trovafoxacin			Ofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	68	62	91.1	58	52 (51)*	89.7 (87.9)*
EOS	56	37	66.1	39	23	59

*no. in parentheses refers to final no. of evaluable patients/see table 119.9

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The 95% CI: - 10.4%, 13.5% (with CCF), applied by the MO at the EOT, did not establish the equivalence of trovafloxacin versus ofloxacin ($\Delta = 10$) for the primary efficacy variable. The EOS 95% CI was - 14.9, 29% ($\Delta = 20$).

However, the revised outcomes (in parentheses), did establish equivalence with a lower bound of the 95% CI with continuity correction factor of 9.1%, (see discussion below).

There were 6 patients on each arm (6/68 (8.8%), trovafloxacin versus 7/58 (12%) ofloxacin) who were clinical failures associated with persistence of the baseline pathogen.

Therefore the 2 agents were clinically equivalent (primary efficacy variable), but bacteriologic equivalence (secondary efficacy variable), was not established. The 2 agents appeared to be numerically comparable for the primary pathogens associated with acute or acute exacerbations of chronic prostatitis, that is *Escherichia coli* and *Enterococcus faecalis*.

Cross Tabulation of Clinical and Bacteriological Efficacy at the EOT for FDA Evaluable Population:

From the line listings provided by the sponsor, the MO found that of the 68 evaluable trovafloxacin patients, 53/68 or 77.9 % of the patients were clinical successes with complete eradication, 0/68 clinical successes had only partial eradication and 9/68 (13.2%) clinical successes had inconsistent results with bacteriologic failure. Additionally there were 4/68 (5.9%) clinical failures associated with complete eradication, 1 clinical failure with partial eradication (1/68 (1.5%) and 1/68 (1.5%) clinical failure with persistence of the baseline pathogen. Therefore, on the trovafloxacin arm, there were 14 patients with inconsistent results between clinical success and bacteriological eradication.

On the ofloxacin arm, there were 49/58 (84.4%) clinical successes with complete eradication, 1/58 (1.7%) with clinical success and partial eradication and 2/58 (3.4%) clinical success with bacteriologic persistence. Additionally, there were 2/58 (3.4%) clinical failures with complete eradication, 0/58 clinical failures with partial eradication and 3/58 (5.2%) clinical failures with persistence. Therefore, there were 4 patients with inconsistent results and an additional 1 with partially inconsistent results on the ofloxacin arm.

Because the CIs for clinical success and bacteriologic eradication between the 2 arms were very close (lower bound: - 10.4%) for clinical response), the MO determined that this difference was negligible. The MO elected to evaluate those patients with partial eradication separately, in order to assess the value of retaining them in the analysis. These patients with partial eradication were reviewed below:

Trovafloxacin:

- #56690297: 66 YO with multiple organisms isolated in baseline culture (primary pathogen was *Enterococcus* spp.). This organism was persistent at days 35 and 64. It was the MO's determination that this patient was a clinical failure with complete persistence.

The patient had already been counted as a clinical failure (primary efficacy variable).

Ofloxacin:

- #58360286: 76 YO with 3 baseline pathogens: *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus epidermidis*. *Escherichia coli* was completely eradicated at day 57 but there were 1000 colonies each of *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*. This patient was classified as a clinical success with partial eradication by the sponsor and as a "relapse" by the investigator. The MO determined that this patient should be a clinical failure with partial persistence.

This change in outcome, changed the clinical efficacy to trovafloxacin 62/68 (91.2%) versus ofloxacin 51/58 (87.9%); 95% CI with continuity correction factor: -9.1%, 15.6% ($\Delta = 10$).

Although the Reviewer recognized that outcome could potentially change on other patients, if a case-by case review was performed, the MO also determined that trovafloxacin and ofloxacin were equivalent. The difference of 1 patient on the 95% CI associated with the primary efficacy variable, although critical, was in this case negligible, in that the sponsor's results were very close to the Δ of 10, thus not justifying a redetermination of outcome in every patient.

Recurrences:

The sponsor provided a table of clinical recurrences by arm. There were 9 recurrences on the trovafloxacin arm and 10 on the ofloxacin. These cases with their causative pathogens, are listed below:

Trovafloxacin (N = 9):

- 56300018: *Enterococcus faecalis/Staphylococcus aureus*.
- 56300355: *Escherichia coli*.
- 56570315: *Staphylococcus epidermidis*
- 58360287: *Staphylococcus epidermidis*
- 60310224: *Staphylococcus epidermidis*
- 61050330: *Klebsiella pneumoniae*
- 61280123: *Enterococcus faecalis*
- 61300109: *Staphylococcus epidermidis*
- 63730281: coagulase-negative staphylococcus

Ofloxacin (N = 10):

- 50050006: Coagulase-negative staphylococcus
- 56300017: *Escherichia coli, Klebsiella pneumoniae*
- 56300019: *Escherichia coli*
- 56420198: *Staphylococcus epidermidis*
- 56450327: *Escherichia coli*
- 56660042: Coagulase-negative staphylococcus
- 56660146: *Staphylococcus haemolyticus*
- 56690235: *Staphylococcus haemolyticus*
- 58360286: Reclassified as failure (see above).
- 60370103: *Staphylococcus aureus*

The MO agreed with the sponsor's determination of recurrence on all patients with the exception of 1 patient on the ofloxacin arm who should have been classified as a failure at the TOC.

The only trend noted by the MO was that 5/9 cases of recurrence on each arm were associated with coagulase-negative staphylococci.

Overall, the MO determined that 8/9 trovafloxacin recurrences and 8/9 ofloxacin recurrences were seen in patients who had improved at the TOC.

Safety Review:

25/142 (18%) trovafloxacin subjects and 9/133 (7%) ofloxacin subjects discontinued therapy because of an adverse event. 20 of the discontinuations on the trovafloxacin arm and 8 on the ofloxacin arm were determined to be related to the study drug. The remainder were discontinued because of adverse events that were attributed to other causes.

The most common adverse events leading to discontinuation on the trovafloxacin arm were related to the central nervous and peripheral nervous systems, with 14/142 subjects or 10% discontinued because of one or more of the following: headache (7), dizziness (12), and confusion (1).

On the ofloxacin arm the system most affected was the gastrointestinal, with 5/133 (4%) of subjects discontinued because of one or more of the following: nausea (3), diarrhea (2), and abdominal pain (2).

There were 4 trovafloxacin and 2 ofloxacin subjects who were temporarily discontinued from therapy due to adverse events. These patients are listed below:

Trovafloxacin (N = 4):

- #56480206: viral infection day 8, unrelated to study drug.
- #56660377: back pain secondary to an injury on day 6, resolved on day 13.
- #61030290: facial rash day 18, related to study drug, resolved on day 20.
- #63730284: dizziness day 3, associated with nausea, sweating, blurry vision, and nervousness. All were thought to be study drug related and resolved on day 8.

Ofloxacin (N = 2):

- #5660218: severe chest pain day 2, unrelated to the study drug. Event resolved.
- #56690053: moderate diarrhea day 3, related to the study drug, resolved the same day.

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

Table 119.15
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin	Ofloxacin
Number of Subjects Treated	142 (100%)	133 (100%)
Subject-Days of Exposure	1468	5214
Subjects With At Least One Event	114 (80%)	95 (71%)
Number of Adverse Events	238	193
Subjects with Serious Adverse Events	2 (1%)	3 (2%)
Subjects with Severe Adverse Events	13 (9%)	9 (7%)
Subjects Discontinued Due to Adverse Events	24 (17%)	9 (7%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	4 (3%)	2 (2%)
Subjects Discontinued Due to Objective Test Findings	5 (4%)	0
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

2 trovafloxacin patients and 3 ofloxacin patients had serious AEs, and 13 and 9 per arm respectively had severe AEs.

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Table 119.16
Adverse Events by Body System, All Causality (Modified Table of Sponsor Table 6.2)

	Trovfloxacin		Ofloxacin	
NUMBER OF SUBJECTS:				
Evaluable for Adverse Events	142	(100%)	133	(100%)
Subjects With At Least One Event	114	(80%)	90	(45%)
Subjects Discontinued due to Adverse Event	24	(17%)	9	(7%)
ADVERSE EVENTS BY BODY SYSTEM:				
Appl./ Inj./ incision/ Insertion Site	0	-	1	(< 1%)
Autonomic Nervous	8	(6%)	6	(5%)
Cardiovascular	6	(4%)	9	(7%)
Centr. & Periph. Nerv.	66	(46%)	21	(16%)
Gastrointestinal	51	(36%)	41	(24%)
General	20	(14%)	20	(9%)
Hematopoietic	0	-	2	(2%)
Musculoskeletal	5	(4%)	8	(2%)
Neoplasms	1	(< 1%)	0	-
Other Adverse Events	3	(2%)	3	(2%)
Psychiatric	17	(12%)	28	(21%)
Reproductive	3	(2%)	1	(< 1%)
Respiratory	8	(6%)	19	(14%)
Skin/ Appendages	10	(7%)	3	(2%)
Special Senses	6	(4%)	8	(6%)
Urinary System	3	(2%)	2	(2%)

Table 119.17
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovfloxacin		Ofloxacin	
NUMBER OF SUBJECTS:				
Evaluable for Adverse Events	142	(100%)	133	(100%)
Subjects With At Least One Event	61	(43%)	39	(29%)
Subjects Discontinued due to Adverse Event	20	(14%)	8	(6%)
ADVERSE EVENTS BY BODY SYSTEM:				
Autonomic Nervous	4	(3%)	1	(< 1%)
Cardiovascular	1	(< 1%)	0	-
Centr. & Periph. Nerv.	40	(28%)	9	(7%)
Gastrointestinal	28	(20%)	23	(17%)
General	4	(3%)	4	(3%)
Psychiatric	7	(5%)	15	(11%)
Skin/ Appendages	7	(5%)	1	(< 1%)
Special Senses	4	(3%)	4	(3%)

Overall and as noted in previous trials, the most frequent AEs were from the CNS and GI systems. The % of nervous system AEs is approximately four times as high for the trovafloxacin patients as compared to the ofloxacin, as opposed to the GI-related AEs where there was a similar number between the arms in this trial. The further breakdown of these events can be found on the MO's Table 119.17.

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Table 119.17
Most Common AEs/Treatment-related/All Treated Patients (as per the MO)

	Trovafoxacin N = 61		Ofloxacin N = 39	
		(28%)		(7%)
Nervous System	40		9	
Headache	18	13	4	3
Dizziness	32	23	5	3
GI System	28	20	23	17
Nausea	15	11	9	7
Constipation	6	4	4	3
Dyspepsia	2	1	4	3
Diarrhea	2	1	7	5
Abdominal Pain	1	<1	4	3

Other events of note included a rash, maculopapular, in 7 (7%) trovafoxacin-treated patients and 1 (<1%) ofloxacin-treated patient, abnormal vision in 2 (1%) trovafoxacin-treated patients and 3 (2%) ofloxacin-treated patients, and insomnia in 1 (<1%) trovafoxacin-treated patient and 11 (8%) ofloxacin-treated patients.

The AE profile in this trial was similar to that seen in the previously reviewed indications and no deaths were reported.

Listed below are the severe adverse events that were considered treatment-related:

Trovafoxacin (7 patients:9 events):

- #60360161: 42 YO dizziness, vertigo, vomiting (all severe) as well as flushing at day 2, discontinued.
- #63730336: 40 YO with dizziness on the first day of therapy that resolved and the patient completed therapy.
- #50050441: 58 YO with headache and toothache, discontinued on day 26.
- #60360388: 61 YO with headache and nausea (moderate) on day 2, discontinued.
- #60360397: 42 YO with headache and anxiety from day 1, discontinued R/x on day 9.
- #61050393: 70 YO with headache on day 3, discontinued from R/x.
- #61050267: 72 YO with maculopapular rash day 34, which was after active therapy had been discontinued.

Ofloxacin (4):

- #56610403: abdominal pain
- #63730334: 36 YO with sever diarrhea, day 2, resolved day 5, therapy was continued. Also had other GI complaints of a mild nature.
- #56610436: 56 YO with dyspepsia starting on day 2 of therapy through day 49. Also had intermittent headache and insomnia of mild severity, evaluable patient.
- #56310066: 63 YO with allergic reaction manifested as a macular/pap rash and itching day 10, discontinued..

Clinical Laboratory Abnormalities:

The sponsor submitted tables 4.1, 4.2, 6.1, and 3.3, which contained listings of patients who discontinued therapy because of laboratory abnormalities.

5 trovafloxacin-treated subjects were discontinued due to increased LFTs that were considered treatment-related by the investigator: (copied from the study report, pages 58 and 59):

#56670045: 71 YO with a history of arthritis, received trovafloxacin for 28 days followed by placebo. This subject developed liver function test abnormalities on Day 34 and was discontinued from treatment. The subject's LDH value, which was within the normal range at baseline, increased to above the normal range on Day 34, returned to within the normal range on Day 49 and remained within the normal range until Day 64, after which it was not re-measured. The subject's SGOT and SGPT values, which were within the normal range at baseline, increased to above the normal range on Day 34 and remained elevated until Day 146, when they both returned to within the normal range

LDH (U/L)	SGOT (U/L)	SGPT (U/L)	LDH (U/L)	SGOT (U/L)	SGPT (U/L)
Baseline			Day 64		
Day 3			Day 70		
Day 17			Day 77		
Day 34			Day 83		
Day 41			Day 90		
Day 44			Day 97		
Day 49			Day 112		
Day 56			Day 146		
Normal Range			Normal Range		

#56690233: 94 YO with a history of hypertension, received trovafloxacin for 29 days followed by placebo. This subject developed liver function test abnormalities on Day 35 and was discontinued from treatment on Day 36. The subject's SGOT and SGPT values, which were within the normal range at baseline, increased to above the normal range on Day 35 and remained elevated until Day 105 and Day 160, respectively.

SGOT (U/L)	SGPT (U/L)	SGOT (U/L)	SGPT (U/L)
Baseline		Day 48	
Day 3		Day 55	
Day 8		Day 76	
Day 20		Day 84	
Day 35		Day 105	
Day 42		Day 160	
Normal Range		Normal Range	

#60370101: 50 YO with a history of hypertension, received trovafloxacin for 28 days followed by placebo. This subject developed liver function test abnormalities on Day 5 with an SGPT level that increased from within the normal range at baseline to above the normal range. On Day 34, the subject's SGOT increased from normal at baseline to above the normal range and the subject was discontinued from treatment. Although resolving, the subject's SGOT and SGPT values remained above the normal range at his final laboratory evaluation (Day 65).

SGOT (U/L)	SGPT (U/L)	SGOT (U/L)	SGPT (U/L)
Baseline		Day 37	
Day 5		Day 41	
Day 21		Day 55	
Day 34		Day 65	
Normal Range		Normal Range	

#61050034: 67 YO with a history of insomnia, received trovafloxacin for 28 days followed by placebo. The subject's SGOT and SGPT values increased from within the normal range at baseline to above the normal range on Day 35 when he was discontinued from treatment. Although resolving, the subject's SGOT and SGPT levels remained above the normal range at his final laboratory evaluation (Day 90).

	SGOT (U/L)	SGPT (U/L)		SGOT (U/L)	SGPT (U/L)
Baseline			Day 49		
Day 5			Day 56		
Day 21			Day 63		
Day 35			Day 70		
Day 37			Day 77		
Day 41			Day 90		
Normal Range			Normal Range		

#61050035: 44 YO received trovafloxacin for 28 days followed by placebo. The subject's SGOT and SGPT values increased from within the normal range at baseline to above the normal range on Day 33, when the subject was discontinued from treatment. The subject's SGOT value remained above the normal range until Day 52 and his SGPT value remained above the normal range until Day 63.

	SGOT (U/L)	SGPT (U/L)		SGOT (U/L)	SGPT (U/L)
Baseline			Day 38		
Day 3			Day 45		
Day 18			Day 52		
Day 33			Day 63		
Normal Range			Normal Range		

None of the subjects in the ofloxacin group was discontinued from treatment due to abnormal laboratory test results.

In addition to the above, the sponsor provided a separate listing of patients with elevated LFTs where the investigator did not consider the abnormalities related to the study drug. This listing consisted of 14 trovafloxacin and 1 ofloxacin patient. 4 of the patients listed above were included in this second listing as well as an additional 10 trovafloxacin patients (9 with LFTs ≥ 3 x normal and 1 with ≥ 2 x normal) and 1 ofloxacin patient. Summaries of these patients are provided below (copied from Appendix 1 of the study report):

APPENDIX 1
 12/19/95

Trovafloxacin (N = 10)

#50140269:

This 73-year-old male entered the study on November 1, 1995 and received 36 days of study drug (28 days active then placebo). The subject's SGPT and SGOT values began rising on Day 36. The subject considered himself a clinical failure and with the approval of the site, discontinued his medication that day. The subject's SGPT and SGOT levels peaked on Day 50 reaching respectively and remained above the normal range. On Day 40 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: negative
 CMV IgM CMV IgG:

The subject was prescribed 30 days' worth of ofloxacin on Day 36. Concurrent medications taken by the subject included Motrin and aspirin for arthritis, Alupent and Beconase for emphysema, and Cardura for benign prostatic hypertrophy. He had no history of related liver function problems. He had no history of alcohol abuse. He was asymptomatic.

The investigator did not believe that the elevated LFT values were clinically significant, nor did the investigator attribute these levels to any particular causality. At the subject's last visit on Day 76, LFT values had not yet returned to normal. At that time, the investigator determined that the subject would no longer be seen in connection with the study.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Day 1		
Day 5		
Day 19		
Day 36		
Day 40		
Day 50		
Day 71		
Day 76		
Normal Ranges		

#56300355: This 50-year-old male entered the study on December 11, 1995 and received 33 days of study drug (28 days active then placebo) was temporarily discontinued for nine days. The subject's SGPT and SGOT values began rising on Day 33, and peaked on Day 48, respectively. The subject completed study drug on Day 42.

Concomitant medications included Tagamet from Day 64 until Day 78 for hyperacidity; Vasotec from 01/–/87 to Day 92 for hypertension; Procardia from Day 92 to present for hypertension; Xanax from Day 92 to present for anxiety; Tenorin from 01/–/87 to present for prostatitis symptoms; Prozac from Day 44 to Day 49 for depression; Phygeum and Saw Palmetto during March 1996 for prostate enlargement. The subject had no history of related liver function problems. He claimed to have consumed more alcohol than "normal" on Day 46, but otherwise described himself as a moderate drinker. He was asymptomatic.

The investigator attributed the LFT abnormalities to the study medication. The subject's SGPT/SGOT values returned to normal as of Day 147.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 5		
Day 22		
Day 33		
Day 47		
Day 48		
Day 54		
Day 64		
Day 78		
Day 92		
Day 147		
Normal Range		

#56480205: This 65-year-old male entered the study on December 7, 1995 and received 31 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 35 and peaked on Day 49 respectively. The subject completed the study drug dosing on Day 42.

Concomitant medication during study drug dosing included Vasotec for hypertension, potassium supplement, multivitamin, Vitamin C, Vitamin B complex, Vitamin E, Prozac for depression and Cardura for benign prostatic hypertrophy. He had no history of related liver function problems nor any history of alcohol abuse. He was asymptomatic.

The investigator believed the study drug may have caused elevated LFTs. The subject's SGPT and SGOT values returned to normal.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 4		
Day 23		
Day 35		
Day 49		
Day 59		
Day 80		
Normal Range		

#56610401:

This 51-year-old male entered the study on January 3, 1996 and received 41 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 41, and peaked on Day 48, with values
The subject completed study medication.

The subject was not on any concomitant medication. He was asymptomatic. He had no history of alcohol or substance abuse.

The investigator attributed the elevated LFT values to the study medication. The subject's values were returning to normal when he was released from being seen for any further follow-up.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 5		
Day 19		
Day 41		
Day 48		
Day 78		
Day 89		
Day 105		
Normal Range		

56660257

This 73-year-old male entered the study on October 19, 1995 and received study drug for 24 days. SGPT and SGOT values began rising on Day 25, and peaked on Day 41, reaching , respectively. The subject discontinued study medication on his own on Day 24 because he believed it was making him constipated. On Day 41 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: neative
CMV IgM CMV IgG

No concomitant medication was taken during the time of study dosing. On Day 46 the subject was prescribed tetracycline for an ENT problem. The investigator switched the subject to Macrobid on Day 50 because he believed the tetracycline was affecting liver function values. The subject had no history of related liver function problems. He described himself as a moderate to heavy drinker and stated that he had been drinking the week prior to the Day 41 labs. He was asymptomatic.

The investigator attributed the elevated LFTs to a combination of excessive alcohol consumption, study drug dosing, and tetracycline dosing. At the last visit on Day 75 the subject's LFT values had almost returned to normal when he refused to be seen for any further follow-up.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 9		
Day 25		
Day 37		
Day 41		
Day 46		
Day 60		
Day 75		
Normal Ranges		

56660321:

This 56-year-old male entered the study on November 24, 1995 and received 42 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 36 and peaked on Day 44, respectively. The subject completed study drug treatment on Day 42. On Day 39 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: negative
 CMV IgM CMV IgG

The subject indicated that he did consume alcohol over the Christmas holiday vacation (the site inferred from the subject's statements that he may have over-indulged). Concomitant medication included Centrum vitamins only. He had a history of low back pain. He was asymptomatic.

The subject's LFT values returned to normal. The investigator determined causality as the study drug in conjunction with the subject's diet. The subject was eating fish between five and six times per week. The investigator believed that the toxins in the fish may have been preventing the LFT values from returning to normal. The investigator believed his assumption was confirmed as the subject stopped eating fish altogether and his LFT values began decreasing shortly thereafter. A summary of the subject's SGPT and SGOT results follows:

Visit	SGPT	SGOT
Screening		
Day 4		
Day 18		
Day 36		
Day 39		
Day 44		
Day 50		
Day 58		
Day 71		
Day 81		
Day 93		
Day 106		
Day 121		
Normal Ranges		

56690054:

This 77-year-old male entered the study on September 7, 1995 and received 42 days of study drug (28 days active then placebo). SGPT and SGOT values began rising on Day 37 and peaked on Day 51 respectively. The subject completed study drug on Day 42.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: negative

The subject's medical history included hypothyroidism and stomach ulcers. Concomitant medications included levothyroxine (since 1958) and ranitidine (since 1991). He had no history of alcohol abuse. The subject was asymptomatic.

The investigator attributed the elevated LFT values to the study drug. The SGPT and SGOT values returned to "normal." A summary of the subject's results follows

Visit	SGPT	SGOT
Screening		
Day 6		
Day 22		
Day 37		
Day 51		
Day 66		
Day 80		
Day 87		
Normal Ranges		

* noted as not clinically significant, per Investigator

#56690234:

This 82-year-old male entered the study on October 25, 1995 and received 17 days of study drug. SGPT and SGOT levels began rising at Day 35 and peaked on Day 42 (12/6/95), respectively. The subject was advised to discontinue his study medication on Day 17.

The subject visited the emergency room on Day 17 complaining of left arm pain and numbness. His medical history included congestive heart failure, angina, GI disorders, back pain, hypertension, and hiatal hernia. The ER physician discontinued the study medication on Day 17. Concomitant medications included Darvocet-N, nitroglycerin, Sectral, Dyazide, isosorbide, Mylanta, ibuprofen and Benadryl. The subject was prescribed Keflex on Day 27 for a genital rash. At Day 50, the subject was asymptomatic and feeling better than at previous visits. He had no history of alcohol abuse, nor any history of related liver function problems.

The investigator believed the study medication was most likely the cause of the elevated LFTs. The subject's SGPT and SGOT levels returned to normal.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening		
Day 5		
Day 21		
Day 35		
Day 42		
Day 49		
Day 57		
Day 77		
Normal Ranges		

#58460426:

This 61-year-old male entered the study on January 31, 1996. SGPT and SGOT values began rising on Day 33, and peaked on Day 50, respectively. The subject completed study drug on Day 42 (28 days active then placebo).

The subject's medical history included hypertension. Concomitant medications included Hytrin from 12/09/95 to 02/07/96 (Day 1); Procardia from 12/--/95 to present for hypertension; and Cozaar from 12/--/95 to present for hypertension. He denied any history of alcohol or substance abuse. He was asymptomatic.

The investigator attributed the elevated LFT values to the study medication. The subject's SGPT and SGOT values returned to normal.

A summary of the subject's results follows:

Visit	SGPT	SGOT
Screening	Not Done	Not Done
Day 3		
Day 20		
Day 33		
Day 50		
Day 75		
Normal Ranges		
<i>Primary Care Lab</i>		
<u>Visit</u>	<u>SGPT</u>	<u>SGOT</u>
Day 123		
Normal Ranges		

#60360386:

This 68-year-old male entered the study on December 8, 1995 and received study drug for 42 days (28 days active then placebo). SGPT, SGOT, LDH and total bilirubin values began rising on Day 28, with SGPT, SGOT and LDH peaking the same Day, respectively. The subject's total bilirubin level peaked on Day 46. He completed study drug dosing on Day 42. On Day 46 the subject had a positive CMV test by IgG antibodies.

Hepatitis B surface antigen: negative Hepatitis A IgM antibody: negative
 CMV IgM CMV Ig

Concomitant medications included water-soluble vitamins (e.g., beta-carotene and B-complex vitamins), and 50 micrograms of selenium. He had no history of alcohol abuse. The subject was asymptomatic.

The investigator attributed the causality of the elevated LFTs to the study medication. The subject's SGPT, SGOT and LDH levels returned to normal. Total bilirubin value was still above the upper limit of normal (0.2-1.2 mg/dL) at the subject's last visit; however this result was below the subject's screening visit value.

A summary of the subject's results follows:

Visit	SGPT	SGOT	LDH	Total bilirubin
Screening				
Day 4				
Day 18				
Day 28				
Day 46				
Day 50				
Day 57				
Normal Ranges				

Conclusions:

As per the Sponsor: (copied from page 63 of the study report and modified by the MO in Times New Roman font):

Trovafloxacin 200 mg QD administered for 28 days was statistically equivalent to ofloxacin 300 mg BID administered for 42 days for sponsor-defined clinical success rates one week post-therapy (101/113 (89%) trovafloxacin versus 96/11 (86%) ofloxacin).

Sponsor-defined subject bacteriological eradication rates one week post-therapy were comparable between both regimens (89/98 (91%) trovafloxacin versus 94/98 (96%) ofloxacin).

The analyses of pathogen eradication rates were similar between the treatment groups for frequently isolated pathogens, including *Escherichia coli* (13/14 (93%) trovafloxacin versus 18/18 (100%) ofloxacin), *Enterococcus faecalis* (14/17 (82%) trovafloxacin versus 15/18 (83%) ofloxacin), *Staphylococcus haemolyticus* (14/19 (74%) trovafloxacin versus 18/21 (86%) ofloxacin), *Staphylococcus epidermidis* (24/33 (73%) trovafloxacin versus 22/34 (65%) ofloxacin), and Coagulase-negative *Staphylococcus* (28/28 trovafloxacin versus 33/33 ofloxacin).

Both treatments were well tolerated, with similar percentages of subjects reporting adverse events. The most frequently reported treatment-related adverse events are those commonly associated with quinolone therapy including dizziness (23%), headache (13%), and nausea (11%) for subjects in the trovafloxacin group and insomnia (8%) and nausea (7%) for subjects in the ofloxacin group. Twenty of 142 subjects (14%) in the trovafloxacin group and eight of 133 subjects (6%) in the ofloxacin group were discontinued from treatment due to treatment-related adverse events. Four trovafloxacin subjects and three ofloxacin subjects reported serious adverse events, none of which was considered treatment-related. No deaths were reported.

A trend was observed for liver enzyme elevations after 3 to 4 weeks of trovafloxacin therapy, suggesting that subjects receiving prolonged treatment (≥ 21 days) may need to have periodic assessment of hepatic function.

Reviewer's Conclusion:

The MO determined that there were 68 patients clinically and bacteriologically evaluable on the trovafloxacin arm as compared to 58 on the ofloxacin arm. These numbers represented a significant decrease from the sponsor's evaluable population. This decrease was due to the application of strict criteria in order to ensure that the sponsor's evaluable population was indeed a "true prostatitis" population. Additionally, the MO wanted to ensure that a fair comparison was made between the 2 study arms. The longer duration of ofloxacin therapy and the different intervals for assessing the patients, as designed and implemented by the sponsor, did not adequately ensure this.

The MO ascertained, prior to the institution of the review, that this trial was designed and implemented in a manner very similar to that utilized for the approval of other quinolone products for this indication and that the protocol was designed in conjunction with the PTC document as well as IDSA guidance.

The MO and the sponsor differed as to the classification of the patients into a specific disease entity. Although the PTC document refers only to "bacterial prostatitis", the antimicrobial agent most recently approved for this indication, ciprofloxacin, was granted the indication as "chronic bacterial prostatitis." Because of the similarities in the populations studied, and after extensive review of the medical literature, the MO concluded that the population in this trial did indeed suffer from what could be termed as a "chronic bacterial prostatitis." This conclusion was not only based on the clinical picture but also on the bacteriology submitted.

In this submission, a significant number of patients presented with coagulase-negative staphylococci as their primary pathogen. The MO did not find evidence in the literature to support the sponsor's contention that all of the isolates submitted were true pathogens and therefore, sought to establish criteria which would

justify the inclusion of some of these organisms in the analyses. The MO did accept that chronic bacterial prostatitis may be associated with increased numbers of these isolates as compared to the more common *Escherichia coli* or *Enterococcus faecalis*, however, in the absence of literature verification and in the face of regulatory precedence wherein all submissions in the last 5 years have excluded this organism, the MO elected to accept only those that met the strict MO criteria.

Clinical efficacy, at the TOC, which was also the primary efficacy variable was 62/68 (91.1%) for the trovafloxacin-treated patients as compared to 51/58 (87.9%) for the ofloxacin-treated patients. The 95 % CI was -9.1%, 15.6%, thus establishing the clinical equivalence of the 2 agents.

Bacteriologic equivalence was not obtained with bacteriologic efficacy rates at the TOC by patient of 57/58 (83.8%) trovafloxacin compared to 52/58 (89.6%) ofloxacin. At the EOS which was only utilized in order to assess recurrence, the bacteriologic efficacy rates were 38/54 (70.4%) trovafloxacin versus 38/35 ofloxacin (80%). These overall EOS rates were comparable to those of previously approved quinolones. Specifically, ofloxacin (75%), norfloxacin (80%), ciprofloxacin (83.6%), and temofloxacin (97.2%).

The analyses of pathogen eradication rates also revealed higher ofloxacin eradication rates of: 60/71 (84.5%) trovafloxacin versus 56/62 (90.3%) ofloxacin (95% CI with CCF: -18.5%, 6.9%, ($\Delta = 10$), thus equivalence was not established.

The eradication rate for *Escherichia coli* was 12/13 (92.3%) trovafloxacin versus 16/16 (100%) ofloxacin.

The eradication rate for *Enterococcus faecalis* (11/14 (78.6%) trovafloxacin versus 11/14 (78.6%) ofloxacin) was equal to that of ofloxacin, but ofloxacin was not approved for this isolate. Only carbenicillin has been approved for this organism

Although not statistically significant, trovafloxacin and ofloxacin appear numerically comparable for these traditional pathogens.

As stated above, the MO's evaluability criteria excluded most of the coagulase-negative staphylococcal isolates. The MO disagrees with the sponsor's claim of superiority of trovafloxacin versus ofloxacin for this unspciated (by the sponsor), category of organisms. As no approvals have been granted previously for any speciated coagulase-negative staphylococci, the MO recommended approval only for *Staphylococcus epidermidis*. For trovafloxacin versus the other requested organisms, not only was the number of isolates too small to be granted an indication but also "superiority, as claimed by the sponsor" could not be established. Specifically, the eradication rates for the speciated requested pathogens were: *Staphylococcus haemolyticus* (4/6 (66.7%) trovafloxacin versus 8/8 (100%) ofloxacin), *Staphylococcus epidermidis* (8/10 (80%) trovafloxacin versus 5/6 (83.3%) ofloxacin, thus revealing numerical superiority of ofloxacin. Coagulase-negative staphylococci were not accepted by the MO for review unless speciated, therefore the sponsor's request to include this category of organisms was rejected.

A review of previous approvals, (see introduction), revealed that approvals have been issued in the past with similar numbers of bacterial isolates. Specifically, norfloxacin was approved with 15 isolates of *Escherichia coli* per arm, and temofloxacin was approved for *Enterococcus faecalis* with 16 isolates on the temofloxacin arm.

Alternatively, and applicable to this trial, no agent has been approved for prostatitis caused by a bacterial isolate that represented less than 10% of the evaluable pathogens.

Based on the above, the Reviewer recommends approval for the indication of prostatitis, expressed as "chronic bacterial prostatitis" due to *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus epidermidis*.

From a safety standpoint, the MO found, as did the sponsor that, 14/140 (10%) of treated patients developed increased transaminases to $\geq 3x$ normal after approximately 3 to 4 weeks of therapy. Additionally, 15/140 (10.7%) of patients developed an increase of transaminases to $\geq 2x$ normal. These abnormalities were not

associated in all cases, with clinical complaints or with concomitant increases in alkaline phosphatase, bilirubin, or GGT. The LFT abnormalities resolved after therapy with trovafloxacin was discontinued over the course of 6 – 10 weeks.

Other adverse events included headache (13%), dizziness (23%), and nausea (7%) and were consistent with those reported in the previously reviewed trials of urinary tract infections.

Recommended Regulatory Action:

The following statement can be added to the labeling:

ses:

/S/ 12/18/97
Regina Alivisatos, MD
Medical Officer, DSPIDPs

- Orig. NDA #20-759
- Orig. NDA #20-760
- HFD-590
- HFD-590/Div. Dir./MGoldberg */S/6*
- HFD-590/Dep. Dir./RALbrecht
- HFD-590/MTL/BLeissa */S/12/18/97*
- HFD-590/MO/RAlivisatos
- HFD-590/CSO/PFogarty
- HFD-725/Biostat/Silliman
- HFD-344/Thomas

Acute Exacerbation of Chronic Bronchitis:

The proposed indication as it will appear in the labeling if approved is:

Acute bacterial exacerbations of chronic bronchitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

The proposed dose is 100 mg PO daily for 7 - 10 days.

In support of this indication, the sponsor submitted three double-blind, comparative trials of the efficacy and safety of trovafloxacin at the proposed dose compared to ofloxacin 400 mg PO BID for 10 days (study 154-101), clarithromycin 250 mg PO BID for 7 days (study 154-109), and ciprofloxacin 500 mg PO BID for 7 days (study 154-141).

The MO located other documents within the electronic submission related to the pharmacokinetics and microbiological properties of trovafloxacin and the requested indication. These were summarized in the MOR.

Oral Antimicrobial Agents Currently Approved for this Indication:

Ofloxacin: (*Haemophilus influenzae* and *Streptococcus pneumoniae*)
 Ciprofloxacin: (LRTI: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
 Cefitin®: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*)
 Cefzil®: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
 Biaxin®: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
 Bactrim DS®: (*Haemophilus influenzae* and *Streptococcus pneumoniae*)
 Septra®: (*Haemophilus influenzae* and *Streptococcus pneumoniae*)
 Cedex®: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
 Lorabid®: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
 Maxaquin®: (*Haemophilus influenzae* and *Moraxella catarrhalis*)
 Spectobid®: (LRTI: *Haemophilus influenzae*, *Streptococcus pneumoniae*, beta hemolytic streptococci, and non-penicillinase producing staphylococci)
 Suprax®: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
 Vantin®: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)
 Sparfloxacin: (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterobacter cloacae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, and *Chlamydia pneumoniae*)
 Levofloxacin: (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*)
 Grepafloxacin: (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*)

Abbreviations used in this section:

Ofloxacin = Floxin®, Oflox
 URTI = upper respiratory tract infection
 LRTI = lower respiratory tract infection
 URT = upper respiratory tract
 LRT = lower respiratory tract
 AEBCB = acute exacerbation of chronic bronchitis
 CB = chronic bronchitis
 AB = acute bronchitis
 COPD = chronic obstructive pulmonary disease
 Biaxin = clarithromycin
 Cipro = ciprofloxacin
 Trovafloxacin = trovafloxacin

V1 = visit one or baseline visit on study day 1
V2 = visit 2, window: study days 3 -5
V3 = visit 3
V4 = visit 4
V5 = visit 5
EOT = End of Therapy
EOS = End of Study
TOC = Test of Cure
AE = Adverse Event
PTC = Points-to-Consider
ELF = epithelial lining cells
MSSA = methicillin-sensitive *Staphylococcus aureus*
MRSA = methicillin-resistant *Staphylococcus aureus*
PMN = polymorphonuclear
AC = advisory committee
AE = adverse event
UTI = urinary tract infection

Materials Reviewed for this Indication:

Electronic submission/December 29, 1996
Fax/July 28, 1997 containing data related to study 101
Fax/July 31, 1997 containing tables related to studies 101, 109, and 141

Background:

Chronic bronchitis is a clinical diagnosis, loosely applied to patients who cough up sputum on most days, during at least three consecutive months for more than 2 successive years. 3 factors that contribute to CB are cigarette smoking, infection, and inhalation of fumes in the workplace. This disease affects about of the adult population and is more common in men than in women as well as in the > 40 years of age group.

Objective findings of a superimposed acute infection are not always obvious. Patients complain of increased sputum production as well as a change in the color and consistency of the sputum. Purulent sputum may or may not be evidence for an AECB. Other symptoms include increasing cough and dyspnea but most patients do not have systemic findings of an acute infectious process (chills and fever).

The evaluation of sputum samples is helpful in establishing the diagnosis. The presence of eosinophils is presumptive evidence of a noninfectious process and the presence of many epithelial cells would indicate a poor specimen. Routinely a gram stain of sputum of patients with CB shows a mixture of gram-positive and gram-negative flora, consistent with contamination by normal oral flora or with tracheal colonization with *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. This colonization can occur in up to of patients. Usually the colonizing isolates are unencapsulated. These organisms can persist in sputum during quiescence.

The following statements can be made:

- Chronic colonization of the airways and sputum with unencapsulated strains of *Haemophilus influenzae* and pneumococci occurs in at least 50% of the affected CB population.
- Many physicians usually attribute an AECB to one or the other organism. *Moraxella catarrhalis* can also be found in up to 17% of the cases.
- Other bacteria such as hemolytic species of streptococci, *Staphylococcus aureus*, and gram-negative enteric bacilli are infrequent causes of AECB

- *Mycoplasma pneumoniae* infections can be responsible for some AECB, although sporadic
- Viruses are frequent causes of AECB, occurring in up to _____ of cases
- Standard chest radiographic films serve the purpose of excluding other diseases such as pneumonia and because they do not confirm the diagnosis of AECB, they are not a useful tool with which to follow patients.

In terms of management of AECB, prophylactic antimicrobial therapy has been found to decrease the number of exacerbations in those who experience more than 4 episodes a year. Additionally, it is generally accepted in clinical practice that the treatment of an AECB with a 7 - 10 day course of antimicrobial therapy decreases the duration of the episode and the incidence of respiratory decompensation associated with it. The mainstays of treatment include antimicrobials effective against the 3 main pathogens. Steroids are also often used in those case where patients do not respond to improved pulmonary toilet and antimicrobials.

Mandell, Douglas, and Bennett's principles and Practice of Infectious Diseases, Fourth edition, pages 608 - 612.

The FDA PTC document suggests that 2 trials are necessary in order to attain approval for the indication of AECB. One should be a statistically adequate and well-controlled trial establishing equivalence or superiority to an approved product. In this trial, patients should be clinically and microbiologically evaluable.

The second study, in which clinical effectiveness should be used as the primary endpoint, does not require that each patient be bacteriologically evaluable. Rather 2 groups of patients should be analyzed; those who were clinically evaluable and a subset of this group who were clinically and microbiologically evaluable.

Although the PTC document states that only *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* should be listed as pathogens, recent regulatory precedence with sparfloxacin indicates the change in approach recently instituted by the Division as regards to bacterial pathogens.

Current IDSA Guidelines for the evaluation of anti-infective drug products, Vol. 15, suppl. 1, Nov. 1992, pages S77 - S80, suggest the following:

The minimal diagnostic criteria permitting the inclusion of patients in clinical trials are:

- the presence of the underlying diagnosis of CB, defined as the presence of a chronic cough for > 2 consecutive years and on most days for 3 consecutive months, and
- the presence of evidence of an acute exacerbation as indicated by the combination of increased cough and/or dyspnea, increased sputum volume or purulence
- the presence of a negative chest radiograph to rule out pneumonia
- the production of purulent sputum defined as the presence on gram stain of > 25 PMN leukocytes and < 10 squamous epithelial cells per low-power magnification, with a predominant bacterial morphology.

In addition to the above, the trial should include only adult patients (≥ 18), who are able to give informed consent. The use of steroids is not necessarily grounds for exclusion. Patients suffering from cystic fibrosis should be excluded.

The duration of treatment should be 7 - 10 days and patients who worsen or who do not improve after 3- 5 days should be removed from the study and classified as clinical failures. The addition of an antimicrobial that is not a study drug should also result in the designation of clinical failure.

The clinical response should be classified as clinical cure, clinical improvement, clinical failure, and indeterminate. Patients should be evaluated at 3 – 5 days after the initiation of therapy and weekly thereafter.

The definitions of clinical response are as follows:

- Clinical cure: the resolution of acute signs and symptoms to a baseline level of dyspnea, cough, sputum production, and , if elevated at enrollment, resolution of fever.
- Clinical improvement: the subjective improvement in dyspnea with reduction in cough, a quantified reduction in 24-hour volume or purulence of sputum and a return of the temperature to normal if initially elevated.
- Clinical failure: the lack of any resolution in the signs and symptoms of the disease.
- Indeterminate: must be substantiated by stated reasons.

The definitions of microbiologic response include:

- Eradication
- Persistence
- Relapse
- Reinfection
- Superinfection.

Clinical and microbiologic reassessment should be done within 48 hours, 7 – 14 days, and 21 – 28 days after completion of therapy.

The current guidance for evaluability criteria of the DAIDP recently addressed the issue of AECB. Amongst the points that were stressed, were:

- The differentiation of an AECB as opposed to a SBIAC (subacute bacterial infection of acute bronchitis), in other words, a true bacterial infection in a population of CB patients from a viral, atypical, or bacterial infection in a population of patients with AB.
- The exclusion of patients on steroid therapy
- The prerequisite of . of therapy for evaluability
- The “optional” EOT visit, as this visit cannot be used as the TOC
- The “required” TOC visit at 1 – 2 weeks after completion of therapy
- Clinical outcome as the primary efficacy variable
- The preference of the division to avoid the category of “improved”
- The addition of the microbiologic response categories of “presumed eradication” and “presumed persistence” and the elimination of the category of “relapse,” while maintaining the categories of “superinfection, reinfection, and colonization.”

The DAIDP advisory committee agreed to all of the above.

Medical Officer's Comment: *The MO determined that there was concurrence from all sources as to the criteria utilized in the diagnosis of an AECB as well as in the design and implementation of clinical trials to assess the efficacy and safety of new agents for this entity.*

The MO adhered to these criteria and made the following determinations with regards to evaluability criteria:

- *The diagnosis of an underlying CB with an acute exacerbation must be well established.*

The sponsor adequately provided this information. A review of the CRFs revealed that the investigators not only had to verify the presence of increased cough, sputum production, increased purulence, dyspnea, and in study 101 only, the presence of fever, but additionally had to obtain a chest radiograph to exclude an underlying pneumonia as well as a sputum culture to assess not only for purulence but also for a predominant organism.

Additionally, the investigator was able to provide in written form, the duration of the underlying CB as well as the duration of the current episode of AECB.

- *The MO carried forward any patient who received any additional antimicrobial during the study as an evaluable failure. Failure was determined after 2 full days of therapy. This was consistent with the protocol design wherein the investigators were able to determine failure on the second day of therapy.*
- *The MO did not consider evaluable those patients who received an alternative antimicrobial within 72 hours of the start of the study, unless the prerequisite clinical and microbiologic criteria were present (that is the isolation of a predominate pathogen on culture in association with the clinical picture of AECB).*
- *The MO excluded patients on steroid therapy or provided separate analyses of clinical response if they were not excluded.*
- *The MO adhered to the categories of clinical and microbiologic assessment as described above in the IDSA Guidelines with the modifications of the advisory committee. This included the use of the primary efficacy variable of clinical response as a determinate of microbiologic outcome. That is, a patient who was cured was assumed to have "eradication/presumed eradication" of the primary pathogen or alternatively, a patient who failed was assumed to have "persistence/presumed persistence" of the primary pathogen.*
- *The MO assessed cure and improvement together in order to provide a dichotomous "cure/fail" analysis.*
- *The MO determined that the TOC should be applied to the EOS visit. This determination differed from that of the sponsor where the primary efficacy variable, clinical response, was applied to the EOT. The logical continuation of this argument was that a patient who was not seen at the later follow-up visit was not evaluable. If, however, the sponsor excluded a patient because they were not seen at the EOT but were seen at the later visit, the MO determined that this patient was evaluable. All failures were carried forward.*
- *Patients were eligible for classification as clinical cures if they received between 80 – 120 % of the study drug or between 5 – 8 days and 10 – 12 days of therapy for the 7 day pivotal studies.*
- *The windows of evaluability provided for by the sponsor were not changed for the EOS as the MO TOC was at the EOS (or 1 – 2 weeks after the EOT), and therefore sufficiently far out from therapy that the presence of active drug or post-drug effect could be excluded.*

The MO reviewed the sponsor's evaluability criteria and general approach in this introduction. Although study 101 was a phase II study as opposed to 109 and 141 which were phase III studies, there were minor differences between them only and these were pointed out in this section. Subsequent to the introduction, each study was reviewed separately and the MO referred back to this introductory section.

Microbiology:

In support of the effectiveness of trovafloxacin against the requested pathogens, the sponsor submitted, (microbiology section of the electronic submission), the results of microbiology studies of trovafloxacin versus the requested pathogens. These MIC-90 results are summarized below:

Streptococcus pneumoniae: 0.06 - 0.25 mcg/mL

Penicillin-resistant pneumococci:

Moraxella catarrhalis:

Haemophilus influenzae.

APPROVED FOR
CIVILIAN

Pharmacokinetics:

The sponsor provided 2 studies assessing the penetration of orally administered trovafloxacin into the bronchial tree (study 154-016: an open study to assess concentrations of trovafloxacin in bronchial washings and serum after administration of a single dose to subjects undergoing bronchoscopy and 154-020: an open study to assess the concentration of trovafloxacin in bronchial mucosa, epithelial lining fluid, and alveolar macrophages compared to that of serum after administration of single and multiple oral 200 mg doses to subjects undergoing fiber-optic bronchoscopy). The pharmacokinetics reviewer reviewed these studies, however, for the purposes of this review, they are briefly reviewed here.

APPROVED FOR
CIVILIAN

Study 154-020:

This open, multiple group study assessed the penetration of orally administered trovafloxacin into bronchial mucosa, epithelial lining fluid, and alveolar macrophages obtained by bronchial lavage during bronchoscopy at 6, 12, and 24 hours after the administration of a single dose of 200 mg trovafloxacin, and 6 hours after the fourth and final dose of a multiple dose regimen of trovafloxacin 200 mg. Nineteen subjects, (15 male and 4 female), ranging in age _____ participated in the single dose arm and 9 subjects, (7 male and 2 female), ranging in age _____ participated in the multidose arm of the study. Among those subjects in the single dose arm, trovafloxacin was administered 6 hours prior to scheduled bronchoscopy in six subjects, 12 hours prior to scheduled bronchoscopy in six subjects, and 24 hours prior to scheduled bronchoscopy in seven subjects. All nine subjects in the multidose arm received their final dose of trovafloxacin 6 hours prior to the scheduled bronchoscopy.

Trovafloxacin concentrations were determined in bronchial mucosal tissue, epithelial lining fluid, and macrophages. Serum concentrations of trovafloxacin were also determined for the calculation of the tissue/serum drug concentration ratio. Seventeen of the 19 subjects in the single dose arm and all nine of the subjects in the multiple dose arm were included in the pharmacokinetic analysis (i.e., had trovafloxacin concentrations determined for serum and at least one of the three tissue samples).

After single doses of trovafloxacin, the mean bronchial mucosal tissue to serum concentration ratios were 1.1 and 1.2 at 6 and 12 hours, respectively.

The mean ELF to serum concentration ratio was 2.3 at 6 hours after dosing and was maintained at 2.2 at 24 hours after dosing. The mean macrophage to serum concentration ratios were 13.3 and 16.3 at 6 and 12 hours after dosing, respectively, and reached 22.4 at 24 hours after dosing.

Multiple dose administration of trovafloxacin resulted in a similar mean mucosal tissue to serum concentration ratio (1.1) and even greater ELF to serum and macrophage to serum ratios (5.8 and 24.1, respectively) when compared to single dosing.

Study 154-016:

This open study assessed the penetration of trovafloxacin into bronchial mucous and bronchial epithelial cells and macrophages obtained by bronchial lavage during bronchoscopy. Twenty-six subjects, (17 female and 9 male), ranging in age entered and completed this study. Bronchial tissues and fluids were collected by bronchial lavage 4 to 6 hours or 18 to 24 hours after the administration of a single dose of 200 mg trovafloxacin.

Trovafloxacin concentrations were determined in bronchial mucous, broncho-alveolar epithelial cells, macrophages, and supernatant of lavage fluid. Serum concentrations of trovafloxacin during bronchoscopy were also determined for the calculation of the tissue/serum drug concentration ratio.

At 4 to 6 hours after the administration of 200 mg trovafloxacin, the mean serum concentration of trovafloxacin was 2.2 µg/mL, while the corresponding mean concentration in epithelial cells/macrophages (cells) was 5.7 µg/g (cells/serum ratio: 2.9). At 18 to 24 hours postdose, the mean serum trovafloxacin concentration was 1.0 µg/mL, while the mean trovafloxacin concentration in the bronchial epithelial cells and macrophages was 6.1 µg/g (cells/serum ratio: 7.3).

The penetration of trovafloxacin into human bronchial tissues was also studied. Following a single 200 mg dose the mean concentrations of trovafloxacin 1-6 h post dose were 2.2 mcg/mL in plasma and 6.1 mcg/mL in cells obtained by broncheolar lavage. At 18-24 h after dosing, mean trovafloxacin concentrations were 1.1 µg/mL and 5.2 mcg/g in serum and cells, respectively.

In another study, nine patients given once daily 200 mg doses of trovafloxacin for four days were evaluated for drug levels in lung tissue. Six hours after the last dose, trovafloxacin levels in serum, alveolar macrophages, epithelial lining fluid, and broncheolar mucosa were 1.5, 34.3, 10.2, and 1.7 mcg/mL, respectively.

The results of these studies are provided below (copied from the electronic submission):

154-016	26	Bronchial epithelial cells/macrophages	2.9 (4-6 hr postdose)
			7.3 (18-24 hr postdose)
154-020	5	Lung mucosa (single dose)	1.1 (6 hr postdose)
	9	Lung mucosa (multiple dose)	1.1 (6 hr postdose)
154-020	5	Lung epithelial lining fluid (single dose)	2.3 (6 hr postdose)
	7	Lung epithelial lining fluid (multiple dose)	5.8 (6 hr postdose)
154-020	5	Alveolar macrophages (single dose)	13.3 (6 hr postdose)
	8	Alveolar macrophages (multiple dose)	24.1 (6 hr postdose)

Medical Officer's Comment: These results indicated that trovafloxacin was well distributed to bronchial mucosal tissue, ELF and macrophages following single and multiple 200 mg doses. In addition, the concentrations obtained were well above the MIC-90s of pathogens commonly responsible for respiratory infections (*Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*).

General Approach to Evaluation:

Copied below from page 9 of section H.3.A, is the sponsor's table of the studies performed in support of this indication:

Acute Bacterial Exacerbations of Chronic Bronchitis					
154-101	100 mg QD (10 days) 300 mg QD (10 days)	74 76	Ofloxacin 400 mg BID (10 days)	73	Phase II DB
154-109	100 mg QD (7 days)	21 0	Clarithromycin 500 mg BID (7 days)	200	Phase III DB
154-141	100 mg QD (7 days)	13 1	Ciprofloxacin 500 mg BID (7 days)	125	Phase III DB

Medical Officer's Comment: Although all studies were comparative, double blinded studies, study 154-101 differed from the others in that it was a Phase II dose-ranging study. This study was included in the submission in order to increase the number of organisms.

Definitions:

As per the sponsor, AECB was defined as follows (copied from page 12 of section H.3.A):

clinical signs and symptoms of chronic bronchitis defined by the presence of cough, dyspnea, lung sounds, (rales and rhonchi; all protocols except 154-101) and excessive secretion of mucus, (subjects were to have coughed up sputum on most days during three consecutive months for two or more successive years.

signs and symptoms characteristic of acute bacterial exacerbations, including increased dyspnea, increased sputum volume and purulence;

presence of purulent sputum defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field [10X];

absence of pneumonia on chest x-ray and absence of cystic fibrosis.

Subjects had to be over 40 years of age (to select subjects with true chronic bronchitis), except in protocol 154-101 where subjects could be enrolled. Subjects with unstable pulmonary disease were excluded from all studies.

Medical Officer's Comment: The MO agreed with this definition.

Systemic Antibiotic Usage (copied from page 13 of section H.3.A):

Prior systemic antibiotic usage for more than 24 hours within 72 hours of baseline was prohibited unless there was documented evidence of bacterial resistance or clinical failure. Subjects with infections that may have required treatment with an antibiotic other than study drug were also excluded.

Medical Officer's Comment: The MO agreed with this definition.

Data Analysis:

Copied below from page 14, section H.3.A, are the sponsor's definitions of subject subsets:

- **All Randomized (Double-Blind Studies) or Enrolled (Non-Randomized Open Studies) Subjects**
The all randomized or enrolled subjects subsets included all subjects who were randomized or enrolled to a treatment group, regardless of whether or not a particular subject received any study medication.

- **All Treated Subjects**
The all treated subjects subset included all subjects who received one or more doses of study medication (active double-blind study medication for the double-blind studies).
- **Clinical Intent-to-Treat Subjects**
The clinical intent-to-treat subjects subset included those subjects in the all randomized or enrolled subjects subset who had a baseline diagnosis of the disease or condition under investigation determined by protocol specific inclusion and exclusion criteria (not applicable to protocol 154-101, which had a check box on the case report form for underlying disease rather than inclusion/exclusion criteria). Some subjects in this subset may never have received any study medication.
- **Clinically Evaluable Subjects**
The clinically evaluable subjects subset included all subjects in the clinical intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied.
- **Bacteriological Intent-to-Treat Subjects**
The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline. Some subjects in this subset may never have received any study medication.
- **Bacteriologically Evaluable Subjects**
The bacteriologically evaluable subjects subset included all subjects in the clinically evaluable subjects subset, unless one or more of the criteria for non-evaluability applied.

***Medical Officer's Comment:** The MO's evaluable population was compromised of a subset of the sponsor's clinically evaluable subset.*

Evaluability Criteria (copied from pages 15- 16 of section H.3.A):

Clinical:

If any of the following were present, the subject was considered non-evaluable for clinical efficacy:

- insufficient therapy (subject discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement);
- non compliance with study drug regimen (phase II, study 101 only);
- prior antibiotic usage (for >24 hours within 3 days before Day 1 of the study);
- use of a concomitant antibiotic, given for intercurrent illness or adverse event, that was potentially effective against the condition under study (unless given for insufficient response);
- or intercurrent illness that could confound clinical evaluation of the condition under study.

Subjects in the Phase II protocol (154-101), were also non-evaluable for clinical efficacy if they were lost to follow-up (i.e., completed protocol specific minimum of study treatment but failed to return for the end of treatment or end of study visits). However, subjects who discontinued for lack of efficacy or subjects who were clinical failures at the end of treatment visit and failed to return for the end of study visit were evaluable.

Subjects in Phase III studies were also non-evaluable for clinical efficacy if the following applied:

- no post-baseline assessment in the evaluable analysis window, unless the investigator's clinical response was failure before the beginning of the end of treatment window,
- or the subject was given an antibiotic for insufficient response at any time during the study.

For Phase II and Phase III studies, a subject was included in the analysis at the end of study assessment if the subject:

was clinically evaluable at the end of treatment visit, and

was not given any antibiotics for intercurrent illness before the assessment at the end of study visit (unless given for insufficient response), and

had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study,

or the subject was:

clinically evaluable at the end of treatment visit, and

the sponsor-defined clinical response was failure or relapse at end of treatment.

Medical Officer's Comment: The MO agreed with the sponsor's evaluability criteria. All failures were carried forward and the EOS visit was necessary to apply the TOC. The MO did not consider the EOT visit necessary. During the review of study 154-101, the MO found several instances of patients who because of an adverse event, were discontinued from the study drug at day 2 or 3. These patients were routinely treated with an alternative antimicrobial but not classified as failures or carried forward as such. The MO determined that these patients had to be evaluated on a case-by-case basis.

Bacteriological:

For subjects with no baseline atypical pathogen, and protocol 154-101, if any of the following were present the subject was considered non-evaluable for bacteriological efficacy:

- no baseline pathogen or baseline culture outside baseline visit window (>2 days before the first dose of study medication).
- no post-baseline culture, except in the instance of no suitable culture material due to clinical cure or improvement based on the investigator-defined clinical response,
- or the subject was given an antibiotic for insufficient response or the investigator's clinical response was failure (at any time up to and including the last day of the evaluable end of study analysis window.
- Subjects with a serologically defined baseline atypical pathogen, except in protocol 154-101, were bacteriologically evaluable if they were clinically evaluable.

For all protocols and for subjects with no baseline atypical pathogens and protocol 154-101, bacteriologically evaluable subjects were excluded from the analysis at the end of study visit if:

they were excluded from the clinical analysis at the end of study visit, or

they did not have a culture result in the end of study window, unless given an antibiotic for inadequate response or the investigator's clinical response was failure any time during the study, up to and including the last day of the end of study analysis window.

Subjects in protocols with a serologically defined baseline atypical pathogen, except protocol 154-101, were included in the bacteriological analysis at end of study if they were included in the clinical analysis at end of study.

Medical Officer's Comment: *The MO agreed with these criteria. The MO's bacteriologically evaluable population was a subset of the clinically evaluable. As the MO TOC was applied to the EOS visit, the presence of a culture result in the EOS window was necessary within the context of making a presumptive versus a definite determination of outcome. However, as stated above, as the main determinant of efficacy is clinical, the MO accepted a presumptive determination in correlation with the clinical.*

Primary and Secondary Endpoints for Efficacy (copied from page 16 of section H.3.A):

The primary efficacy endpoints were:

Sponsor-defined subject clinical response at the end of treatment visit;

Pathogen eradication rates at the end of treatment visit.

Secondary efficacy endpoints were:

Pathogen eradication rates at the end of study visit;

Investigator-defined subject clinical response at the end of treatment visit, and sponsor-defined and investigator-defined subject clinical response at the end of study visit.

Medical Officer's Comment: *As stated previously, in accordance with regulatory precedence as well as the DAIDP's guidance document and the AC recommendations, the MO elected to assess outcome, clinical and bacteriological, at the EOS as opposed to the EOT visit. Any patient without an EOS visit was not considered evaluable and any patient excluded by the sponsor because they did not have an EOT visit but did have an EOS visit was considered evaluable. Additionally, if there was no bacteriologic response documented at the EOS, the EOT response was carried forward from the EOT to the EOS by the MO as a presumptive response.*

Definitions of Response (copied from pages 17,18, and 19 of section H.3.A.A):

Sponsor-Defined Subject Clinical Response:

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the global evaluations made by the investigator at the end of treatment and end of study visits.

The investigator classified the clinical response of the subject as cure (resolution of all signs and symptoms of the disease under study to the level that existed before baseline), improvement (incomplete resolution of signs and symptoms), or failure (lack of resolution of any of the signs and symptoms of infection).

The occurrence of the following conditions superseded the investigator's assessment:

Failure. If the investigator defined subject clinical response was failure at any visit, then the sponsor-defined subject clinical response was failure at all subsequent visits.

Failure. If a subject was given a concomitant antibiotic for insufficient clinical response or failure then the sponsor-defined subject clinical response was failure at that visit and at all subsequent visits.

Failure: If a subject had no post-baseline assessment, that subject was classified as a clinical failure at both the end of treatment and end of study visits (ITT only).

Relapse:

If a subject was a clinical cure or improvement at the end of treatment visit, and was assessed by the investigator to be a failure at a subsequent visit, then that subject was classified as a clinical relapse at the end of study visit.

If a subject was a clinical cure or improvement at the end of treatment visit, but required additional antibiotic therapy for the primary disease before the end of study visit, then the subject was classified as a clinical relapse at the end of study visit.

Medical Officer's Comment: *As the MO determined outcome at the EOS as opposed to the EOT, patients would be unable to be classified as "relapses" in the MO's analysis. The MO provided a detailed analysis of all of the sponsor's patients who were classified as either "failures" or "relapses."*

For the analysis of the Clinically Intent-to-Treat Subject subset, a 'last observation carried forward' strategy will be used for subjects who are lost to follow-up before the End of Study visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment will be treated as missing data.

Sponsor-Defined Pathogen Outcome

For both evaluable and intent-to-treat subjects, the sponsor classified each baseline organism as a pathogen or as a non-pathogen. Each baseline organism classified as a pathogen was assigned a sponsor-defined pathogen outcome. Multiple baseline pathogens identified in culture samples from the same subject were assigned separate outcomes. Baseline pathogens were assigned a separate outcome for the end of treatment and end of study visits. If multiple visits occurred in the end of treatment analysis window, the last outcome assigned to each baseline pathogen was used. If multiple visits occurred in the end of study window, the worst case outcome was used. Selection of the worst case outcome followed the order persistence or relapse, presumed persistence, presumptive eradication, eradication.

The sponsor-defined pathogen outcomes were defined as follows:

1. **Eradication:** Baseline pathogen absent from a culture from the same site. If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this negative culture, the eradication was carried forward to all subsequent visits, regardless of subsequent culture results.
2. **Presumptive eradication:** Absence of adequate culture material for evaluation and the sponsor-defined subject clinical response was cure or improvement.
3. **Persistence:** Baseline pathogen present in a culture sample from the same site (or any relevant site, including blood). If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this positive culture, the persistence was carried forward to all subsequent visits, regardless of subsequent culture results.
4. **Presumed Persistence:**

Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day, or within 3 days after, a positive or negative culture, in the absence of prior microbiological data in the same evaluable analysis window resulted in a sponsor-defined pathogen outcome of presumed persistence at that visit and all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up, the presumed persistence was carried forward to subsequent implied visits. Absence of microbiological data was either no visit in the window or culture not done at all visits in the window.

No culture was obtained (either not done or absence of adequate culturable material) and the sponsor-defined subject clinical response was failure.

- The baseline pathogens of subjects who were lost to follow-up (i.e., no visit) at either the end of treatment or end of study visits were assigned the outcome of presumed persistence if the pathogen was persistent at any previous visit.

5. Relapse: The original baseline pathogen was present at the end of study visit in a culture from the same site after the end of treatment culture was negative.

Organisms not present at baseline were classified as superinfection or colonization, defined as follows:

6. Superinfection: A pathogen, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and associated with emergence or worsening of clinical and laboratory evidence of infection.

7. Colonization: Any organism, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and not associated with signs or symptoms of active infections.

Each atypical pathogen, identified by serology test, was assigned a sponsor-defined pathogen outcome as follows:

1. Presumed persistence: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and sponsor-defined subject clinical response was failure.
2. Presumed eradication: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and the sponsor-defined subject clinical response was cure or improvement.

Medical Officer's Comment: The MO agreed with the sponsor's definitions of bacteriologic outcome for those cases where the change in the TOC did not affect the response. For the purposes of this review, the MO elected to evaluate only the 3 requested pathogens.

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Evaluability Windows:

The sponsor, as in previously reviewed indications, for the purposes of their analyses, did not adhere to the by-protocol specified windows. Specifically in study 101, the sponsor applied the EOT window to study days 9 - 15 and the EOS to study days 21 - 35. For the pivotal studies, 109 and 141, the EOT window was applied from study days 3 - 18 and the EOS from study days 19 - 40.

On July 24, 1997, the sponsor was queried as to the meaning of these windows from the standpoint of evaluable cures and failures and the minimum duration of therapy necessary for either. The sponsor

responded that in their analyses, a failure could have been classified as such from the second day of therapy onwards and was always carried forward.

The minimum duration of therapy necessary to be classified as a cure was changed to 3 days (42.8% of a 7-day regimen).

The MO elected not to accept this minimum duration with regards to “cures” but instead required a minimum duration of 5 days of therapy. Therefore for the MO’s analyses, the EOT visit was applied for study 101, anywhere from study days 6 – 13 for those patients who received 7 days of therapy or from days 9 – 15 for those patients who received 10 days of therapy. The EOS window was maintained unchanged.

For the pivotal studies 109 and 141, the EOT window for cure was changed to study days 5 – 18 and the EOS (MO TOC window), was maintained at days 19 – 40.

In the MO’s analysis as in the sponsor’s, failures were carried forward from day 2 of therapy.

Study 154-101**TITLE:**

A RANDOMIZED, DOUBLE BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (TROVAFLOXACIN) (100 MG OR 300 MG DAILY) OR OFLOXACIN (800 MG DAILY) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study dates: November 24, 1993 - July 11, 1994

Objective: The objective of this Phase II study was to compare the safety and efficacy of 2 doses of trovafloxacin and ofloxacin in the treatment of subjects with AECB,

List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5004	Harold Schnaper, M.D.
	5015	Sanford Chodosh, M.D.
	5016	H. Charles Miller, M.D.
	5017	John Gezon, M.D.
	5018	George Bell, M.D.
	5019	Nazir Memon, M.D.
	5021	Steven Pace, M.D.
	5022	Lee Payne, M.D.
	5023	Warren Whitlock, M.D.
	5026	Mark Peacock, M.D.
	5033	Thomas Parker, M.D.
	5045	Lawrence Repsher, M.D.
	5047	Roger Menendez, M.D.
	5048	Daniel Gremillion, M.D.
	5050	Charles VanHook, M.D.
	5051	Robin Miller, M.D.
	5052	Madeleine Neems, M.D.
	5053	F. Stephen Herrington, M.D.
	5054	Steven Becker, M.D.
	5055	Pasquale Dilorenzo, M.D.
5056	Stuart Topkis, D.O.	
5057	Jack Tomlinson, M.D.	
5058	Stephen Kreitzer, M.D.	
5059	Narayan Krishnamurthy, M.D.	
5060	Anjuli Nayak, M.D.	
5061	Michael Kalafer, M.D.	
5066	Robert Pieroni, M.D.	
Costa Rica	5034	Guillermo Rodriguez, M.D.

Study Design: Study 154-101 was a Phase II, randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg or 300 mg daily as a single dose in the morning), versus ofloxacin (400 mg in the morning and evening), administered orally for 10 days for the treatment of acute exacerbation of chronic bronchitis.

Efficacy was evaluated through clinical assessments of signs and symptoms of AECB. Safety was assessed throughout the study by recording concomitant medication, vital signs, study drug dosing, adverse events, and laboratory evaluations. In addition, serum trough concentrations of study drug were also determined.

Protocol Overview:

Copied below from the electronic submission, appendix A of the study report is the sponsor's schedule of visits and procedures:

Schedule Of Study Visits and Procedures

Visit Number:	1	2	3	4	5
Study Day:	Day 1	Day 6	Day 11	Day 18	Day 25
Allowable Window:	Day 1	Day 4-8	Day 9-13	Day 14-22	Day 23-27
Treatment Period:	Day 1 to Day 11		Day 12 to Day 25		
Follow-up Period:					
Informed Consent	X				
Demographic Information	X				
Medical History	X				
Physical Examination	X				
Concomitant Medication	X	X	X	X	X
Vital Signs	X	X	X	X	X
Dosing Record			X		
Adverse Experiences		X	X	X	X
Clinical Signs and Symptoms ¹	X	X	X	X	X
Chest x-ray ²	X				
Microbiology sputum gram stain ³	X	X	X	X	X
culture & sensitivity ⁴	X*	X	X	X	X
serology ⁵	X				X
Safety Laboratory ESR, PT, APTT ⁶	X	X	X	abn	abn
CBC + chemistry ⁷	X	X	X	abn	abn
urinalysis ⁵	X	X	X	abn	abn
Serum Drug Level		X			
Pregnancy Test ⁸	X				
Investigator's Clinical Evaluation			x		x

1. includes assessment of sputum volume and degree of sputum purulence
 2. should be repeated after baseline only if clinically indicated
 3. to be done by local site
 4. to be done initially by the local laboratory with pure culture sent to the central laboratory for reanalysis and storage
 5. to be done by central laboratory
 6. to be done by the local laboratory
 7. to be done by central laboratory and includes CBC with differential and platelet count, ALT, AST, AP, GGT, serum total protein and albumin, serum bilirubin, LDH, BUN, serum creatinine, serum calcium and phosphorus, electrolytes, blood glucose, uric acid, serum cholesterol and triglycerides
 8. to be done by local site for women of childbearing potential only
- * only on isolates obtained from adequate sputum based on Gram stain results (other subjects are to be excluded)
- abn only for clinically significant abnormalities persisting at Visit 3

As noted from the above schedule, all baseline evaluations were performed within 48 hours prior to the start of therapy.

At the baseline assessment (Visit 1, Day 1), all subjects had to have a clinical picture characterized by all of the criteria defined below:

Clinical signs and symptoms of chronic bronchitis defined by cough and excessive secretion of mucus. Subjects were to have coughed up sputum on most days during three consecutive months for two or more successive years.

- Signs and symptoms characteristic of acute exacerbation, including increased cough or dyspnea, increased sputum volume, or increased sputum purulence.
- Purulent sputum was to be present and defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field (LPF) [10X].
- The absence of acute infiltrate on chest x-ray.

Those patients who met the above definition and who gave informed consent were eligible for randomization, if they also fulfilled the inclusion and exclusion criteria. Baseline assessments included the collection of demographic information, medical history, physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature).

The clinical assessment of signs and symptoms of AECSB included sputum characteristics, cough, dyspnea, chills/rigors, constitutional symptoms, lung sounds, and chest x-ray (unless one had been taken within 48 hours of the baseline assessment).

Macroscopic sputum examination (i.e., color, consistency, and volume), followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per LPF, squamous epithelial cells per LPF) of sputum were performed. Subjects with inadequate sputum specimens were excluded from randomization. Any intercurrent illness was to be appropriately recorded on the CRF.

Susceptibility to the study drugs, trovafloxacin and ofloxacin, was determined for all causative organisms isolated from adequate sputum specimens. In addition, hematology, coagulation, serum chemistry, and urinalysis determinations, and *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* serologies were performed. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. If no pathogen was detected on baseline culture, continuation of the study drug was at the discretion of the investigator. If a pathogen was resistant to study medication, study treatment could continue at the investigator's discretion, only if there was evidence of clinical improvement.

At Visits 2 (V2: Day 6), and 3 (V3: Day 11: EOT), a determination of efficacy was made. These determinations included clinical assessments of signs and symptoms of AECSB, excluding chest x-ray, to assess response to study therapy. Safety was also assessed at these timepoints, by the recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory evaluations. Serum trough study drug concentrations were also determined at Visit 2. If no clinical improvement had occurred by Visit 2, study drug was discontinued and the patient started on an appropriate alternative antimicrobial. All discontinued patients were followed through the EOS, when possible. The investigators provided an evaluation of clinical response, (the primary efficacy variable), at V3.

At Visits 4 and 5 (V4: Day 18 and V5: Day 25, respectively, 7 and 14 days after completion of study therapy), efficacy and safety observations were again performed as at V2 with the exception of the

laboratory analyses which were only performed if a clinically significant abnormality was present at V3 (Day 11). At V5 (Day 25), final serologies were performed and the investigators provided a final evaluation of clinical response.

Compliance:

This study was conducted in compliance with local or central Institutional Review Board (IRB) and informed consent regulations.

Protocol Amendments:

This protocol was amended once, in December 1994, to reflect:

- the addition of pharmacokinetic data from study 154-004, "Phase I Study Comparing the Apparent Bioavailability of Solid Dosage Formulation of TROVAFLOXACIN in a Fed and Fasted State, Relative to the Solution in Healthy Male Subjects", regarding the effect of food intake on C_{max} and T_{max} to the introduction of the protocol. Subsequent to this amendment, dosing with meals was no longer prohibited.
- that sensitivity testing at the local laboratory was only to be performed on sputum specimens from some centers rather than at all centers.
- the addition of monitoring procedures for subjects who were taking theophylline or warfarin during the study.

Concomitant Medications:

The investigator documented all concomitant medication usage at each visit. This included any therapeutic interventions. No other antimicrobials were allowed. If another antimicrobial was used, the patient was classified as a treatment failure.

Patients taking theophylline had levels monitored at each study visit. Subjects receiving warfarin had prothrombin time monitored at each study visit. Dose adjustments for theophylline or warfarin were made as clinically appropriate. The concomitant use of systemic corticosteroids was allowed. The use of other (non-anti-infective) medications was limited to those essential to the care of the subject. The use of any other investigational drug was prohibited. Mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing.

Discontinuation of Therapy:

Discontinuation of therapy was allowed, at the discretion of the investigator:

- in the event of *in vitro* resistance to a study drug, only if there were no signs of clinical improvement by V2
- In the event of a serious or severe adverse event, limiting side effects or significant laboratory abnormalities

All discontinuations were recorded on the CRF and alternative therapy was instituted. If possible, these patients were followed through the EOS.

Precautions:

Subjects were advised to avoid direct or indirect sunlight and artificial ultraviolet light during treatment and for several days thereafter. In addition, subjects were instructed to discontinue study therapy at the first sign or symptom of phototoxicity reaction such as a sensation of skin burning, redness, swelling, blisters, rash, itching, or dermatitis. Subjects were instructed not to donate blood during and for 6 weeks following administration of study drug.

Study Population:

Approximately 200 subjects with acute exacerbation of chronic bronchitis were expected to be randomized to one of three treatment groups. One hundred fifty (150) of these subjects were expected to be clinically evaluable.

Inclusion and Exclusion Criteria:

(Copied from pages 3 and 4 of the original protocol)

A. Inclusions:

1. Age at baseline.
2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or $\leq$ one year post-menopausal) must have a negative urine gonadotrophin pregnancy test immediately prior to entry in the study and must use adequate contraception both during and for one month after the end of the study.
3. Clinically documented acute exacerbation of chronic bronchitis as defined below.
4. Written informed consent must be obtained.

Medical Officer's Comment: *The definition of AECEB was provided in the study overview and is in accordance with the generally accepted definition.*

B. Exclusions:

1. Pregnant women or nursing mothers.
2. Known hypersensitivity or intolerance to any quinolone antibiotics.
3. Subjects who are currently hospitalized for any reason.
4. Treatment with any other systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline visit.
5. Subjects with unstable pulmonary disease, cystic fibrosis, or evidence of pneumonia on chest radiography.
6. Subjects with infections that may require treatment with an antibiotic other than the study drugs.
7. Subjects with significant gastrointestinal or other conditions which may affect study drug absorption.
8. Subjects with evidence or history of significant hematological, renal or cardiovascular disease or immunologic compromise (i.e. neutropenia, ARC/AIDS, non-skin cancers or malignant melanoma).
9. Subjects with any significant neurologic disease including all forms of epilepsy or any other condition that increases the risk of seizure (e.g. significant head injury, intracranial hemorrhage).
10. Treatment with another investigational drug within four weeks prior to the baseline visit.
11. Prior enrollment in this protocol.
12. Evidence of drug or alcohol abuse or dependence.

Medical Officer's Comment: *The MO agreed with the standard exclusion criteria.*

Randomization and Blinding:

The investigator sequentially assigned study numbers to the subjects as they were determined to be eligible for treatment. The study number was entered onto the subject's case report form and the subject received study medication with the corresponding number.

Dosage Form and Administration:

Study drug was in the form of tablets and was packaged in blister cards using a double dummy technique to maintain blinding. The study drug administration schedule provided one of the following three doses of study drug, dependent on the random assignment:

Trovafloxacin: 100 mg daily as a single active dose in the morning.

Trovafloxacin: 300 mg daily as a single active dose in the morning.

Ofloxacin: 800 mg daily in two equally divided doses (morning, evening).

The blister cards contained sufficient supplies for a 10 day course of treatment, along with an extra day of medication, should it be needed.

In order to maintain blinding, subjects were instructed to take the following tablets during each day of the 10 days of treatment:

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloxacin (100 mg/d)	1-placebo for ofloxacin 1-Trovafloxacin x 100 mg 2-Trovafloxacin placebo	1-placebo for ofloxacin
Trovafloxacin (300 mg/d)	1-placebo for ofloxacin 3-Trovafloxacin x 100 mg	1-placebo for ofloxacin
Ofloxacin (800 mg/d)	1-ofloxacin x 400 mg 3-Trovafloxacin placebo	1-ofloxacin x 400 mg

The blister card with the randomization number corresponding to that assigned to the subject was given to the subject at V1. Subjects were instructed to begin study drug medication with the morning dose (even if it was not the morning) and to complete a full day of medication on Day 1. They were also informed that compliance with taking all tablets as instructed was imperative. The investigator reviewed the following with the subjects:

- blister card labeling, clearly indicating those to be used for morning administration and evening administration
- morning and evening dosing was to be approximately 12 hours apart
- mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium based antacids were not to be taken within (before or after) two hours of dosing.
- not to take their study medication for day 6, (V2) until the visit was completed, because a serum trough level was determined at that visit.

Indices of Compliance

Subjects were informed that compliance with taking all tablets and capsules as instructed was imperative and were asked to bring all unused medication to visits 2 and 3, and again (or empty packs) to visits 4 and 5. All doses taken were recorded in the case report form.

Microbiologic Methods:

Bacteriologic response was assessed at V3 (EOT) and V5 (EOS). Only those sputum specimens that were adequate, as defined previously, were cultured. If there was no obtainable “adequate” specimen, at the EOT or EOS, and the patient was cured or improved, a presumptive assignment of eradication was made.

All specimens were initially sent to the local laboratory for culture. Isolates considered significant were sent to the central laboratory where susceptibility testing was performed. Local susceptibility data was used only if the central laboratory’s data was missing.

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 17 of the study report)

Criteria	<u>Trovafloxacin</u>	<u>Ofloxacin</u>	Zone Diameter (mm) (5 µg Disk)
	MIC (µg/mL)	MIC (µg/mL)	
Susceptible	≤ 2	≤ 2	≥ 16
Intermediate	4	4	13-15
Resistant	≥ 8	≥ 8	≤ 12

MIC for trovafloxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and Zone diameter (mm) for 5 µg disk for ofloxacin were based on NCCLS criteria.

Legionella pneumophila, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* serology were performed at baseline (Day 1) and at Visit 5 (Day 25). A four-fold increase in titer was considered positive for the presence of the organism.

Medical Officer’s Comment: *This methodology was standard throughout the NDA.*

Clinical Response:

Clinical response was determined by the investigator and evaluated at the EOT: V3 (Day 11) and at the EOS: V5 (Day 25), or at the time of discontinuation from study. Clinical response was primarily based on the global assessment of the clinical presentation of the subject at the evaluation time point.

Clinical assessment was based upon resolution or improvement of clinical laboratory signs of infection such as defervescence, disappearance or decreased purulent sputum production, changes in dyspnea and cough, and stabilization in general physical condition. Supporting data to evaluate clinical response was to include reduction in leukocytosis. Clinical response was to be classified as cure, improvement, failure, or indeterminate, as defined in the introduction of the MOR.

Subjects were assessed for signs and symptoms, as detailed below, and these assessments were recorded on the CRF.

1. Sputum was obtained at baseline (V1) and at every visit thereafter. Macro and micro evaluations were performed.
2. Chest x-ray was obtained at baseline (V1) and at any other time point deemed necessary by the investigator.
3. Cough, dyspnea, chills/rigors, constitutional symptoms, and lung sounds were each assessed at baseline (V1) and at every visit thereafter and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Medical Officer's Comment: *This method of evaluation of clinical response was standard throughout the indication of AECB. The only difference in this study is that chills and fever were recorded and graded. A sum of the symptom ratings was not provided.*

Bacteriologic Response

Bacteriological response was determined by the sponsor and evaluated at the EOT (V3) and at the EOS (V5), or at the time of discontinuation from the study. Bacteriologic response was classified by the sponsor as indeterminate (unevaluable), eradication, presumptive eradication, persistence, relapse, superinfection, colonization, eradication with reinfection, or presumed persistence, as defined in the introduction of the MOR.

Medical Officer's Comment: *As noted above, clinical response, the primary efficacy variable, was determined by the investigator and bacteriologic response by the sponsor. Assessments were made both at the EOT and the EOS, when possible.*

Safety Assessments:

Adverse Events:

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the CRF. Following resolution of the adverse event or at the EOS, the investigator's judgment of causality of the adverse event was recorded.

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the sponsor project clinician immediately by telephone. In the case of death, a summary of available autopsy findings was submitted as soon as possible to the sponsor.

In addition, physical examination was performed at baseline (V1). Concomitant medication use and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) were evaluated at the V1 and at V2, V3 (EOT), V4, and V5 (EOS).

Clinical Laboratory Tests:

Hematology, coagulation, serum chemistry, and urinalysis determinations were performed at baseline (V1), and at V2 and V3. At V4 and V5, hematology, coagulation, serum chemistry, and urinalysis were only performed if a clinically significant abnormality was present at V3.

Study Monitoring

The sponsor appointed monitor monitored the study routinely through site visits. In addition, CROs (Contract Research Organizations), monitored designated sites under the supervision of the sponsor.

Data Analysis:

See the introduction to the MOR for a review of the sponsor's subsets and their definitions.

Clinical Evaluability Criteria:

See the introduction to the MOR for a review of the sponsor's criteria.

Criteria for Bacteriological Evaluability:

See the introduction of a review of the sponsor's criteria.

Primary and Secondary Endpoints for Efficacy:

In this study, the primary efficacy endpoint was the sponsor-defined clinical response at the EOT.

Medical Officer's Comment: *As stated in the introduction, the MO applied the TOC to the later EOS visit, therefore the primary endpoint for the MO's analysis was clinical response at that timepoint.*

Secondary efficacy endpoints were:

- Pathogen eradication rates at the EOT and at the EOS
- Investigator-defined clinical response at the EOT and the EOS.

Medical Officer's Comment: *The MO determined that in the MO analysis, the secondary endpoints would be applied to the EOS. However, if there was a patient with a bacteriologic response at the EOT of eradication and no response at the EOS, the MO elected to carry this response forward as a "presumed eradication." Failures/persistences were always carried forward in both the sponsor's and the MO's analyses.*

Definitions of Response:

Please refer to the introduction of the MOR for the sponsor's definitions.

Interim Analyses:

2 planned and 2 unplanned analyses were performed during the course of this study. These were performed for administrative reasons. The data was not unblinded and no modifications were made.

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ON 08/11/2014

Demographics:

As per the sponsor, 223 patients were randomized to treatment (74 subjects to receive trovafloxacin 100 mg (33.1%), 76 to receive trovafloxacin 300 mg (34%), and 73 to receive ofloxacin (32.7%)). 221 of the randomized patients received study drug (73 trovafloxacin-100, 75 trovafloxacin-300, and all of the 73 randomized ofloxacin patients). 2 randomized subjects, one from each trovafloxacin arm did not receive therapy (see below).

Of the treated groups, 187 completed treatment (67/73 (92%) trovafloxacin-100 patients, 56/75 (75%) trovafloxacin-300 patients, and 64/73 (88%) ofloxacin patients).

The MO has recreated sponsor's Table 1.1, the Disposition of Enrolled subjects.

Table 101.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin 100 mg	Trovafloxacin 300 mg	Ofloxacin 400 mg bid
Subjects with Signed Consent	229			
Withdrawn Prior to Randomization	0			
Randomized		74	76	73
Randomized, But Not Treated		1	1	0
All Treated Subjects		73 (100%)	75 (100%)	73 (100%)
Withdrawn During Treatment		6 (8%)	19 (25%)	9 (12%)
Completed Treatment		67 (92%)	56 (75%)	64 (88%)
Withdrawn During Follow- up		1 (1%)	1 (1%)	1 (1%)
Completed Study		66 (90%)	55 (73%)	63 (86%)
Completed Treatment and Study		66 (90%)	55 (73%)	63 (86%)
Withdrawn During Treatment and Study		7 (10%)	20 (27%)	10 (14%)

Medical Officer's Comment: *There was a higher dropout rate from the trovafloxacin-300 arm as compared to the lower dose trovafloxacin and ofloxacin arms. As can be seen below, there were 19 patients who discontinued therapy because of adverse events (related to study drug), on the trovafloxacin-300 arm as compared to 4 on the trovafloxacin-100 arm and 6 on the ofloxacin arm.*

Additionally, there were 2 patients, who were randomized but did not receive study medication:

Trovafloxacin-100:

- #50210313: *withdrew consent at screening visit, normal flora in sputum culture.*

Trovafloxacin-300:

- #50220057: *Streptococcus pneumoniae, withdrawn because of protocol violation.*

Copied and modified below is sponsor's Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

Table 101.2
**Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor,
 Modified by MO)**

Center	Trovafloxacin						Trovafloxacin				Ofloxacin			
			100 mg				300 mg				400 mg b. i. d.			
	Total Randomized N=223 (100%)		Randomized N=74 (100%)		N=73	Treated (100%)	Randomized N=76 (100%)		N=75	Treated (100%)	Randomized N=73 (100%)		N=75	Treated (100%)
5015	18	8.1	6	8.1	6	8.2	6	7.9	6	8	6	8.2	6	8.2
5016	1	0.4	0	0	0	0	1	1.3	1	1.3	0	0	0	0
5017	8	3.5	3	4.0	3	4.1	3	3.9	3	3.9	2	2.7	2	2.7
5018	16	7.0	5	6.7	5	6.8	5	6.8	5	6.6	6	8.2	6	8.2
5019	8	3.5	3	4.0	3	4.1	3	3.9	3	3.9	2	2.7	2	2.7
5021	13	5.8	5	6.7	4	5.8	4	5.3	4	5.3	4	5.4	4	5.4
5022	11	4.9	4	5.4	4	5.8	3	3.9	2	2.6	4	5.4	4	5.4
5023	4	1.8	1	1.3	1	1.3	1	1.3	1	1.3	2	2.7	2	2.7
5026	3	1.3	0	0	0	0	2	2.6	2	2.6	1	1.3	1	1.3
5033	4	1.8	0	0	0	0	2	2.6	2	2.6	2	2.7	2	2.7
5034	66	29.5	22	29.7	22	30.1	22	28.9	22	29.3	22	30.1	22	30.1
5047	4	1.8	1	1.3	1	1.3	2	2.6	2	2.6	1	1.3	1	1.3
5048	2	0.8	1	1.3	1	1.3	1	1.3	1	1.3	0	0	0	0
5051	4	1.8	1	1.3	1	1.3	1	1.3	1	1.3	2	2.7	2	2.7
5053	1	0.4	0	0	0	0	0	0	0	0	1	1.3	1	1.3
5054	1	0.4	0	0	0	0	0	0	0	0	1	1.3	1	1.3
5055	23	10.3	8	10.8	8	11	8	10.5	8	10.6	7	9.6	7	9.6
5056	4	1.8	2	2.7	2	2.7	1	1.3	1	1.3	1	1.3	1	1.3
5057	12	5.4	4	5.4	4	5.8	4	5.3	4	5.3	4	5.4	4	5.4
5058	5	2.5	2	2.7	2	2.7	2	2.6	2	2.6	1	1.3	1	1.3
5059	5	2.5	2	2.7	2	2.7	2	2.6	2	2.6	1	1.3	1	1.3
5060	10	5.0	4	5.4	4	5.8	3	3.9	3	3.9	3	4.1	3	4.1

Medical Officer's Comment: *There were 22 centers, all of which were in the US with the exception of #5034. This center, which enrolled and treated approximately 30% of the patients, was located in Costa Rica. The MO evaluated the patients from this center separately in order to ascertain the advisability of pooling the data. The MO found no specific inconsistencies in the recordation of the data from this center and agreed with the classification of clinical and bacteriological efficacy from this center. However, the DSI investigator, Dr. Thomas, on a site visit found many recording abnormalities which were of concern and partially unresolved.*

Amongst the irregularities were:

- *The lack of CxRs for review because of the recycling policy at the hospitals where this investigator enrolled patients.*
- *On those X/R reports that were available, there was no signature.*
- *All gram stains performed at the site were sent for a second opinion. Neither the original gram stains nor the second opinions were available for review.*

Copied below is the sponsor's table of all randomized patients and the study evaluation groups:

Table 101.3
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

	Trovafloxacin 100 mg	Trovafloxacin 100 mg bid	Ofloxacin 400 mg bid
All Randomized Subjects	74 (100%)	76 (100%)	73 (100%)
All Treated Subjects	73 (99%)	75 (99%)	73 (100%)
Subjects with Inappropriate Baseline Diagnosis	0	0	0
Clinically Intent- to- Treat Subjects	74 (100%)	76 (100%)	73 (100%)
Clinically Evaluable Subjects	65 (88%)	58 (76%)	62 (85%)
Clinically Not Evaluable Subjects	9 (12%)	18 (24%)	11 (15%)
Randomized, Not Treated	1 (1%)	1 (1%)	0
Insufficient Therapy	4 (5%)	14 (18%)	7 (10%)
Non-compliance	0	0	1 (1%)
Prior Antibiotic therapy	3 (4%)	2 (3%)	1 (1%)
Concomitant Antibiotic therapy	2 (3%)	3 (4%)	0
Lost to Follow- up	1 (1%)	1 (1%)	2 (3%)
Clinically évaluable at EOS	64 (86%)	55 (72%)	61 (84%)
Subjects with Negative baseline Culture	41 (55%)	43 (57%)	43 (59%)
Bacteriologically Intent- to- Treat Subjects	33 (45%)	33 (43%)	30 (41%)
Bacteriologically Evaluable Subjects	25 (34%)	19 (25%)	21 (29%)
Bacteriologically Not Evaluable Subjects	49 (66%)	57 (75%)	52 (71%)
Randomized, Not treated	1 (1%)	1 (1%)	0
No Baseline Pathogen	39 (53%)	43 (57%)	42 (58%)
Baseline culture Outside Window	1 (1%)	0	1 (1%)
Not assessable at EOT	17 (23%)	25 (33%)	24 (33%)
Not Clinically Evaluable	2 (3%)	2 (3%)	2 (3%)
Bacteriologically Evaluable at EOS	24 (32%)	15 (20%)	20 (27%)
Analyzed for Safety			
Adverse Events	73 (99%)	75 (99%)	73 (100%)
Laboratory Data	72 (99%)	72 (96%)	69 (95%)

* Subjects may have had more than one reason to have been unevaluable

Medical Officer's Comment: 38 of the randomized subjects were not clinically evaluable (9/74 (12%) trovafloxacin-100, 18/76 (24%) trovafloxacin-300, and 11/73 (15%) ofloxacin).

The bacteriologically evaluable population was a subset of the clinically evaluable population and the bacteriological ITT population, which were both subsets of the clinical ITT population.

There were a total of 6/73(8%) trovafloxacin-100 treated patients who discontinued therapy and who did not complete the study, as compared to 20/75 (26.6%) trovafloxacin-300 treated patients and 9/73 (12%) ofloxacin-treated patients.

Additionally, there was 1 trovafloxacin-100 patient (#50190006) who completed treatment but who was lost to follow-up. This patient received 11 days of therapy, was followed up until day 27, and was excluded from the analyses because he did not have a follow-up visit. The investigator classified this patient as non-assessable. In the sponsor's ITT analysis, this patient was classified as a failure. Haemophilus parainfluenzae was the initial isolate, and this patient would have been evaluable as a failure as per the MO.

There was a similar patient on the trovafloxacin-300 arm, (#50150063), who received 10 days of therapy and was excluded on day 13 for insufficient response. This patient had Streptococcus pneumoniae in the initial isolate, no follow-up cultures were obtained, and the patient was included in the clinical and bacteriological efficacy analyses as a "failure/eradication." This patient was evaluable as a failure as per the Reviewer.

There was also 1 patient (#50340035), on the ofloxacin arm, who completed therapy but not the study. This patient received 11 days of therapy. The initial sputum isolate was Haemophilus influenzae. The

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patient was withdrawn for severe dizziness and was classified as not assessable by the investigator and as a failure by the sponsor. This patient was not included in the evaluable analyses but only in the ITT. This patient was evaluable as a failure as per the Reviewer.

The patients who were clinically unevaluable by arm follow:

Trovafloxacin-100 (N = 9):

- *#50170125: Prior antibiotic therapy. Patient had received Biaxin® up until 48 hours prior to the start of the study. Pseudomonas aeruginosa was isolated from his sputum and he received 11 days of therapy with an initial response of improvement, which was changed to failure at the EOS. This patient was unevaluable as per the MO's criteria.*
- *#50180248: Insufficient therapy. Discontinued on day 2 because of an AE. Reviewer agreed.*
- *#50190006: Lost to follow-up: this patient received 11 days of therapy but did not have an EOS visit. Reviewer agreed.*
- *#50120313: Randomized, not treated. Reviewer agreed.*
- *#50220055: Insufficient therapy: Discontinued on day 2 because she did not meet randomization criteria. Reviewer agreed.*
- *#50480164: Prior antibiotic therapy. Received amoxicillin up until day -2. Reviewer agreed.*
- *#50560176: Insufficient Therapy: Discontinued after 4 days because of an AE. Patient could have been a "cure" but did not receive an adequate course as per the sponsor. Reviewer agreed.*
- *#50600297: Insufficient therapy: Discontinued after 2 days because of an AE. Reviewer agreed.*
- *#50600376: Prior antibiotic therapy: Received amoxicillin up until day -2. Reviewer agreed.*

Thus there were 74 patients initially, 1 was excluded prior to randomization and 8 during the study. Thus the clinically evaluable population as per the sponsor was 65 at the EOT. One additional patient was excluded at the EOS: #50590263. Therefore there were 64 clinically evaluable patients at the EOS. The bacteriologically evaluable population at the EOT was and at the EOS All patients excluded from this group had no baseline pathogen.

Trovafloxacin-300 (N = 18):

- *#50160013: Insufficient therapy: Excluded on day 1 because of an AE. Reviewer agreed.*
- *#50180089: Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed.*
- *#50180250: Prior antibiotic therapy. Received Augmentin® up until day -2. Reviewer agreed.*
- *#50190003: Lost to follow-up: Patient did not return after 7 days. The sponsor did not assess the patient. The sponsor classified this patient as a "failure" in the ITT. Reviewer agreed.*
- *#50190004: Insufficient therapy: Excluded on day 3 because of an AE. Reviewer agreed because the patient did not receive an alternative antimicrobial.*
- *#50220057: Randomized, not treated. Reviewer agreed.*
- *#50230037: Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*

- #50340280: *Insufficient therapy. Excluded on day 5 because of an AE. Classified as a “cure” and no further antimicrobial therapy was given. Reviewer agreed*
- #50340371: *Insufficient therapy. Excluded on day 4 because of an AE. Classified as a “cure” and no further antimicrobial therapy was given. Reviewer agreed*
- #50470134: *Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed*
- #50510218: *Prior antibiotic therapy. Received Biaxin® up until study start. Reviewer agreed.*
- #50550174: *Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- #50550216: *Insufficient therapy. Excluded on day 4 because of an AE. Classified as a “cure” and no further antimicrobial therapy was given. Reviewer agreed.*
- #50570200: *Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed*
- #50570253: *Insufficient therapy. Excluded on day 4 because of an AE. Classified as a “cure” and no further antimicrobial therapy was given. Reviewer agreed*
- #50580207: *Insufficient therapy. Excluded on day 1 because of an AE. Reviewer agreed*
- #50590261: *Insufficient therapy. Excluded on day 4 because of an AE. Classified as a “cure” and no further antimicrobial therapy was given. Reviewer agreed*
- #50600300: *Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*

Thus of the initial 76 patients, 1 was excluded prior to randomization. Of the 75 randomized, 17 were excluded during the study, leaving 58 clinically evaluable at the EOT. An additional 3 patients did not follow-up at the EOS, (#50180090, #50330110, #60600296), thus leaving 55 clinically evaluable patients at that timepoint. There were 19 subjects bacteriologically evaluable at the EOT and 15 at the EOS. All patient excluded from this subgroup had no baseline pathogen.

Ofloxacin (N = 11)

- #50170124: *Lost to follow-up. Did not return after day 1. Reviewer agreed.*
- #50180247: *Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- #50210097: *Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- #50210100: *Insufficient therapy. Excluded on day 2 because of an AE. Reviewer agreed*
- #50220051: *Insufficient therapy. Excluded on day 3 because of an AE. Reviewer agreed because the patient did not receive an alternative antimicrobial.*
- #50230039: *Insufficient therapy. Excluded on day 3 because of an AE. Reviewer agreed because the patient did not receive an alternative antimicrobial.*
- #50330112: *Prior antibiotic therapy. Ceftin® until day –2. Reviewer agreed.*
- #50340282: *Insufficient therapy. Excluded on day 4 because of an AE. Classified as a “cure” and no further antimicrobial therapy was given. Reviewer agreed*

- #50340335: *Lost to follow-up. See above. Reviewer agreed.*
- #50540187: *Lost to follow-up. Did not return after 8 days. Reviewer agreed.*
- #50570203: *Non-compliant. Patient stopped therapy for 2 days. Reviewer agreed that patient did not receive the by-protocol specified minimum amount of therapy.*

Thus of the initial 72 ofloxacin patients, 11 were excluded and 62 were clinically evaluable at the EOT. One additional patient was excluded at the EOS (#60600374). Thus, 61 were clinically evaluable at the EOS. 21 patients were bacteriologically evaluable at the EOT and 20 at the EOS. All excluded patients had no baseline pathogen.

In addition to the above, the MO requested that the sponsor provide a listing of patients who were included in the sponsor's clinically evaluable population and who had either no EOS or no EOT visit. In this study as well as in previously reviewed studies for other requested indications, the sponsor's population has not been the same at these timepoints. These differences do not occur because the patients are lost to follow-up but because of an either/or approach that the sponsor applied to their analyses. Specifically for this study, there were 5 patients who did not have an EOS visit and who were excluded from the MO evaluable population:

Trovafloxacin-100 (N = 1)

- #50590263: *cure at the EOT (this patient however, was reevaluated by the MO and carried forward as an evaluable failure).*

Trovafloxacin-300 (N = 3)

- #50180090: *improvement at EOT*
- #50330110: *improvement at EOT*
- #50600296: *cure at EOT*

Ofloxacin (N=1)

- #50600374: *cure at EOT*

Additionally, there were 13 patients in the sponsor's clinically evaluable population who had an EOS visit but not an EOT visit. These patients were included in the MO's analysis as well as the sponsor's. The MO included them because the MO's TOC was applied to the EOS. The sponsor included them because their TOC was applied both to the EOT and the EOS.

These patients are listed below by treatment arm:

Trovafloxacin-100 (N = 4)

- #50570257: *cure at EOS*
- #50510219: *failure at EOS*
- #50340362: *cure at EOS*
- #50340238: *cure at EOS*

Trovafloxacin-300 (N = 5)

- #50170128: *cure at EOS*
- #50210099: *cure at EOS*
- #50340236: *cure at EOS*
- #50340363: *cure at EOS*

- #50550212: cure at EOS

Ofloxacin (N = 4)

- #50340305: cure at EOS
- #50340327: cure at EOS
- #50340356: cure at EOS
- #50570255: improvement at EOS

As stated previously, the MO's TOC was applied to the EOS and therefore the MO's clinically evaluable population was that which was analyzed at that timepoint. The MO also presented efficacy analyses at the EOT but the FDA patient population was compromised of significantly fewer patients.

Baseline Characteristics:

The 3 groups were comparable in terms of age, race, weight, sex, and smoking history. The distribution of smokers was approximately _____ for all groups, for non-smokers, it was _____, and for ex-smokers, it was _____.

The mean age of the patients was 50 and > 95% were white.

The median duration since the onset of the underlying primary diagnosis of CB was 7 years for the trovafloxacin-100 group, 6 years for the trovafloxacin-300 group, and 7 years for the ofloxacin group.

The respective means were 10.8, 9, and 10.4 years.

The median duration since the onset of the present episode was 7 days for the trovafloxacin-100 group, 7 days for the trovafloxacin-300 group, and 6 days for the ofloxacin group.

The respective means were 14.1, 17.9, and 10 days per arm.

Duration of Treatment:

The median duration of treatment was 10 days for subjects in the 3 treatment groups.

Concomitant Medications:

The majority of patients were on concomitant medications during therapy. The most commonly used medications were bronchodilators.

Steroids were taken by 18 (25%) of the trovafloxacin-100 patients, 14 (19%) of the trovafloxacin-300 patients, and 18 (25%) of the ofloxacin patients.

Medical Officer's Comment: *The MO did not exclude patients taking steroids in this pilot study but did provide separate analyses of clinical and bacteriological response with and without these patients in the MO's efficacy analysis.*

Concomitant Antimicrobials:

Of the clinically evaluable patients, 7 trovafloxacin-100 patients, 5 trovafloxacin-300 patients, and 2 ofloxacin patients received concomitant antimicrobials for the following reasons:

(This information was located in sponsor's table 2.4, appendix 1).

- inadequate response: 5 trovafloxacin-100, 1 trovafloxacin-300, and 2 ofloxacin (all carried forward as evaluable failures)
- discontinued early due to adverse events: 1 trovafloxacin-300 patient
- other or no reason: 1 trovafloxacin-100, 3 trovafloxacin-300 and 0 ofloxacin patients.

The other category was compromised of the following patients:

Trovafloxacin-100 (N = 1):

- #50590263: Exacerbation of bronchitis. This patient was clinically evaluable but not bacteriologically evaluable (no baseline pathogen). The patient received 10 days of therapy and was classified as a “cure” by both the investigator and the sponsor. The patient received Bactrim® starting on day 17. A repeat sputum culture at the EOT and EOS were negative. At the EOS, the sponsor classified this patient as an “improvement.” The Reviewer disagreed and determined that this patient should have been included in the analyses as an evaluable failure.

Trovafloxacin-300 (N = 3):

- #50170122: Sinus infection. This patient was clinically evaluable but not bacteriologically evaluable (no baseline pathogen). The patient received 11 days of therapy and was classified as a “cure” by both the investigator and the sponsor. The patient received amoxicillin starting on day 17. A repeat sputum culture at the EOT and EOS were negative. At the EOS, the sponsor classified this patient as a “cure.” The Reviewer disagreed and determined that this patient should have been excluded from the analyses.
- #50180090: UTI. This patients was clinically evaluable and bacteriologically evaluable (*Moraxella catarrhalis*). The patient received 10 days of therapy and was classified as an “improvement” by both the investigator and the sponsor. The patient received Bactrim® for 5 days on days 20-25. A repeat sputum culture at the EOT and EOS was negative. At the EOS, the sponsor classified this patient as a “cure.” The Reviewer disagreed and determined that this patient should have been excluded from the analyses.
- #50210107: New episode of bronchitis. This patient was clinically evaluable but not bacteriologically evaluable. The patient received 10 days of therapy and was classified as a “cure” by both the investigator and the sponsor. The patient received Bactrim® starting on day 24. A repeat sputum culture at the EOT and EOS was negative. At the EOS, the sponsor classified this patient as an “improvement.” The Reviewer disagreed and determined that this patient should have been included in the analyses as an “evaluable failure.”

The Reviewer requested that these patients be either excluded from the FDA evaluable population or carried forward as failures. Although the patients were not classified as “failures,” the MO determined that the addition of the other antimicrobial agents before the EOS and also for “other” respiratory indications, when applicable”, was not appropriate.

Protocol Deviations:

There were 16 subjects in whom deviations occurred.

The inclusion criteria violations included subjects who exceeded the age limits, had pneumonia on CxR, and unacceptable sputum samples.

There was one violation of the exclusion criteria where a patient who had received chemotherapy was included.

There was 1 patient who took 2 tablets a day for 3 days instead of 1.

Medical Officer's Comment: *The sponsor provided a list of patients but did not state if there were excluded from the analyses. The MO queried the sponsor as to the disposition of these patients on July 27, 1997. The sponsor's representative responded that 4 of these patients were evaluable:*

- #50150069: > 73 years of age. Reviewer agreed.
- #50590259: *Bacteriologically and clinically evaluable on the trovafloxacin-100 arm. Classified as a clinical cure with relapse at EOS. Reviewer included patient as a failure with persistence of the baseline pathogen, Haemophilus influenzae.*
- #50590260: > 73 YO *Clinically evaluable only, as a cure on the ofloxacin arm. Reviewer agreed.*
- #50600295: *Clinically evaluable only, as a cure on the ofloxacin arm. Reviewer agreed.*

Medical Officer's Comment: *Based on the above demographic information, the MO determined that:*

- *Patients receiving steroid therapy should be evaluated in a separate analysis.*
- *Patients who received antimicrobials for an AECB (2) should be included in the analyses as "evaluable failures"*
- *Patients who received antimicrobials for other well-documented infections (2) should be excluded from the MO evaluable population.*
- *Patients who did not have an EOS visit (5), should be excluded from the MO evaluable population.*

Sponsor's Efficacy Analysis:**Sponsor-Defined Clinical Response:****Table 101.4****Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)**

Timepoint	Trovafloxacin-100 N= 65	Trovafloxacin-300 N = 58	Ofloxacin N =62
Number of patients evaluated at EOT	N = 61 (100%)	N = 53 (100%)	N = 58 (100%)
Cure	43 (70%)	34 (64%)	39 (67%)
Improvement	16 (26%)	18 (34%)	17 (29%)
Failure	2 (3%)	1 (2%)	2 (3%)
Success (Cure + Improvement)	59 (97%)	52 (98%)	56 (97%)
Number of patients evaluated at EOS	N = 64 (100%)	N = 65 (100%)	N = 61 (100%)
Cure	55 (86%)	47 (85%)	50 (82%)
Improvement	3 (5%)	7 (13%)	7 (11%)
Failure	3 (5%)	1 (2%)	2 (3%)
Relapse	3 (5%)	0	2 (3%)
Success (Cure + Improvement)	58 (91%)	54 (98%)	57 (93%)

The sponsor provided the following 95% CIs, without continuity correction factor ($\Delta = 10$):

EOT: Trovafloxacin-100 versus Trovafloxacin-300: -7.2%, 4.4% ($\Delta = 10$):

Trovafloxacin-100 versus Ofloxacin: - 6.3%, 6.7% ($\Delta = 10$)

Trovafloxacin-300 versus Ofloxacin: - 4.4%, 7.5% ($\Delta = 10$)

EOS: Trovafloxacin-100 versus Trovafloxacin-300: -15.5%, 0.4% ($\Delta = 10$)

Trovafloxacin-100 versus Ofloxacin: - 12.3%, 6.6% ($\Delta = 10$)

Trovafloxacin-300 versus Ofloxacin: - 2.4%, 11.9% ($\Delta = 10$)

The sponsor stated that (copied from page 28 of the study report):

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the second follow-up evaluation showed that the three treatments were similar. Because this study was not powered to fall within the confidence limits for equivalence, no definitive conclusions regarding equivalency of the three treatments could be drawn.

Medical Officer's Comment: *The MO agreed that the results of all 3 arms were numerically comparable at both timepoints and that the 95% CI was met for all 3 arms at the EOT but not at the EOS as per the sponsor's analysis.*

The MO requested that the FDA statistical reviewer, Dr. Silliman, provide a 95% CI with continuity correction factor for the above. The results were as follows:

EOT: Trovafloxacin-100 versus Trovafloxacin-300: - 8.9%, 6.1% ($\Delta = 10$):
 Trovafloxacin-100 versus Ofloxacin: - 8.0%, 8.3% ($\Delta = 10$)
 Trovafloxacin-300 versus Ofloxacin: - 6.2%, 9.3% ($\Delta = 10$)

EOS: Trovafloxacin-100 versus Trovafloxacin-300: -17.1%, 1.5% ($\Delta = 10$)
 Trovafloxacin-100 versus Ofloxacin: - 13.9%, 8.2% ($\Delta = 10$)
 Trovafloxacin-300 versus Ofloxacin: - 3.5%, 13.5% ($\Delta = 10$)

Based on the FDA analysis, there was therapeutic equivalence between all 3 arms at the EOT only. At the EOS, the FDA TOC, therapeutic equivalence was achieved only for the trovafloxacin-300 arm versus ofloxacin, but not for the trovafloxacin-100 arm versus ofloxacin or versus trovafloxacin-300.

Similar but slightly lower efficacy was seen for the clinical ITT population, with success rates of 63/69 (91%) trovafloxacin-100, 60/70 (86%) trovafloxacin-300, and 59/69 (86%) ofloxacin at the EOT. The respective values at the EOS were 63/74 (85%), 66/76 (87%), and 61/73 (84%). The sponsor did not provide a 95% CI for this analysis.

Clinical Response by Baseline Pathogen:

Table 101.5
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3 by MO)

Pathogen		Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
		N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	12	12	100	7	7	100	6	6	100
	EOS	13	6	46.1	9	9	100	6	4	66.6
<i>Moraxella catarrhalis</i>	EOT	6	6	100	3	3	100	9	9	100
	EOS	6	5	83.3	2	2	100	9	9	100
<i>Streptococcus pneumoniae</i>	EOT	3	3	100	4	3	75	3	3	100
	EOS	3	2	66.6	5	4	80	3	3	100
<i>Haemophilus parahaemolyticus</i>	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	2	2	100	4	4	100	3	3	100
	EOS	2	2	100	4	4	100	3	3	100
<i>Klebsiella pneumoniae</i>	EOT	3	3	100	-	-	-	-	-	-
	EOS	4	4	100	-	-	-	-	-	-
<i>Pseudomonas aeruginosa</i>	EOT	1	1	100	1	1	100	3	2	66.6
	EOS	1	1	100	1	1	100	3	2	66.6
<i>Haemophilus hemolyticus</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
<i>Mycoplasma pneumoniae</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
<i>Chlamydia pneumoniae</i>	EOT	3	3	100	2	2	100	3	3	100
	EOS	4	3	75	2	2	100	3	3	100
Beta-hemolytic streptococcus	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	EOT	32	32	100	25	25	100	27	26	96.2
	EOS	35	25	71.4	27	26	96.2	27	24	88.8

Copied below from page 29 of the study report is the sponsor's text:

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Among clinically evaluable subjects with the most frequently isolated baseline pathogens, sponsor-defined clinical success rates (cure + improvement) at the end of treatment were 100% in all three treatment groups with two exceptions. One of four subjects in the trovafloxacin 300 mg group with *Streptococcus pneumoniae* isolated at baseline and one of three subjects in the ofloxacin group with *Pseudomonas aeruginosa* isolated at baseline were clinical failures.

The two subjects who were clinical failures at end of treatment were failures at the second follow-up evaluation. In addition, three subjects in the trovafloxacin 100 mg group with baseline isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* and two subjects in the ofloxacin group with baseline isolates of *Haemophilus influenzae* were clinical successes at end of treatment and clinical relapses at follow-up. One subject in the trovafloxacin 100 mg group with a positive titer for *Chlamydia pneumoniae* at baseline was not assessed at end of treatment and was designated a clinical failure at follow-up.

Medical Officer's Comment: *The MO agreed with the sponsor's analysis and determined that all 3 treatment groups appeared numerically comparable at the EOT but not at the EOS, where trovafloxacin-300 appeared superior to both comparators and trovafloxacin-100 was inferior to both comparators when total clinical response rates by pathogen were compared. A 95% CI was not applied because of the small numbers of isolates.*

For the 3 primary pathogens, the clinical response rates were the same at the EOT for Haemophilus influenzae and Moraxella catarrhalis. The clinical response rate for the trovafloxacin-300 arm for patients with Streptococcus pneumoniae was 75% compared to 100% for the 2 comparator arms at the EOT.

At the EOS however, only the trovafloxacin-300 arm maintained 100% efficacy against Haemophilus influenzae, and once again, trovafloxacin-100 appeared to be inferior to ofloxacin. The response rates were also lower for trovafloxacin-100 compared to the other 2 arms in patients with Moraxella catarrhalis and Streptococcus pneumoniae at this timepoint.

A review of Table 16, appendix V and the PID's of the "failures/relapses," revealed the following:

Trovafloxacin-100 (N = 3):

- *#50150070: Moraxella catarrhalis: improvement/relapse. This patient initially had Moraxella catarrhalis which was eradicated. The patient relapsed and a sputum specimen at the EOS revealed Haemophilus influenzae. The patient was treated with Bactrim®.*
- *#50580205: Streptococcus pneumoniae: cure/relapse. This patient was a clinical cure at the EOT with eradication of the baseline pathogen. At the EOS the patient was classified as a relapse with growth of Escherichia coli. (Day 18 had Streptococcus pneumoniae). Patient was treated with Cefuroxime®.*
- *#50580208: Haemophilus influenzae: improvement/relapse. This patient initially was classified as a clinical cure with eradication of the baseline pathogen. On day 25, the patient had clinically relapsed with Haemophilus influenzae again isolated. The patient was treated with Bactrim®.*

Trovafloxacin-300 (N = 1):

- *#50150063: Streptococcus pneumoniae: failure/failure. This patient clinically failed despite eradication at the EOT of the baseline pathogen. The patient received ampicillin on day 13 until the EOS.*

Ofloxacin (N = 2):

- #50230038: *Pseudomonas aeruginosa*: failure/failure. This patient was a clinical failure with persistence of the baseline pathogen. From days 11- 25, the patients received Bactrim® and then was changed to Augmentin® on day 25 for an unspecified duration.
- #50260025: *Haemophilus influenzae*: cure/relapse. This patient was a clinical cure with eradication of the baseline pathogen at the EOT. At the EOS, the patient relapsed and *Moraxella catarrhalis* was cultured. The patient was treated with Augmentin®.

Bacteriological Response:

Sponsor-Defined Pathogen Eradication Rates at EOT and EOS can be seen in Sponsor's Table 5.4.1, copied and modified by the MO:

Table 101.6

Sponsor-Defined Pathogen Eradication Rates/Bacteriologically Evaluable Population: (Modified from Sponsor Table 5.4.1)

Pathogen		Trovafloracin-100			Trovafloracin-300			Ofloxacin		
		N	No. Erad.	%	N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	12	12	100	7	7	100	5	5	100
	EOS	12	10	83	9	9	100	6	5	66.6
<i>Moraxella catarrhalis</i>	EOT	6	6	100	4	3	75	9	9	100
	EOS	5	5	100	4	3	75	10	10	100
<i>Streptococcus pneumoniae</i>	EOT	3	3	100	5	5	100	3	3	100
	EOS	3	2	66.6	5	5	100	3	3	100
<i>Haemophilus parahemolyticus</i>	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	2	2	100	4	4	100	4	4	100
	EOS	2	2	100	3	3	100	4	4	100
<i>Klebsiella pneumoniae</i>	EOT	3	3	100	-	-	-	-	-	-
	EOS	3	3	100	-	-	-	-	-	-
<i>Pseudomonas aeruginosa</i>	EOT	1	1	100	1	1	100	3	2	66.6
	EOS	1	0	0	1	1	100	3	2	66.6
<i>Haemophilus hemolyticus</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Beta-hemolytic <i>streptococcus</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	EOT	29	28	96.5	24	23	95.8	24	23	95.8
	EOS	28	24	85.7	25	24	96	26	24	92.3

The sponsor's comment has been copied from page 32 of the study report:

At the end of treatment, a sponsor-defined pathogen outcome of persistence was observed for one subject in the ofloxacin group with *Pseudomonas aeruginosa* isolated at baseline (Subject number 50230038). At baseline, this isolate of *Pseudomonas aeruginosa* was found to be of intermediate susceptibility to trovafloxacin (MIC = 4 mcg/mL) and resistant to ofloxacin (MIC = 16 mcg/mL; disk zone = 7 mm); at the end of treatment, the recovered pathogen was susceptible to trovafloxacin (MIC = 1 mcg/mL) and resistant to ofloxacin (MIC = 8 mcg/mL; disk zone = 10 mm).

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At the second follow-up visit, sponsor-defined pathogen outcomes of relapse were observed for three subjects in the trovafloxacin 100 mg group, two with *Haemophilus influenzae* isolated at baseline and one with *Pseudomonas aeruginosa* isolated at baseline. Persistence was observed for one subject in the trovafloxacin-100 mg group with *Streptococcus pneumoniae* isolated at baseline. None of these four pathogens developed resistance to trovafloxacin during the course of the study. No bacteriologic relapses or persistence were observed in the trovafloxacin 300 mg and ofloxacin groups.

Medical Officer's Comment: *The MO agreed with the sponsor's determination of pathogen outcome in all cases after review of the PIDs. Overall, the 3 treatment arms were numerically comparable at the EOT but trovafloxacin-300 appeared numerically superior to the 2 comparator arms at the EOS, and trovafloxacin-100 was inferior to both comparators at this timepoint.*

Pathogen eradication rates for Haemophilus influenzae, were similar at the EOT but trovafloxacin-300 was numerically superior to both comparators at the EOS and trovafloxacin-100 was numerically superior to ofloxacin.

The numbers of Moraxella catarrhalis and Streptococcus pneumoniae isolates were too small to be able to make any valid comparisons.

Superinfecting Pathogens:

One bacteriologically evaluable subject in the trovafloxacin-100 mg group (Subject number 5058-0205) developed a superinfection (sputum: *Escherichia coli*). There were no superinfections observed in the trovafloxacin-300 mg and ofloxacin groups. Colonizing organisms were isolated from three subjects (12%) in the trovafloxacin 100-mg group, one subject (5%) in the trovafloxacin-300 mg group, and two subjects (10%) in the ofloxacin group.

Medical Officer's Comment: *The MO reviewed Table 5.6, a table of superinfecting and colonizing organisms as well as the PIDs for these patients and Table 18 appendix V and found the following:*

Trovafloxacin-100 (N = 4):

- *#50150070: Haemophilus influenzae at day 25. Classified as a colonizing organism. Patient had normal flora in the baseline and EOT specimens. The patient relapsed and a sputum specimen at the EOS revealed Haemophilus influenzae. The patient was treated with Bactrim®. The MO determined that this patient was a failure with a superinfecting organism.*
- *#50220058: Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter calcoaceticus v. lwoffii at day 25. Classified as "colonizing organisms." Patient had normal flora in the baseline and EOT specimens. This patient was classified as a clinical improvement at the EOT and a "cure" at the EOS. Reviewer agreed.*
- *#50580205: Escherichia coli day 25. Classified as a superinfecting pathogen. Streptococcus pneumoniae found at baseline, eradicated. This patient was a clinical cure at the EOT with eradication of the baseline pathogen. At the EOS the patient was classified as a relapse with growth of Escherichia coli. (Day 18 had Streptococcus pneumoniae). Patient was treated with Cefuroxime®. Reviewer agreed.*
- *#50580208: Klebsiella pneumoniae at day 18. Classified as a colonizing organism. Haemophilus influenzae also found at day 25 and at baseline. This patient initially was classified as a clinical cure with eradication of the baseline pathogen. On day 25, the patient had clinically relapsed with Haemophilus influenzae again isolated. The patient was treated with Bactrim®. Reviewer agreed.*

Trovafloxacin-300 (N = 1):

- #50600373: *Enterobacter aerogenes* isolated at day 25 and classified as a colonizing organism. Patient had normal flora in the baseline and EOT specimens. Reviewer agreed.

Ofloxacin (N = 2):

- #50180092: *Moraxella catarrhalis* and *Streptococcus pneumoniae* day 25. Classified as colonizing organisms. This patient was initially classified as a clinical cure with eradication of the baseline pathogen, *Haemophilus influenzae*. No further therapy was prescribed. Reviewer agreed with designation of organisms as colonizers.
- #50580206: *Haemophilus parahaemolyticus* day 25. Classified as a colonizing organism. Patient had *Pseudomonas aeruginosa* in the baseline specimen which was eradicated. This patient was classified as a clinical improvement at the EOT and clinical cure at the EOS. Reviewer agreed.

Medical Officer's Comment: Overall, the MO agreed with the sponsor's determinations with the exception of 1 patient on the trovafloxacin-100 arm. This patient would have been classified as a failure/superinfection by the MO.

Bacteriological ITT Subjects:

The sponsor stated that (copied from page 43 for the study report):

Results differed from those obtained in the bacteriologically evaluable population due to the inclusion of additional intent-to-treat subjects who were not included in the analysis of bacteriologically evaluable subjects. Additional bacteriological failures (persistent, presumed persistent, and relapse) observed in the intent-to-treat analysis were as follows:

One subject in the trovafloxacin 300 mg group had a pathogen outcome of presumed persistent for one isolate of *Moraxella catarrhalis* at the end of treatment. At the second follow-up evaluation, five subjects (2 trovafloxacin 100 mg; 1 trovafloxacin 300 mg; 2 ofloxacin) had pathogen outcomes of presumed persistent (*Moraxella catarrhalis*, one isolate) or persistent (*Streptococcus pneumoniae*, one isolate; *Pseudomonas aeruginosa*, two isolates; and *Haemophilus influenzae*, two isolates). None of these pathogens, for which susceptibility testing was done, developed resistance to trovafloxacin during the course of the study.

Medical Officer's Comment: The MO did not incorporate all of the ITT subjects into the document because these patients were not bacteriologically evaluable as per the MO.

Cross Tabulation of Sponsor-Defined Clinical Response and Sponsor-Defined Bacteriological Response and Pathogen Outcome:

As per the sponsor, there was an inconsistent response at the EOT (TOC) analysis in 1 trovafloxacin-300 and 1 ofloxacin patient.

Specifically:

Trovafloxacin-300 patient 50150063 was a clinical failure with bacteriologic persistence of the baseline pathogen (*Streptococcus pneumoniae*). The MO agreed with this determination. This patient was reviewed above in the clinical failures section.

Ofloxacin patient #50230038 was a clinical cure with bacteriologic persistence of the baseline pathogen, *Pseudomonas aeruginosa*. This isolate was of intermediate sensitivity to trovafloxacin and resistant to ofloxacin

Medical Officer's Comment: *The MO reviewed the sponsor's tables 5.7.1 and 5.7.2 and agreed with the presentation of the data.*

Signs and Symptoms:

(Copied from the study report, page 34)

Among the clinically evaluable subjects, the number of subjects with dyspnea, cough, or DAAF (diffuse abnormal auscultatory findings) decreased from baseline to the end of treatment in all three treatment groups. Further decreases were observed at the second follow-up visit. Among the subjects who continued to display these signs or symptoms, the severity was decreased. Similar results were observed for the clinical intent-to-treat subjects.

Medical Officer's Comment: *The MO reviewed the sponsor's tables and agreed with their conclusion.*

Sponsor's Conclusion: (Copied from the Esub and modified by the MO, in Times New Roman font, to reflect the numerators and denominators):

Two hundred twenty-three (223) subjects with acute exacerbation of chronic bronchitis were randomized to treatment with trovafloxacin 100 mg once daily, trovafloxacin 300 mg once daily, or ofloxacin 400 mg twice daily for 10 days.

The three treatment groups were comparable with respect to demographic characteristics at baseline, medical history, and prior and concomitant medications.

One hundred eighty-five (185) subjects were clinically evaluable (65, trovafloxacin 100 mg; 58, trovafloxacin 300 mg; and 62, ofloxacin) and 65 subjects were bacteriologically evaluable (25, trovafloxacin 100 mg; 19, trovafloxacin 300 mg; and 21, ofloxacin). All treated subjects were included in analysis of safety.

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the second follow-up evaluation showed that the three treatment groups were similar for both evaluable and intent-to-treat subjects. Clinically evaluable: trovafloxacin-100: EOT: 59/61 (97%); EOS: 58/64 (91%), trovafloxacin-300: EOT: 52/53 (98%); EOS: 54/55 (98%); ofloxacin EOT: 56/58 (97%); EOS 57/61 (93%).

At the second follow-up evaluation among clinically evaluable subjects, clinical relapses were observed for three subjects in the trovafloxacin 100 mg group with *Moraxella catarrhalis*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* isolated at baseline and two subjects in the ofloxacin group with *Haemophilus influenzae* isolated at baseline. No subjects in the trovafloxacin 300 mg group were designated as a clinical relapse at the second follow-up evaluation.

Sponsor-defined pathogen eradication rates were comparable among the three treatment groups at the end of treatment. A sponsor-defined pathogen outcome of persistence was observed for only one subject in the ofloxacin group with *Pseudomonas aeruginosa* isolated at baseline.

EOT Trovafloxacin-100:

Haemophilus influenzae: 12/12 (100%)

Moraxella catarrhalis: 6/6 (100%)

Streptococcus pneumoniae: 3/3 (100%)

EOS Trovafloxacin-100:

Haemophilus influenzae: 10/12 (80%)

Moraxella catarrhalis: 5/5 (100%)

Streptococcus pneumoniae: 2/3 (67%)

EOT Trovafloxacin-300:

Haemophilus influenzae: 6/6 (100%)
Moraxella catarrhalis: 3/3 (100%)
Streptococcus pneumoniae: 4/4 (100%)

EOS Trovafloxacin-300:

Haemophilus influenzae: 5/5 (100%)
Moraxella catarrhalis: 2/2 (100%)
Streptococcus pneumoniae: 3/3 (67%)

EOT Ofloxacin:

Haemophilus influenzae: 5/5 (100%)
Moraxella catarrhalis: 8/8 (100%)
Streptococcus pneumoniae: 3/3 (100%)

EOS Ofloxacin:

Haemophilus influenzae: 5/5 (100%)
Moraxella catarrhalis: 8/8 (100%)
Streptococcus pneumoniae: 3/3 (100%)

At the second follow-up visit, sponsor-defined pathogen outcomes of relapse were observed for three subjects in the trovafloxacin 100 mg group, two with *Haemophilus influenzae* isolated at baseline and one with *Pseudomonas aeruginosa* isolated at baseline. Persistence was observed for one subject in the trovafloxacin 100 mg group with *Streptococcus pneumoniae* isolated at baseline. None of these four pathogens developed resistance to trovafloxacin during the course of the study. No bacteriologic relapses or persistence were observed in the trovafloxacin 300 mg and ofloxacin groups.

Trovafloxacin 100 mg or 300 mg and ofloxacin 400 mg BID were similar with respect to clinical response rates at the end of treatment and at the second follow-up evaluation for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment. At the second follow-up evaluation, bacteriologic relapses were observed in four subjects in the trovafloxacin 100 mg group.

Because of the small number of bacteriologically evaluable subjects in this treatment group (N=24), no definitive conclusions could be drawn.

Medical Officer's Efficacy Analysis:

On July 31, 1997, the sponsor faxed partial tables and listings of the MO evaluable population, in accordance with the evaluability criteria laid out previously. The MO ascertained that all of the patients that the MO had requested excluded from the analyses because they did not have an EOS visit, (4) were excluded. 1 trovafloxacin-100 patient, #50590263 was not excluded but carried forward as an evaluable failure at the MO's request. The MO changed the outcome on 1 patient #50590259 to a clinical failure. The MO's evaluable population can be seen in table 101.7. Although the MO had the same # of patients evaluable on the trovafloxacin-100 arm, as the sponsor, these were not the same patients (see demographics).

Table 101.7
Clinically Evaluable Population (as per the MO)

Reason for exclusion	Trovafloxacin- 100	Trovafloxacin- 300	Ofloxacin
Total Randomized	N= 221		
Total Treated	N=73	N=75	N=73
Sponsor Evaluable	65	58	62
MO Excluded			
No EOS Visit	-	3	1
Antimicrobial R/x	-	1	-
Total Evaluated at EOS	65 (89%)	54 (72%)	61 (83.5%)

The numbers of evaluable patients per arm at the EOT were 61, 49, and 57, respectively. There were fewer patients at the EOT because the MO accepted patients in the FDA evaluable population who did not have an EOT evaluation but did have an EOS.

The MO's bacteriologically evaluable population was a subset of the clinically evaluable.

A by-center breakdown of the MO's evaluable population is presented in Table 101.8:

Table 101.8
Clinically Evaluable Population by Center (as per MO)

Center	Total Randomized N=223 (100%)		Trovafloxacin				Trovafloxacin				Ofloxacin			
			100 mg				300 mg				400 mg b. i. d.			
			Sponsor Eval. N = 65 (100%)		MO Eval. N= 65 (100%)		Sponsor Eval. N = 58 (100%)		MO Eval. N= 54 (100%)		Sponsor Eval. N = 62 (100%)		MO Eval. N= 61 (100%)	
5015	18	8.1	6	9.2	6	9.2	6	10.3	6	11.1	6	9.7	6	9.8
5016	1	0.4	0	-	0	-	0	-	0	-	0	-	0	-
5017	8	3.5	2	3.1	2	3.1	3	5.2	2	3.7	1	1.6	1	1.6
5018	16	7.0	4	6.2	4	6.2	3	5.2	2	3.7	5	8.1	5	8.2
5019	8	3.5	2	3.1	2	3.1	1	1.7	1	1.9	2	3.2	2	3.3
5021	13	5.8	4	6.2	4	6.2	4	6.9	4	7.4	2	3.2	2	3.3
5022	11	4.9	3	4.6	3	4.6	2	3.4	2	3.7	3	4.8	3	4.9
5023	4	1.8	1	1.5	1	1.5	0	-	0	-	1	1.6	1	1.6
5026	3	1.3	0	-	0	-	2	3.4	2	3.7	1	1.6	1	1.6
5033	4	1.8	0	-	0	-	2	3.4	1	1.9	1	1.6	1	1.6
5034	66	29.5	22	33.8	22	33.8	20	34.5	20	37	20	32.3	20	32.8
5047	4	1.8	1	1.5	1	1.5	1	1.7	1	1.9	1	1.6	1	1.6
5048	2	0.8	0	-	0	-	1	1.7	1	1.9	0	-	0	-
5051	4	1.8	1	1.5	1	1.5	0	-	0	-	2	3.2	2	3.3
5053	1	0.4	0	-	0	-	0	-	0	-	1	1.6	1	1.6
5054	1	0.4	0	-	0	-	0	-	0	-	0	-	0	-
5055	23	10.3	8	12.3	8	12.3	6	10.3	6	11.1	7	11.3	7	11.5
5056	4	1.8	1	1.5	1	1.5	1	1.7	1	1.9	1	1.6	1	1.6
5057	12	5.4	4	6.2	4	6.2	2	3.4	2	3.7	3	4.8	4	4.9
5058	5	2.5	2	3.1	2	3.1	1	1.7	1	1.9	1	1.6	1	1.6
5059	5	2.5	2	3.1	2	3.1	1	1.7	1	1.9	1	1.6	1	1.6
5060	10	5.0	2	3.1	2	3.1	2	3.4	1	1.9	3	4.8	2	3.3

Approximately 30% of the patients per arm were from center 5034. However, the number of patients in this study was very small and therefore all centers were pooled.

The demographics of the FDA evaluable population can be seen in Table 101.9.

Table 101.9
Demographic Characteristics of the FDA Evaluable Population:

Characteristics	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
	N = 65	N = 54	N = 61
Sex (Female)	30	22	30
(Male)	35	32	31
Age (years) 16 -44	23	21	20
45 - 64	27	18	27
≥ 65	15	15	14
Mean	50.2	48.9	50.1
Race: Asian	0	0	0
Black	1	1	1
White	63	53	57
Hispanic	1	0	3
Nat Am.	0	0	0
Body weight (kg) mean	77.5	78.2	76.9

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All 3 arms consisted of a comparable population in terms of weight and age.

Concomitant Medications:

The MO elected not to exclude patients who had been on steroids during this study. The MO's rationale was that this was a Phase II pilot study and that the number of the evaluable patients per arm on systemic steroids was proportionate. Systemic steroids are often used in-patients with CB and at increased doses during acute exacerbations. This implies a standard of care that the MO determined would be appropriate to include in the analysis.

The MO ascertained through review of the line listings, that 12/65(18.4%) of the MO evaluable trovafloxacin-100 patients, 5/54 (9.2%) of the evaluable trovafloxacin-300 patients and 9/61 (14.7%) of the MO evaluable ofloxacin patients received systemic steroids.

6 patients on the trovafloxacin-100 arm were started on systemic steroids during the study as compared to 4 patients on the trovafloxacin-300 arm and 2 on the ofloxacin arm. The remainder had been on steroids prior to the study and continued throughout.

Of the 12 trovafloxacin-100 patients on steroids, 9 were clinically cured and 3 were failures (2 failures and 4 cures started during the study). On the trovafloxacin-300 arm, all 5 of the patients on steroids were clinical cures (4 started during the study). Of the 9 ofloxacin patients on steroids, 6 were clinical cures and 3 were failures (1 failure and 1 cure started steroids during the study).

The MO requested that a separate clinical efficacy analysis be performed excluding these patients. For accounting purposes, these patients were listed below with their clinical outcome and the time that systemic steroids were started.

Trovafloxacin-100 (N =12)

#50180086: cure, during
#50210101: cure, during
#50220050: cure, during
#50220052: cure, during
#50230040: cure, pretherapy
#50470136: failure, during
#50550270: cure, pretherapy
#50560175: cure, pretherapy
#50570189: cure, pretherapy
#50580205: failure, during
#50580208: failure, pretherapy
#50590263: failure, pretherapy

Trovafloxacin-300 (N = 5)

#50210102: cure, during
#50260026: cure, pretherapy
#50250027: cure, during
#50340236: cure, during
#50470133: cure, during

Ofloxacin (N = 9)

#50150069: cure, during
#58180085: cure, pretherapy
350180087: failure, during

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- #50180249: cure, pretherapy
- #50230038: failure, pretherapy
- #50260025: failure, pretherapy
- #50570255: cure, pretherapy
- #50570258: cure, pretherapy
- #50600295: cure, pretherapy

Although, the MO did not exclude these patients from tables 101.7 and 101.8, a separate analysis of clinical efficacy was performed after their exclusion. In the analyses where they were excluded, the number of evaluable patients would be 53 trovafloxacin-100, 49 trovafloxacin-300, and 52 ofloxacin at the EOS.

EFFICACY:

**Table 101.10
Clinical Response by Patient (as per the MO):**

Timepoint	Trovafoxacin-100			Trovafoxacin-300			Ofloxacin		
	N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
EOT	61	58	95	49	48	98	57	55	96.4
EOS	65	57	87.7	54	52	96.3	61	57	93.4

The MO and the FDA statistician, Dr. Nancy Silliman, applied a 95% CI using stat xact-3 to these results and found the following:

- EOT: Trovafoxacin-100 versus Trovafoxacin-300: - 16.4%, 10.1% ($\Delta = 10$):
 Trovafoxacin-100 versus Ofloxacin: - 15.2%, 10.7% ($\Delta = 10$)
 Trovafoxacin-300 versus Ofloxacin: - 11.4%, 15.0% ($\Delta = 10$)

- EOS: Trovafoxacin-100 versus Trovafoxacin-300: - 23.8%, 5.1% ($\Delta = 10$)
 Trovafoxacin-100 versus Ofloxacin: - 21.1%, 7.9% ($\Delta = 10$)
 Trovafoxacin-300 versus Ofloxacin: - 10.3%, 17.1% ($\Delta = 10$)

Thus, the MO's results mirrored those of the sponsor in that trovafloxacin-100 was NOT equivalent to either of the 2 other arms at the EOS for the primary efficacy variable of clinical response, and trovafloxacin-300 was marginally equivalent to ofloxacin.

At the EOT, the trovafloxacin-100 arm was marginally equivalent to the ofloxacin arm. As in the sponsor's analysis, trovafloxacin-300 was equivalent to ofloxacin at the EOT.

At the EOS, trovafloxacin-300 was equivalent to ofloxacin but trovafloxacin-100 was NOT equivalent to either comparator arm.

The following results were obtained when patients on systemic steroids were excluded:

**Table 101.11
Clinical Response at EOS by Patient Excluding Patients on Systemic Steroids (as per MO):**

Timepoint	Trovafoxacin-100			Trovafoxacin-300			Ofloxacin		
	N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
EOS	53	49	92.5	49	47	95.9	52	51	98.1

The 95% CI using the previously applied exact method was:

EOS: Trovafloxacin-100 versus Trovafloxacin-300: -19.6%, 10.8% ($\Delta = 10$)
 Trovafloxacin-100 versus Ofloxacin: - 21.6%, 6.9% ($\Delta = 10$)
 Trovafloxacin-300 versus Ofloxacin: - 16.7%, 10.8% ($\Delta = 10$)

Based on this analysis, neither trovafloxacin-100 nor trovafloxacin-300 was equivalent to ofloxacin. These results essentially mirror those of the total population.

The MO does qualify the above by stating that this was a small pilot study, not adequately powered and that 3 arms were numerically comparable.

Clinical Response by Baseline Pathogen:

Table 101.12
Clinical Response by Baseline Pathogen at the EOT and EOS (as per MO)

Pathogen		Trovafloxacin-100			Trovafloxacin-300			Ofloxacin		
		N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	12	12	100	7	7	100	6	6	100
	EOS	13	12	92.3	9	9	100	6	4	67
<i>Moraxella catarrhalis</i>	EOT	6	6	100	2	2	100	9	9	100
	EOS	6	5	83.3	2	2	100	9	9	100
<i>Streptococcus pneumoniae</i>	EOT	3	3	100	4	3	75	3	3	100
	EOS	3	2	67	5	4	80	3	3	100
<i>Haemophilus parahaemolyticus</i>	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	2	2	100	4	4	100	3	3	100
	EOS	2	2	100	4	4	100	3	3	100
<i>Klebsiella pneumoniae</i>	EOT	3	3	100	-	-	-	-	-	-
	EOS	4	4	100	-	-	-	-	-	-
<i>Pseudomonas aeruginosa</i>	EOT	1	1	100	1	1	100	3	2	67
	EOS	1	1	100	1	1	100	3	2	67
<i>Haemophilus haemolyticus</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
<i>Mycoplasma pneumoniae</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
<i>Chlamydia pneumoniae</i>	EOT	3	3	100	2	2	100	3	3	100
	EOS	4	3	75	2	2	100	3	3	100
Beta-hemolytic <i>streptococcus</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	EOT	32	32	100	25	25	100	27	26	96.2
	EOS	35	31	88.6	27	26	96.2	27	24	88.8

The MO's results mirrored those of the sponsor. A 95% CI was not applied because of the small numbers. However, all 3 treatment arms were numerically comparable at the EOT. The 1 failure on the ofloxacin arm was due to a patient with a *Pseudomonas* isolate resistant to ofloxacin.

At the EOS, as in the sponsor's analysis, trovafloxacin-300 was superior to both comparators. Trovafloxacin-100 and ofloxacin appeared equal at the EOS. All failures were reviewed previously.

Bacteriological Response:

Pathogen Eradication Rates at EOT and EOS as per the MO can be seen table 101.13:

Table 101.13**Pathogen Eradication Rates at the EOT and EOS (as per the MO)**

Pathogen		Trovafloracin-100			Trovafloracin-300			Ofloxacin		
		N	No. Erad.	%	N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	12	12	100	6	6	100	5	5	100
	EOS	12	10	83.3	6	6	100	5	5	100
<i>Moraxella catarrhalis</i>	EOT	6	6	100	2	2	100	8	8	100
	EOS	6	6	100	2	2	100	8	8	100
<i>Streptococcus pneumoniae</i>	EOT	3	3	100	4	4	100	3	3	100
	EOS	3	2	67	4	4	100	3	3	100
<i>Haemophilus parahaemolyticus</i>	EOT	2	2	100	1	1	100	-	-	-
	EOS	2	2	100	1	1	100	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	2	2	100	4	4	100	3	3	100
	EOS	2	2	100	4	4	100	3	3	100
<i>Klebsiella pneumoniae</i>	EOT	3	3	100	-	-	-	-	-	-
	EOS	3	3	100	-	-	-	-	-	-
<i>Pseudomonas aeruginosa</i>	EOT	1	1	100	1	1	100	3	2	67
	EOS	1	0	0	1	1	100	3	2	67
<i>Haemophilus haemolyticus</i>	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Beta-hemolytic streptococcus	EOT	-	-	-	1	1	100	-	-	-
	EOS	-	-	-	1	1	100	-	-	-
Total	EOT	29	29	100	20	20	100	22	21	95.4
	EOS	29	25	86.2	20	20	100	22	21	95.4

Once again all 3 treatment arms attained 100% efficacy at the EOT. At the EOS however, trovafloxacin-300 was numerically superior to ofloxacin and to trovafloxacin-100. Additionally, ofloxacin was numerically superior to trovafloxacin-100. The MO's results were similar to those of the sponsor. However, both trovafloxacin-300 and ofloxacin maintained almost 100% bacteriologic eradication rates at the EOS as compared to trovafloxacin-100. This loss of efficacy was not attributable to decreased eradication of any one pathogen but rather to 4 patients classified as clinical failures, with persistence or presumed persistence of their baseline pathogens, (2 isolates *Haemophilus influenzae*, 1 *Streptococcus pneumoniae* and 1 *Pseudomonas aeruginosa*).

Safety Review:

22/73 (30%) trovafloxacin-100 subjects, 52/75 (69%) of the trovafloxacin-300 subjects, and 25/73 (26%) ofloxacin subjects had at least one AE, (all causality). 4/73 (5%) trovafloxacin-100 patients, 19/75 (25%) trovafloxacin-300 patients, and 7/73 (10%) ofloxacin patients discontinued therapy because of an adverse event. All of the discontinuations on the trovafloxacin arms and 8 on the ofloxacin arm were determined to be related to the study drug. The remaining ofloxacin patient (#50210100) was discontinued because of an adverse event (exacerbation of COPD), that was not considered to be treatment-related by the investigator.

The most common adverse events leading to discontinuation on the trovafloxacin arms were related to the central nervous and peripheral nervous systems, with 3/73 (4%) subjects on the trovafloxacin-100 arm

discontinued because of headache or dizziness and 13/75 (17%) subjects on the trovafloxacin-300 arm discontinued because of dizziness, confusion, vertigo, tremor, headache, and/or abnormal gait.

On the trovafloxacin-300 arm, adverse events from the gastrointestinal system also led to discontinuation in 12/75 (16%) subjects. These events included nausea, vomiting, diarrhea, dyspepsia, abdominal pain, and/or gastritis. This is compared to 1/73 (1%) subjects on the trovafloxacin-100 arm who discontinued because of nausea, vomiting, diarrhea, and gingivitis.

On the ofloxacin arm the system most affected and leading to discontinuation was the psychiatric, with 4/73 (5%) subjects discontinued because of insomnia, impaired concentration, or nervousness.

Adverse events from the gastrointestinal tract occurred in 2/73 (3%) subjects on the ofloxacin arm, (abdominal pain, nausea, and/or vomiting).

No subjects were temporarily discontinued from therapy due to adverse events on the trovafloxacin arms. 1/73 (1%) subjects on the ofloxacin arm were temporarily discontinued because of dyspepsia (#50570203).

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

Table 101.14
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
Number of Subjects Treated	73 (100%)	75 (100%)	73 (100%)
Subject-Months of Exposure	24	23.4	22.3
Subjects With At Least One Event	22 (30%)	52 (69%)	26 (36%)
Number of Adverse Events	44	124	47
Subjects with Serious Adverse Events	0	0	1
Subjects with Severe Adverse Events	4 (5%)	4 (5%)	5 (7%)
Subjects Discontinued Due to Adverse Events	4 (5%)	19 (25%)	7 (10%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0	1 (1%)
Subjects Discontinued Due to Objective Test Findings	0	0	0
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0	0

Table 101.15
Adverse Events by Body System, All Causality (Modified Table of Sponsor Table 6.2)

	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
Evaluable for Adverse Events	73 (100%)	75 (100%)	73 (100%)
Subjects With At Least One Event	22 (30%)	52 (69%)	26 (36%)
Subjects Discontinued due to Adverse Event	4 (5%)	19 (25%)	7 (10%)
ADVERSE EVENTS BY BODY SYSTEM:			
Autonomic Nervous	1 (1%)	7 (9%)	1 (1%)
Cardiovascular	1 (1%)	3 (4%)	4 (5%)
Centr. & Periph. Nerv.	8 (11%)	38 (57%)	10 (14%)
Gastrointestinal	9 (12%)	27 (36%)	10 (14%)
General	2 (3%)	7 (9%)	2 (3%)
Liver/Biliary	2 (3%)	0	0
Musculoskeletal	2 (3%)	1 (1%)	0
Other Adverse Events	0	1 (1%)	0
Psychiatric	2 (3%)	4 (5%)	9 (12%)
Reproductive	3 (4%)	0	1 (1%)
Respiratory	3 (4%)	3 (4%)	3 (4%)
Skin/ Appendages	1 (1%)	4 (5%)	1 (1%)
Special Senses	2 (3%)	7 (9%)	2 (3%)

Table 101.16
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
NUMBER OF SUBJECTS:			
Evaluable for Adverse Events	73 (100%)	75 (100%)	73 (100%)
Subjects With At Least One Event	10 (14%)	46 (61%)	21 (29%)
Subjects Discontinued due to Adverse Event	4 (5%)	19 (25%)	6 (8%)
ADVERSE EVENTS BY BODY SYSTEM:			
Autonomic Nervous	1 (1%)	7 (9%)	-
Cardiovascular	-	3 (4%)	-
Centr. & Periph. Nerv.	3 (4%)	34 (45%)	9 (12%)
Gastrointestinal	4 (5%)	24 (32%)	8 (11%)
General	-	5 (7%)	-
Psychiatric	1 (1%)	2 (3%)	9 (12%)
Skin/ Appendages	1 (1%)	4 (5%)	1 (1%)
Special Senses	2 (3%)	7 (9%)	2 (3%)
Liver/Biliary	1 (1%)	-	-
Musculoskeletal	-	1 (1%)	-
Reproductive	-	1 (1%)	1 (1%)
Respiratory	-	4 (5%)	-

Overall, and as noted in previous trials, the most frequent AEs were from the CNS and GI systems. The % of nervous system AEs was approximately five times as high for the trovafloxacin-300 patients as compared to the ofloxacin, and ten times as high as compared to the trovafloxacin-100 arm. However, the incidence of these events on the ofloxacin arm was three times that of the trovafloxacin-100 arm.

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There was also a significantly higher incidence of GI-related AEs on the trovafloxacin-300 arm as compared to the trovafloxacin-100 and the ofloxacin arms. However, the incidence of these events was higher on the ofloxacin arm as compared to the trovafloxacin-100 arm.

The further breakdown of these events can be found on the MO's Table 101.17.

Table 101.17
Most Common CNS and GI AEs/Treatment-related/All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin-100 N = 73		Trovafloxacin-300 N = 75		Ofloxacin N = 73	
	10	14%	46 (61%)		21 (29%)	
Nervous system						
Headache	2	3%	7	9%	1	1%
Dizziness	3	4%	28	37%	7	10%
GI System						
Nausea	2	3%	11	15%	3	4%
Vomiting	1	1%	7	9%	2	3%
Dyspepsia	1	1%	3	4%	1	1%
Diarrhea	2	3%	1	1%	-	-
Abdominal Pain	-	-	4	4%	2	3%
Increased Appetite	-	-	2	3%	-	-

Other events of note included:

Flushing and sweating in 1% of the trovafloxacin-100 patients, 4% of the trovafloxacin-300 patients, and none of the ofloxacin patients.

Fatigue in 7% of the trovafloxacin-300 patients and none of the trovafloxacin-100 and ofloxacin patients.

Insomnia in 10% of the ofloxacin and none of the trovafloxacin-300 or trovafloxacin-100 patients.

Pruritus in 1% of the trovafloxacin-100, 5% of the trovafloxacin-300, and 1% of the ofloxacin patients.

Tinnitus in 1% of the trovafloxacin-100 and 3% of the trovafloxacin-300 patients.

Visual abnormalities in 1% of the trovafloxacin-100 and ofloxacin patients and 4% of the trovafloxacin-300 patients.

Overall, the AE profile in this trial was similar to that seen in the previously reviewed indications and no deaths were reported.

Listed below are the severe adverse events that were considered treatment-related:

Trovafloxacin-100 (N= 2):

- #50340331: dizziness, day 1, therapy discontinued.
- #50560176: headache, day 3, therapy discontinued.

Trovafloxacin-300 (N =2):

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- #50470134: flushing, tachycardia, dizziness, tremors, nausea, and vomiting, day 1, therapy discontinued.
- #50590261: lightheaded, day 3, therapy discontinued.

Ofloxacin (N = 4):

- #50210097: sleeplessness, day 1, therapy discontinued
- #50220051: abnormal vision, dizziness, day 3, therapy discontinued
- #50230039: insomnia, day 1, therapy discontinued
- #50340282: nervousness, day 7, therapy discontinued

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Serious Adverse Events:

3 subjects had serious adverse events, one on the trovafloxacin-300 arm and 2 on the ofloxacin arm. None was considered related to therapy. In all cases the patients developed pneumonia after being discontinued from the study drugs for other adverse events within the first 2 days of therapy.

Clinical Laboratory Abnormalities:

The sponsor submitted tables 4.1, 4.2, 6.1, and 3.3, all of which include listings of patients who discontinued therapy because of abnormalities.

The sponsor's text has been copied from page 40 of the study report:

The percentage of subjects with laboratory values that met the criteria for clinical significance during the study was $\leq 4\%$ in all three treatment groups for individual laboratory parameters except erythrocyte sedimentation rate (ESR), triglycerides, urine white blood cells, and urine red blood cells (trovafloxacin 100 mg and ofloxacin groups only).

For liver function parameters, the percentage of subjects with clinically significant abnormalities in alanine aminotransferase (SGPT, $>2.0 \times \text{ULN}$), aspartate aminotransferase (SGOT, $>2.0 \times \text{ULN}$), and lactate dehydrogenase (LDH, $>2.0 \times \text{ULN}$) values was 1% (SGPT) in the trovafloxacin 100 mg group and 2% each for SGOT and LDH in the ofloxacin group. No other clinically significant liver function abnormalities were reported in any of the three treatment groups.

Medical Officer's Comment: The MO reviewed table 3.3, appendix III, clinical laboratory abnormalities, and found the following:

Trovafloxacin-100 (N = 2):

- #50150070: increased serum creatinine after 10 days of therapy, remained elevated. Final value
- #50340246: increased ALT after 11 days of therapy. by the EOS.

Trovafloxacin-300 (N = 1):

- #50150311: increased serum creatinine after 10 days of therapy, remained elevated. Final value

Ofloxacin (N = 2)

- #50340230: increased AST after 9 days of therapy *Final value remained elevated.*
- #50340226: increased LDH after 11 days of therapy *Final value had*

No other abnormalities were of significance as per the MO, including the ESR elevations which may have been due to the underlying disease process.

Conclusions:

As per the Sponsor:

The main portion of the sponsor's conclusion can be found at the conclusion of the sponsor's efficacy analysis. Before proceeding to the Phase III trials, the sponsor concluded:

(Copied from page 42 of the study report):

Trovafloxacin 100 mg or 300 mg and ofloxacin 400 mg BID were similar with respect to clinical response rates at the end of treatment and at the second follow-up evaluation for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment. At the second follow-up evaluation, bacteriologic relapses were observed in four subjects in the trovafloxacin 100 mg group. However, because of the small number of bacteriologically evaluable subjects in this treatment group (N=24), no definitive conclusions could be drawn. Both trovafloxacin 100 mg and 300 mg once daily were generally well tolerated; however, the incidence of adverse events in the 100 mg group was lower than that observed in the 300 mg group.

Reviewer's Conclusions:

Few conclusions could be drawn from this Phase II, pilot study comparing trovafloxacin 100 mg, trovafloxacin 300 mg, and ofloxacin in the treatment of AECB for 10 days. The study was not adequately powered to be able to ascertain true differences between the treatment arms.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 57/65 (87.6%) for the trovafloxacin-100 patients, 52/54 (96.3%) for the trovafloxacin-300 patients, and 57/61 (93.4%) for the ofloxacin patients. Based on a 95% CI, trovafloxacin-300 was equivalent to both comparator arms and ofloxacin was superior to the trovafloxacin-100 arm. Equivalence was not shown between the trovafloxacin-100 arm and the ofloxacin arm.

When patients receiving systemic steroids were excluded, the clinical response at the EOS was 49/53 (92.4%) for the trovafloxacin-100 patients, 47/49 (95.9%) for the trovafloxacin-300 patients, and 51/52 (94.4%) for the ofloxacin patients. Based on a 95% CI, trovafloxacin-300 was superior to both comparators and ofloxacin was superior to trovafloxacin-100.

Thus, the results for this variable were similar, whether or not patients on systemic steroids were included in the analyses.

The bacteriologic efficacy analysis yielded the following at the EOT, 29/29 (100%) for the trovafloxacin-100 arm, as compared to 20/20 (100%) and 21/22 (95.4%) for the trovafloxacin-300 and ofloxacin arms respectively.

Numerically all 3 arms were comparable at the EOT.

At the EOS, the pathogen eradication rate decreased to 25/39 (86.2%) on the trovafloxacin-100 arm, but remained the same for the trovafloxacin-300 and ofloxacin arms. This decrease in eradication rate was also seen in the sponsor's analysis. Statistical significance could not be drawn from these results, as the number of bacterial isolates was very small.

Specific pathogen eradication rates for the three main pathogens, can be seen in the table below:

Table 101.18
Bacteriologic Eradication Rates (as per the MO)

Pathogen	Trovafloxacin-100		Trovafloxacin-300		Ofloxacin	
	EOT	EOS	EOT	EOS	EOT	EOS
<i>Haemophilus influenzae</i>	12/12 (100%)	10/12 (80%)	6/6 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
<i>Moraxella catarrhalis</i>	6/6 (100%)	6/6 (100%)	2/2 (100%)	2/2 (100%)	8/8 (100%)	8/8 (100%)
<i>Streptococcus pneumoniae</i>	3/3 (100%)	2/3 (67%)	4/4 (100%)	4/4 (100%)	3/3 (100%)	3/3 (100%)

These results mirrored those of the sponsor.

There were no deaths in this study. The primary adverse events were from the central and peripheral nervous systems, and consisted of multiple complaints of dizziness, visual disturbances, and headache. The trovafloxacin-300 arm had a much higher number of treatment-related adverse events from these systems, 34/75 (45%) as compared to the trovafloxacin-100 arm 3/73 (4%). Additionally, there was a higher incidence of GI complaints on the trovafloxacin-300 arm 24/75 (32%) as compared to the trovafloxacin-100 arm, 4/73 (5%).

There were no significant laboratory abnormalities.

In conclusion, trovafloxacin appeared effective in the treatment of AECB caused by the three main pathogens; however, equivalence was shown only for the trovafloxacin-300 arm versus the approved comparator, ofloxacin. Unfortunately, there was also a high incidence of adverse events on this arm. The trovafloxacin-100 arm was inferior to both comparator arms and additionally, at the EOS, the pathogen eradication rate decreased only for this arm.

Based on the above, no real conclusions could be drawn by the MO. The sponsor elected to proceed with the pivotal trials at the lower dose of trovafloxacin, 100 mg qd orally, for 7 days.

Study 154-109

TITLE:

A RANDOMIZED, DOUBLE BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study dates: November 16, 1994 - June 22, 1995

Objective: The objective of this study was to compare the safety and efficacy of trovafloxacin with clarithromycin in the treatment of subjects with acute exacerbation of chronic bronchitis.

List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
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	5072	George Bensch, M.D.
	5073	Jean-Paul Bonnet, D.O.
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	5075	Edwin Bronsky, M.D.
	5076	Timothy Bruya, M.D.
	5077	Jacques Caldwell, M.D.
	5078	C. Andrew Deabate, M.D.
	5079	W. Travis Ellison, M.D.
	5080	Frank Garamy, Jr., M.D.
	5081	James Garofalo, M.D.
	5082	Mark Gotfried, M.D.
	5083	Robert Frost Jones, M.D.
	5084	Craig Laforce, M.D.
	5085	Thomas Littlejohn, III, M.D.
	5086	Michael Peveler, M.D.
	5087	Gary Post, M.D.
	5088	Robert Rosen, M.D.
	5089	David Stryker, M.D.
	5090	Alan Wanderer, M.D.
	5091	W. Murray Yarbrough, M.D.
5092	William Ziering, M.D.	
5094	William McCall, Jr, M.D.	
5095	Robert Hippert, M.D.	
5121	Marcus Zervos, M.D.	
5124	Kent Anthony, M.D.	
5125	Steven Bowman, M.D.	
5127	Meera Dewan, M.D.	
5129	Jeffrey Hartford, M.D.	
5130	Spencer Jones, M.D.	
5132	Michael McAdoo, M.D.	
5133	Dennis Mikolich, M.D.	
5134	David Miller, D.O.	

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	5135	Michael Nelson, M.D.
	5136	David Schreck, M.D.
	5137	Richard Sterling, M.D.
	5138	Randall Stoltz, M.D.
	5139	James Sullivan, M.D.
	5140	John Upchurch, M.D.
	5181	James Taylor, M.D.
	5213	Jason Chu, M.D.
	5215	George Knull, M.D.
	5250	Carlos Morales, M.D.
	5499	Harvey Tilker, Ph.D.
	5743	Boyd Harrison, M.D.
	5776	Daniel Krichbaum, PharmD.
	5777	Alan Rosenthal, PharmD.
	5853	Chandra Khurana, M.D.
	6428	Alan Storrow, M.D.

Study Design: Study 154-109 was a Phase III, randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg daily as a single dose in the morning), versus clarithromycin (1000 mg daily as 500 mg in the morning and evening), administered orally for 7 days for the treatment of AECB.

Protocol Overview:

Copied below from the electronic submission, appendix A of the study report is the sponsor's schedule of visits and procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number	1	2	3	4
Study day:	Day 1	Day 4	Day 8	Day 28
Allowable Window:	-48 hours	Day 3-5	Day 7-9	Day 25-31
Treatment Period	Day 1 to Day 7			
Follow-up period	Day 8 to Day 31			
Informed consent	X			
Demographic Information	X			
Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record			X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X			
Microbiology				
Sputum Gm stain	X	X	X	X
culture & sensitivity	X	X	X	X
serology	X			
Safety laboratory tests				
hematology	X		X	abn
biochemistry	X		X	abn
urinalysis	X		X	abn
Pregnancy test*	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's evaluation				
clinical		X	X	X

abn= abnormal at previous visit or clinically significant adverse event
 *to be done by local site for women of child bearing potential

As noted from the above schedule, all baseline assessments were performed within the 48 hours prior to the start of the study.

At the baseline visit (V1, Day 1), all subjects were to have a clinical picture characterized by the following criteria:

- Clinical signs and symptoms of chronic bronchitis defined by the presence of cough, dyspnea, lung sounds (rales and rhonchi), and excessive secretion of mucus. Subjects were to have coughed up sputum on most days during three consecutive months for two or more successive years.
- Signs and symptoms characteristic of acute bacterial exacerbation, including increased dyspnea and increased sputum volume and purulence.
- Purulent sputum was to be present and defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field (LPF) [10X].
- The absence of pneumonia on chest x-ray.

Those patients who met the above definition and who gave informed consent were eligible for randomization, if they fulfilled the inclusion and exclusion criteria. Baseline visit assessments also included collection of demographic information, concurrent disease, medical history and physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature).

The clinical assessment of signs and symptoms of AECB was to include sputum characteristics, cough, dyspnea, lung sounds, and chest x-ray (unless one had been taken within 48 hours of the baseline assessment).

Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per LPF, squamous epithelial cells per LPF), of sputum were performed. Subjects with inadequate sputum specimens were not randomized and no further evaluation was performed. Hematology, serum chemistry, and urinalysis determinations were performed and serum was obtained at baseline for the determination of antibodies to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Susceptibility to the study drugs, trovafloxacin and clarithromycin, was determined from bacterial isolates grown from adequate sputum specimens. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. However, if no pathogen was detected on baseline culture, the continuation of the study drug was at the discretion of the investigator. If a pathogen was resistant to study medication, study treatment could have continued at the investigator's discretion, only if there was evidence of clinical improvement.

At Visits 2 (V2: Day 4) and 3 (V3: Day 8; EOT), a determination of clinical efficacy was performed. These determinations included clinical assessments of signs and symptoms of AECB and adequate sputum samples for culture and sensitivity to assess bacteriological response to study therapy. Safety was assessed through the recording of concomitant medication, vital signs, study drug dosing, and adverse events. At Visit 3, hematology, chemistry, and urinalysis tests were performed.

At Visit 4 (V4: Day 28; EOS) efficacy and safety observations were again performed as in V2 and V3 with the exception of the laboratory analyses which were only performed if a clinically significant abnormality was present at V3 (Day 8) or if the subject was experiencing a clinically significant adverse event. Final serology was performed at this visit and the investigator provided a final evaluation of clinical response.

Compliance:

This study was conducted in compliance with a local or central Institutional Review Board (IRB) and informed consent regulations.

Concomitant Illnesses and Medications:

The investigator documented all concomitant medication usage at each visit. This included any therapeutic interventions. No other antimicrobials were allowed. If another antimicrobial was used, the patient was classified as a treatment failure.

Patients taking theophylline had levels monitored at each study visit. Subjects receiving warfarin had prothrombin time monitored at each study visit. Dose adjustments for theophylline or warfarin were made as clinically appropriate. The concomitant use of systemic corticosteroids was allowed in the form of 10 mg of prednisone or less daily. The use of other (non-anti-infective) medications was limited to those essential to the care of the subject. The use of any other investigational drug was prohibited. Mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing.

Discontinuation of Study Therapy:

Discontinuations were allowed at the discretion of the investigator only if the patient showed no signs of clinical improvement or worsening before the EOT (V3).

Additionally, patients could discontinue therapy if they developed an adverse event or a clinically significant laboratory abnormality.

The reason for discontinuation was recorded on the CRF and the patient followed through the EOS, if possible. The investigator made a final evaluation at the time of discontinuation.

Protocol Amendments:

This protocol was amended once on October 11, 1994, as detailed below:

- Subjects receiving treatment with terfenadine or who may have required treatment were excluded from study enrollment.
- Monitoring procedures for subjects who took theophylline during the study were specified.

Precautions:

Because clarithromycin may raise theophylline levels, all subjects on concomitant theophylline were to have had serum theophylline levels monitored periodically at a local laboratory. Subjects were also instructed not to donate blood during the study or for one month after the end of the study.

Study Population:

Approximately 400 subjects with acute exacerbation of chronic bronchitis were expected to be randomized to one of the treatment groups. Each study site attempted to enrol at least 10 patients.

Inclusion and Exclusion Criteria:

(Copied from page 16 of the original protocol)

Inclusion criteria

1. Age $\geq$ 40 at baseline.
2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or $\leq$ one year post-menopausal) must have a negative urine gonadotrophin pregnancy test immediately prior to entry in the study and must use adequate contraception both during and for one month after the end of the study.
3. Clinically documented acute exacerbation of chronic bronchitis. Diagnostic criteria for chronic bronchitis will include sputum production on most days during three

consecutive months for two or more successive years. The criteria for an acute exacerbation is defined as the presence of increased dyspnea, sputum volume and sputum purulence.

4. Purulent sputum must be present and defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field (10X).
5. Written informed consent must be obtained.

Exclusion Criteria

1. Pregnant women or nursing mothers.
2. Known hypersensitivity to any quinolone or macrolide antibiotic.
3. Subjects who are currently hospitalized for any reason.
4. Treatment with any other systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline visit.
5. Subjects with infections that may require treatment with an antibiotic other than the study drugs.
6. Subjects with any of the following conditions:
 - a. pulmonary disease whose severity is sufficient to warrant initial intravenous antibiotic therapy
 - b. evidence of pneumonia on chest X-ray
 - c. cystic fibrosis
 - d. significant gastrointestinal or other conditions which may affect study drug absorption.
 - e. known Acquired Immunodeficiency Syndrome (AIDS)
 - f. neutropenia, defined as a total white blood cell count less than 2500 leukocytes/mm³ or absolute neutrophil count less than 1000/mm³
 - g. immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including treatment with greater than 10 mg/day of systemic prednisone or equivalent)
 - h. history of epilepsy or seizures
7. Treatment with another investigational drug within four weeks prior to the baseline visit.
8. Prior enrollment in this protocol.
9. Evidence of recent drug or alcohol abuse or dependence.

Medical Officer's Comment: *Although this Phase III study was very similar in design to the Phase II study, 154-101, the following major differences were noted:*

- *The exclusion of patients < 40 years of age, in order to ensure the enrollment of an appropriate population.*
- *The change in the duration of therapy to 7 days.*

- *The exclusion of severely immunosuppressed patients on steroids by including only those patients on no more than 10 mg prednisone daily.*
- *The decrease in the number of visits to 4 as compared to 5.*

Overall, the MO agreed with the inclusion and exclusion criteria.

Randomization and Blinding:

The investigator sequentially assigned study numbers to the patients as they were determined to be eligible for treatment. The study number was entered onto the patient's CRF and the patient received study medication with the corresponding number. Study medication was blinded by a double-dummy technique.

Dosage Form and Administration:

Study drug was in the form of tablets and packaged in blister cards using a double dummy technique to maintain blinding. The study drug administration schedule provided one of the following two doses of study drug, dependent on the random assignment:

- Trovafloxacin: 100 mg daily (1 x 100 mg tablets) as a single dose in the morning.
- Clarithromycin: 1000 mg daily in two equally divided doses (morning, evening).

The blister cards contained sufficient supplies for a 7 day course of treatment.

In order to maintain blinding, subjects were instructed to take the following tablets during each day of the 7 days of treatment:

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloxacin (100 mg/d)	1-placebo for clarithromycin 1-trovafloxacin x 100 mg	1-placebo for clarithromycin
Clarithromycin (1,000 mg/d)	1-clarithromycin 500 mg	1-clarithromycin 500 mg 1-placebo for trovafloxacin

The blister card with the randomization number corresponding to that assigned to the subject was given to the subject at V1. Subjects began study drug medication with the morning dose (even if it was not the morning), and completed a full day of medication on Day 1.

The subjects were informed that compliance with taking all tablets as instructed was imperative.

Note: The concomitant use of systemic corticosteroids was allowed in patients receiving chronic, low dose oral steroids (10 mg prednisone daily or less).

The investigator was responsible for recording the receipt of study drug, its usage, and for ensuring the supervision of the storage and allocation of these supplies. At intervals as appropriate, or upon completion or termination of the study, all drug supplies unallocated or unused by the patient were returned to Pfizer.

To ensure adequate records of disposition of unused supplies at the study site and to facilitate the final drug accountability process a Drug Inventory Record was maintained by the investigator.

Compliance:

Patients were informed that compliance with taking all tablets as instructed was imperative. Outpatients were asked to bring all unused medication and empty containers to the first follow-up visit. All doses taken were charted in the case report form.

Microbiologic Methods:

Bacteriologic response was assessed at V3 (EOT) and V4 (EOS). Only those sputum specimens that were adequate, as defined previously, were cultured. If there was no obtainable “adequate” specimen, at the EOT or EOS, and the patient was cured or improved, a presumptive assignment of eradication was made.

All specimens were initially sent to the local laboratory for culture. Isolates considered significant were sent to the central laboratory where susceptibility testing was performed. Local susceptibility data was used only if the central laboratory’s data was missing.

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 17 of the study report)

<u>Criteria</u>	<u>Trovafloxacin</u>	<u>Clarithromycin</u>	
	MIC µg/mL	Zone size (mm) 15 µg disc	MIC µg/mL
Susceptible	≤2	≥18 [≥13]	≤2 [≤8]
Intermediate	4	14-17 [11-12]	3-7 N/A
Resistant	≥8	≤13 [≤10]	≥8 [≥32]

Susceptibility breakpoints for trovafloxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and Zone diameter (mm) for 15 µg disk for clarithromycin are based on National Center for Clinical Laboratory Standards (NCCLS) criteria for organisms other than *Haemophilus*. The criteria for *Haemophilus* is given in brackets.

Chlamydia pneumoniae and *M. pneumoniae* serology were to be performed at baseline (Day 1) and at Visit 4 (Day 28; end of study). A four-fold increase in titer was considered positive for the presence of the organism.

Clinical Response:

Clinical response was determined by the sponsor and evaluated at the EOT: V3 (Day 8), and at the EOS: V4 (Day 28), or at the time of discontinuation from study. Clinical response was primarily based on the global assessment of the clinical presentation of the subject at the evaluation time point.

Clinical assessment was based upon resolution or improvement of clinical laboratory signs of infection such as, disappearance or decreased purulent sputum production, changes in dyspnea and cough, and stabilization in general physical condition. Supporting data to evaluate clinical response was to include reduction in leukocytosis. Clinical response was to be classified as cure, improvement, failure, or indeterminate, as defined in the introduction of the MOR.

Copied below, from page 18 of the original protocol, are the parameters of assessment:

Subjects were assessed for signs and symptoms, as detailed below, and these assessments were recorded on the CRF.

1. Sputum was obtained at baseline (V1) and at every visit thereafter. Macro and micro evaluations were performed.
2. Chest x-ray was obtained at baseline (V1) and at any other time point deemed necessary by the investigator.
3. Cough, dyspnea, chills/rigors, constitutional symptoms, and lung sounds were each assessed at baseline (V1) and at every visit thereafter and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

Medical Officer's Comment: For the MO's comment on both clinical and bacteriologic response, see the MOR of study 154-101. The MO points out that in this study, the determination of clinical response was made by the sponsor and not by the investigator (154-101). The sponsor's TOC visit was the EOT but as noted previously, assessments could be made at either visit. Therefore, the sponsor's population was not static but could contain patients with either visit and not necessarily both.

Safety Assessments:**Adverse Events:**

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the CRF. Following resolution of the adverse event or at the EOS, the investigator's judgment of causality of the adverse event was recorded.

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the sponsor project clinician immediately by telephone. In the case of death, a summary of available autopsy findings was submitted as soon as possible to the sponsor.

In addition, physical examination was performed at baseline (V1). Concomitant medication use and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) were evaluated at V1 and at V2, V3 (EOT), and V4 (EOS).

Clinical Laboratory Tests:

Hematology, coagulation, serum chemistry, and urinalysis determinations were performed at baseline (V1), and at V2 and V3. At V4, hematology, coagulation, serum chemistry, and urinalysis were only performed if a clinically significant abnormality was present at V3.

Data Analysis:

See the introduction to the MOR for a review of the sponsor's subsets and their definitions.

Clinical Evaluability Criteria:

See the introduction to the MOR for a review of the sponsor's criteria.

Criteria for Bacteriological Evaluability:

See the introduction of a review of the sponsor's criteria.

Primary and Secondary Endpoints for Efficacy:

Primary efficacy endpoints were:

- Sponsor-defined subject clinical response at the EOT and;
- Pathogen eradication rates at the EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at the EOS;
- Investigator-defined subject clinical response at the EOT, and sponsor-defined and investigator-defined subject clinical response at the EOS.

Medical Officer's Comment: *As stated in the introduction, the MO applied the TOC to the later EOS visit, therefore the primary endpoint for the MO's analysis was clinical response at that timepoint. This study differed from 154-101, in that there were 2 primary efficacy variables, that is, both clinical and bacteriological at the EOT. The MO's management of the data was unchanged.*

The MO determined that in the MO analysis, the secondary endpoints would be applied to the EOS. However, if there was a bacteriologic response at the EOT of eradication and no response at the EOS, the MO elected to carry this response forward as a "presumed eradication." Failures/persistences were always carried forward in both the sponsor's and the MO's analyses.

Definitions of Response:

Please refer to the introduction of the MOR for the sponsor's definitions.

Interim Analyses:

No interim analyses were performed.

Demographics:

As per the sponsor, 410 patients were randomized to treatment (210 subjects to receive trovafloxacin (51.2%), and 200 to receive clarithromycin (48.7%)).

Of the treated patients, 384 completed treatment (201/210 (95.7%) trovafloxacin-treated patients and 183/200 (91.5%) clarithromycin-treated patients). 26 patients were withdrawn from treatment, (9 trovafloxacin, and 17 clarithromycin), but 14 of these completed the study. In addition to these 12 (4 trovafloxacin and 8 clarithromycin patients withdrawn during the study), an additional 4 clarithromycin patients were withdrawn during follow-up, thus 16 patients were withdrawn from the study (4 trovafloxacin and 12 clarithromycin).

The MO has recreated sponsor's Table 1.1, the Disposition of Enrolled subjects.

Table 109.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin 100 mg	Clarithromycin 500 mg bid
Subjects with Signed Consent	443		
Withdrawn Prior to Randomization	33		
Randomized		210	200
Randomized, But Not Treated		0	0
All Treated Subjects		210 (100%)	200 (100%)
Withdrawn During Treatment		9 (4%)	17 (9%)
Completed Treatment		201 (96%)	183 (92%)
Withdrawn During Follow-up		0 (0%)	4 (2%)
Completed Study		206 (98%)	188 (94%)
Completed Treatment and Study		201 (96%)	170 (90%)
Withdrawn During Treatment and Study		4 (2%)	8 (4%)

Medical Officer's Comment: *There was a higher dropout rate from the clarithromycin arm as compared to the trovafloxacin arm.*

Copied and modified below is sponsor's Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

**Table 109.2
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)**

Center	Total Randomized N = 410 (100%)		Trovafloxacin Randomized and Treated N = 210 100%		Clarithromycin Randomized and Treated N = 200 100 %	
5005	6	1.5	4	2	2	1
5022	4	1	2	1	2	1
5032	4	1	2	1	2	1
5041	12	2.9	6	2.9	6	3
5042	8	.2	4	2	4	2
5072	12	2.9	6	2.9	6	3
5073	1	0.2	1	0.5	0	0
5074	6	1.5	2	1	4	2
5075	3	0.7	1	0.5	2	1
5076	40	9.7	20	9.5	20	10
5077	1	0.2	1	0.5	0	0
5078	36	8.8	18	8.6	18	9
5079	7	1.7	4	2	3	1.5
5080	24	5.8	12	5.7	12	6
5081	8	2	4	2	4	2
5082	2	0.5	2	1	0	0
5083	6	1.5	3	1.5	3	1.5
5085	2	0.5	1	0.5	1	0.5
5087	2	0.5	1	0.5	1	0.5
5089	3	0.7	1	0.5	2	1
5091	8	2	4	2	4	2
5092	16	3.9	8	4	8	4
5095	5	1.2	2	1	3	1.5
5121	3	0.7	1	0.5	2	1
5124	1	0.2	1	0.5	0	0
5125	3	0.7	2	1	1	0.5
5127	65	15.9	33	15.7	32	16
5129	14	3.4	7	3.3	7	3.5
5130	16	3.9	8	4	8	4
5132	9	2.2	4	2	5	2.5
5133	3	0.7	2	1	1	0.5
5134	5	1.2	3	1.5	2	1
5135	2	0.5	1	0.5	1	0.5
5136	1	0.2	1	0.5	0	0
5137	8	2	4	2	4	2
5138	7	1.7	3	1.5	4	2
5139	16	3.9	8	4	8	4
5140	21	5.1	10	4.8	11	5.5
5181	3	0.7	2	1	1	0.5
5213	1	0.2	1	0.5	0	0
5250	2	0.5	2	1	0	0
5499	4	1	2	1	2	1
5743	1	0.2	1	0.5	0	0
5776	1	0.2	1	0.5	0	0
5853	8	2	4	2	4	2

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Medical Officer's Comment: There were 45 centers, all of which enrolled patients. There was no center with > 20% of the patients, however, there was 1 center with approximately 15% of the patients (#5127).

Copied below is the sponsor's table of all randomized patients and the study evaluation groups:

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ON ORIGINAL

Table 109.3
Study Evaluation Groups/All Randomized Patients as per the Sponsor
(Format modified by MO)

	Trovafloxacin 100 mg	Clarithromycin 500 mg bid
All Randomized Subjects	210 (100%)	200 (100%)
All Treated Subjects	210 (100%)	200 (100%)
Subjects with Inappropriate Baseline Diagnosis	2 (< 1%)	1 (<1%)
Clinically Intent- to- Treat Subjects	208 (>99%)	199 (>99%)
Clinically Eyaluable Subjects	203 (97%)	188 (94%)
Clinically evaluable with baseline pathogen	93 (44%)	86 (43%)
Clinically Not Evaluable Subjects	5 (2%)	11 (6%)
Insufficient Therapy	1 (< 1%)	4 (2%)
No post-baseline clinical assessment	1 (<1%)	2 (1%)
Prior Antibiotic therapy	4 (2%)	3 (2%)
Concomitant Antibiotic therapy	0	6 (3%)
Clinically evaluable at EOS	197 (94%)	178 (89%)
Clinically evaluable at EOS with baseline pathogen	91 (43%)	80 (40%)
Bacteriologically Eyaluable Subjects	93 (44%)	81 (41%)
Bacteriologically Not Evaluable Subjects	110 (52%)	107 (54%)
No Baseline Pathogen	108 (51%)	105 (53%)
Baseline culture Outside Window	2 (<1%)	1 (<1%)
No post-baseline cultures	0	2 (1%)
Bacteriologically Eyaluable at EOS	87 (41%)	77 (39%)
Analyzed for Safety		
Adverse Events	210 (100%)	200 (100%)
Laboratory Data	204 (97%)	189 (95%)

* Subjects may have had more than one reason to have been unevaluable

Medical Officer's Comment: 16 of the randomized subjects were not clinically evaluable, (5/210 (2%) trovafloxacin-treated subjects and 11/200 (6%) clarithromycin-treated subjects).

The bacteriologically evaluable population was a subset of the clinically evaluable population and the bacteriological ITT population, which were both subsets of the clinical ITT population.

There were a total of 9/210 (4.2%) trovafloxacin-treated patients who discontinued therapy. 5 of these patients continued the study and 4 did not. 7/9 were clinically evaluable.

On the clarithromycin arm, 17 patients discontinued treatment. 9 of these patients continued the study and 8 did not. 11/17 were clinically evaluable.

All patients who discontinued treatment were reviewed (see below):

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Trovafloxacin (N = 9):

- #50410683: 67 YO developed nausea after 5 days and discontinued both the study and treatment. This patient had *Moraxella catarrhalis* in all sputum cultures. Clinically evaluable at the EOS as an improvement with presumed persistence of the pathogen. Reviewer agreed because the patient did not receive alternative therapy.
- #50420165: 40 YO withdrawn from treatment on day 3 because of a laboratory abnormality (low platelet count). This patient completed the study and was clinically and bacteriologically evaluable.

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specimen at the EOS. The patient was classified as a cure with presumed eradication. Reviewer disagreed because the patient did not receive the MO-specified minimum duration of therapy and therefore was unevaluable.

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- #50780282: 41 YO discontinued treatment and the study on day 5 because of nausea and vomiting. The patient was clinically and bacteriologically evaluable and had *Staphylococcus aureus* as the initial isolate. Sputum was not re-cultured and the patient was classified as a cure at the EOT. This patient was not evaluable for MO because there was no EOS visit.
- #50830108: 60 YO withdrawn on day 5 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed. This patient had no baseline pathogen.
- #50950097: 41 YO withdrawn on day 7 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed. This patient had *Candida spp.* and *Citrobacter* as baseline pathogens and was treated with Augmentin®.
- #51330345: 60 YO withdrawn from treatment and study after 5 days of therapy because he was found to have pneumonia on CxR. This patient was clinically and bacteriologically evaluable. *Haemophilus influenzae* was isolated from the baseline and EOT sample and he was carried forward as a failure. Reviewer agreed. The patient was treated with Augmentin®.
- #51390399: 73 YO withdrawn from treatment on day 5 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed. This patient had *Moraxella catarrhalis* as a baseline pathogen which was eradicated with amoxicillin.
- #51400457: 63 YO withdrawn from treatment on day 1 because of an adverse event. The patient completed the study but was not clinically or bacteriologically evaluable. *Streptococcus pneumoniae* was isolated at baseline and the patient was treated with Ceclor® and clarithromycin. Reviewer agreed. *
- #51810561: 70 YO withdrawn on day 3 because of an exacerbation of COPD. The patient did not complete the study and was not clinically or bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed. *

**APPEARS THIS WAY
ON ORIGINAL**

Clarithromycin (N=17):

- #50220524: 53 YO withdrawn from treatment on day 1 because of an exacerbation of COPD. The patient did not complete the study and was not clinically or bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed. *
- #50720010: 71 YO withdrawn from treatment on day 5 because he received an alternative antimicrobial in error. The patient completed the study and was clinically and bacteriologically evaluable. This patient was classified as an evaluable failure with presumed persistence of the baseline pathogen, *Serratia marcescens*. Reviewer agreed.
- #50720013: 72 YO withdrawn from treatment on day 4 because of an adverse event, (leg pain). The patient completed the study and was clinically but not bacteriologically evaluable. This patient was classified as an evaluable failure. Reviewer agreed.
- #50760039: 73 YO withdrawn on day 1 because of a protocol violation, (seizure disorder). The patient did not complete the study and was not clinically or bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed. *

- #50760221: 66 YO withdrawn from treatment on day 3 because of an adverse event, (atrial fibrillation). The patient did not complete the study and was clinically and bacteriologically evaluable. This patient was classified as an improvement with presumed eradication of the baseline pathogen, *Haemophilus influenzae*. No further antibiotics were prescribed. Reviewer disagreed because patient did not receive the minimum duration of therapy necessary to be evaluable per the MO. Additionally, this patient was excluded from the MO evaluable population because of a missing EOS visit.
- #50790059: 73 YO withdrawn from treatment on day 5 because of an adverse event, (laceration, and nausea). The patient did not complete the study and was clinically but not bacteriologically evaluable. This patient was carried forward as an evaluable failure. Reviewer agreed.
- #50790061: 43 YO withdrawn from treatment on day 7 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. This patient was clinically but not bacteriologically evaluable. Reviewer agreed.
- #50920239: 76 YP withdrawn from treatment on day 1 because of an adverse event, (hives). The patient completed the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. *
- #50950101: 47 YO withdrawn from treatment on day 2 because of LFT elevations. The patient completed the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. *
- #51210406: 60 YO withdrawn on day 4 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. Reviewer agreed.
- #51270473: 48 YO withdrawn from treatment on day 2 because of an adverse event, (nausea). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #51270545: 48 YO withdrawn from treatment on day 5 because of an adverse event, (nausea). The patient completed the study and was clinically but not bacteriologically evaluable. This patient was carried forward as an evaluable failure. Reviewer agreed. Patient received an additional week of ofloxacin.
- #51270587: 43 YO withdrawn on day 7 for insufficient response. The patient completed the study and was carried forward as an evaluable failure. This patient was clinically and bacteriologically evaluable. Reviewer agreed. *Staphylococcus aureus* was isolated as the baseline pathogen and was eradicated after Augmentin® treatment.
- #51340454: 48 YO withdrawn from treatment on day 5 because of an adverse event, (nausea). The patient completed the study and was clinically but not bacteriologically evaluable. This patient was carried forward as an improvement at the EOS. Reviewer disagreed because the patient did not receive the minimum duration of therapy necessary as per the MO criteria and therefore was excluded.
- #51370508: 55 YO withdrawn from treatment on day 3 because of an adverse event, (nausea). The patient did not complete the study and was clinically but not bacteriologically evaluable. This patient was classified as an improvement at the EOT but was not seen at the EOS. This patient was unevaluable by MO criteria.
- #51400358: 47 YO withdrawn from treatment on day 5 because of an adverse event, (nausea). The patient completed the study and was clinically and bacteriologically evaluable. This patient was carried forward as a clinical failure with eradication of the baseline pathogen, *Streptococcus pneumoniae*. Reviewer agreed.

- #51810562: 71 YO withdrawn on day 3 because he did not meet randomization criteria (incorrectly performed Gram stain). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #54990539: 50 YO withdrawn on day 4 because of an adverse event. The patient was classified as a "cure" by the sponsor but was excluded by the MO because he did not receive the minimum duration of therapy necessary to be evaluable.

Although the 9 trovafloxacin and 17 clarithromycin patients listed above, represent discontinuations from therapy or the study, only those patients with a * are those patients who were excluded from the sponsor's clinical efficacy analysis (1 trovafloxacin and 6 clarithromycin). An additional 6 trovafloxacin-treated patients and 5 clarithromycin-treated patients were clinically unevaluable as per the sponsor. The most common reason for exclusion was prior antimicrobial therapy, (4 trovafloxacin, and 3 clarithromycin).

All clinically unevaluable patients (as per the sponsor), are listed below:

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Trovafloxacin (N = 7)

- #50828089: Prior antibiotic therapy: Ciprofloxacin up until day -1. *Pseudomonas aeruginosa* at baseline. Reviewer agreed.
- #51270439: Inappropriate baseline diagnosis (sputum sample was not adequate): *Moraxella catarrhalis* and *Streptococcus pneumoniae* at baseline. *Moraxella* eradicated but *Streptococcus* was persistent. Patient would have been a failure at EOS. Received ofloxacin on day 25. Reviewer agreed.
- #51270480: Prior antibiotic therapy: chronic suppressive therapy with Bactrim® up until day -2. Reviewer agreed.
- #51270490: Prior antibiotic therapy: Prior antibiotic therapy: amoxicillin up until day -1. *Pseudomonas aeruginosa* at baseline. Reviewer agreed.
- #51270547: Prior antibiotic therapy: Cefuroxime axetil® up until day -1, Reviewer agreed.
- #51400457: Discontinued day 2 because of an adverse event. Reviewer agreed (see above listing).
- #51810561: Inappropriate baseline diagnosis: COPD. Reviewer agreed (see above listing).

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ON ORIGINAL

Clarithromycin (N = 11):

- #50050391: Concomitant antimicrobial (Augmentin®) for infected thoracotomy site, days 9 -17. Reviewer agreed.
- #50220524: Developed pneumonia after 1 day and received alternative therapy. Reviewer agreed (see above listing).
- #50750026: Non-compliant after 1 day and changed to doxycycline. Reviewer agreed.
- #50760039: No post-baseline assessments. Lost to follow-up. Reviewer agreed.
- #50920239: Discontinued after 1 day because of an adverse event. Reviewer agreed (see above listing).
- #50950101: Discontinued after 3 days because of laboratory abnormalities. Reviewer agreed (see above listing).

- #51270473: Discontinued after 3 days because of an adverse event. Reviewer agreed (see above listing).
- #51270478: Concomitant antimicrobial (amoxicillin), day 1. Reviewer agreed.
- #51270592: Prior antibiotic therapy. Ceclor® up until day -2. Reviewer agreed.
- #51400465: Prior antibiotic therapy. Cefpodoxime® up until day -2. Reviewer agreed.
- #51810562: Patient dropped out after 3 days and had no follow-up visit. The patient was excluded because of a protocol violation (incorrectly performed Gram stain). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed.

**APPEARS THIS WAY
ON ORIGINAL**

Based on the above listings and in conjunction with the study report, the MO found that the sponsor's clinically evaluable trovafloxacin population consisted of 203 patients and the clarithromycin of 188. The bacteriologically evaluable population consisted of 93 trovafloxacin and 81 clarithromycin patients. The most common reason for exclusion from the bacteriologically evaluable population was "no baseline pathogen" in 108 trovafloxacin and 105 clarithromycin patients. Other reasons included "baseline culture outside of window" and "no post-baseline cultures."

The sponsor provided the Reviewer with a listing of patients that were clinically evaluable as per the sponsor but who had no EOS analysis. This listing included the following patients:

Trovafloxacin (N = 4):

- #50410683: Improvement at EOT.
- #50780282: Cure at EOT.
- #50920235: Cure at EOT.
- #51270517: Improvement at EOT

Clarithromycin (N =12)

- #51400471: Cure at EOT.
- #54990538: Improvement at EOT
- #50720261: Improvement at EOT.
- #50760221: Improvement at EOT.
- #50410071: Improvement at EOT.
- #50790061: Improvement at EOT.
- #50910189: Improvement at EOT.
- #51400431: Improvement at EOT
- #51270551: Cure at EOT.
- #51210405: Cure at EOT.

**APPEARS THIS WAY
ON ORIGINAL**

- # 51270417: *Cure at EOT.*
- #51370508: *Improvement at EOT*

The MO excluded all of the patients who did not have an EOS visit because the MO TOC was applied to the EOS. The above listing excluded failures, which were always carried forward.

**APPEARS THIS WAY
ON ORIGINAL**

Baseline Characteristics:

The 3 groups were comparable in terms of age, race, weight, sex, and smoking history. The distribution of smokers was similar between the trovafloxacin and clarithromycin groups (33% and 37% ex-smokers, 30% and 26% non-smokers, and 36% and 38% smokers, respectively.)

97 of the trovafloxacin patients were male with a mean age of 59.6 and 83% were white.
106 of the trovafloxacin patients were women with a mean age of 56 and 88% were white.

**APPEARS THIS WAY
ON ORIGINAL**

82 of the clarithromycin patients were male with a mean age of 61.4 and 84% were white.
106 of the clarithromycin patients were women with a mean age of 55.6 and 85% were white.

The median duration since the onset of the underlying primary diagnosis of CB was not provided.

The median duration since the onset of the present episode was 7 days for both treatment groups

The respective means were 11.4 days for the trovafloxacin patients and 10.2 days for the clarithromycin patients.

**APPEARS THIS WAY
ON ORIGINAL**

Duration of Treatment:

The median duration of treatment was 7 days for subjects in the both treatment groups.

Concomitant Medications:

The majority of patients were on concomitant medications during therapy. The most commonly used medications were bronchodilators (98 and 106 patients per arm, respectively)

Systemic steroids were taken by 42 (21%) of the trovafloxacin-treated patients and 49 (28%) of the clarithromycin-treated patients.

Medical Officer's Comment: *The MO did not exclude patients taking systemic steroids in the pilot study 154-101 but did provide separate analyses of clinical and bacteriological response with and without these patients in the MO's efficacy analysis. The MO elected to do the same for this study. The rationale was that there was no major difference in efficacy with or without these patients. The MO found that 34 clinically evaluable trovafloxacin patients and 42 clarithromycin patients received systemic steroids.*

Concomitant Antimicrobials:

Of the clinically evaluable patients, 34 trovafloxacin-treated patients and 39 clarithromycin-treated patients received concomitant antimicrobials for the following reasons:

**APPEARS THIS WAY
ON ORIGINAL**

(This information was located in sponsor's table 2.4, appendix 1).

- inadequate response: 25 trovafloxacin and 27 clarithromycin (all carried forward as evaluable failures)
- other reason: 9 trovafloxacin and 12 clarithromycin patients.

The other category was compromised of the following patients:

Trovafloracin (N = 9):

- #50420167: Other/relapse: Cefixime® day 28, classified as a failure. Reviewer agreed.
- #50820093: Other/relapse: Cefuroxime® day 14, classified as a failure. Reviewer agreed.
- #50920199: Other/abscessed tooth: amoxicillin day 23, classified as a failure. Reviewer agreed.
- #50920235: Other/Strep throat: amoxicillin day 45. Patient would have been excluded from MO analysis because of a missing EOS visit.
- #51270517: Other/URI: erythromycin day 18. Patient would have been excluded from MO analysis because of a missing EOS visit.
- #51290384: Other/UTI: ofloxacin day 25. Reviewer agreed to include the patient as an evaluable cure because the ofloxacin was started after the EOS.
- #51330345: Other/protocol violation: Augmentin® day 5. Patient was included in the MO's analysis as an evaluable failure
- #51400468: Other/sinusitis: Cefpodoxime® day 29: Reviewer agreed to include the patient as an evaluable cure because the antimicrobial was started after the EOS.
- #54990538: Other/URI: azithromycin day 14. Classified as a cure in ITT only. Reviewer agreed.

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ON ORIGINAL

Clarithromycin (N= 12):

- #50720013: Adverse event: amoxicillin day 8, classified as a failure. Reviewer agreed.
- #50720261: Other/sinusitis: ampicillin day 22. Classified as an improvement at EOT. The patient was excluded from the MO evaluable population because there was no EOS visit.
- #50790061: Adverse event: cefazolin day 8. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #50870145: Other/recurrence of bronchitis: amoxicillin day 26, classified as a failure. Reviewer agreed.
- #50920234: Other/sinusitis: tetracycline day 19, classified as a failure. Reviewer agreed.
- #51270417: Other/dental work: erythromycin day 26, classified as a cure. Reviewer agreed but the patient was excluded from the MO population because there was no EOS visit.
- #51270551: Other/inflammatory nodule left lung: clarithromycin day 13, classified as a cure at the EOT. The patient was excluded from the MO population because there was no EOS visit.
- #51300526: Other/sinusitis: Cefuroxime® day 26, classified as a cure. Reviewer agreed as antimicrobial was started after the EOS visit.
- #51390355: Other/sinus congestion: lincomycin day 31. Reviewer agreed as antimicrobial was started after the EOS visit.

- #51390398: Other/persistent sinus drainage: lincomycin day 30. Reviewer agreed as antimicrobial was started after the EOS visit.
- #51400358: Other/failed rescue drug: Bactrim® day 10, classified as a failure. Reviewer agreed.
- #51400431: Other/erysipelas: benzathine penicillin day 10. Patient was excluded from MO analysis because of a missing EOS visit.

**APPEARS THIS WAY
ON ORIGINAL**

Protocol Deviations:
(Copied from page 30 of the study report)

Deviations from protocol were noted for 24 subjects, two of whom had more than one deviation, during the study. These deviations were categorized as follows:

- Inclusion criteria deviations included subjects <40 years of age (3 subjects), subjects with an inappropriate diagnosis due to insufficient symptoms or inappropriate sputum histology (3 subjects);
- Other (study procedure) deviations included subjects randomized out of order (6 subjects) or sputum samples sent to laboratory for culture with at Visits 2-4 (1 subject);
- Deviations that involved taking medications other than those specified by the protocol (Seldane) (1 subject) or taking an allowed medication in amounts greater than specified by protocol (prednisone >10 mg/day) (5 subjects);
- Exclusion criteria deviations included subjects with positive chest x-ray for pneumonia (3 subjects) and history of seizures (2 subjects);
- Study drug administration deviations included administration of study drug 3 or 4 days after baseline (2 subjects).

The one trovafloxacin (5072-0011) subject with a history of seizures received 7 days of study drug and reported no seizure activity or any adverse event. The one clarithromycin (5076-0039) with a history of seizures received one day of treatment and also reported no seizure activity or any adverse event.

Subjects with an inappropriate baseline diagnosis were not included in the clinical and bacteriological intent-to-treat and evaluable analyses. All other deviations did not effect evaluability. Subjects with protocol deviations are listed in the following table.

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ON ORIGINAL**

Inclusion	5078-0284; 5078-0318; 5091-0190; 5127-0439; 5181-0561; 5181-0562
Other (Randomized out of order or inadequate sputum sample sent to laboratory at Visits 2-4)	5081-0083; 5082-0093; 5127-0501; 5127-0503; 5139-0529; 5140-0468; 5140-0509
Taking Medications Not Specified by Protocol or Taking an Allowed Medication in Amounts Greater Than Specified by Protocol	5032-0581; 5072-0011; 5072-0013; 5076-0036; 5076-0037; 5091-0190
Exclusion	5133-0345; 5072-0011; 5075-9005; 5076-0039; 5092-0237
Study Drug Administration	5499-0539; 6168-0598

Medical Officer's Comment: *The MO reviewed all deviations and agreed with the sponsor's judgement. Notable was the inclusion of patients on higher systemic steroid doses than those allowed for in the protocol. As stated previously, the MO elected not to exclude these patients but to provide a separate efficacy analysis.*

Medical Officer's Comment: *Based on the above demographic information, the MO determined that:*

- *Patients receiving steroid therapy should be evaluated in a separate analysis in order to ascertain if their inclusion in the evaluable population affected outcome.*
- *Patients who received antimicrobials for other well-documented infections (3) should be excluded from the MO evaluable population.*
- *Patients who did not have an EOS visit (16), should be excluded from the MO evaluable population.*

Overall, there was concordance between the MO and the sponsor in terms of outcome assessments and evaluability.

Sponsor's Efficacy Analysis:

**APPEARS THIS WAY
ON ORIGINAL**

Sponsor-Defined Clinical Response:

Table 109.4
Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)

Timepoint	Trovafloxacin N= 203	Clarithromycin N = 188
Number of patients evaluated at EOT	203 (100%)	188 (100%)
Cure	87 (43%)	75 (40%)
Improvement	94 (46%)	85 (45%)
Failure	22 (11%)	28 (15%)
Success (Cure + Improvement)	181 (89%)	160 (85%)
Number of patients evaluated at EOS	197(100%)	178 (100%)
Cure	140 (71%)	110 (62%)
Improvement	18 (9%)	21 (12%)
Failure	22 (11%)	28 (16%)
Relapse	17 (9%)	19 (11%)
Success (Cure + Improvement)	158 (80%)	131 (74%)

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Clarithromycin: - 2.6%, 10.7% ($\Delta = 15$)

EOS: Trovafloxacin versus Clarithromycin: -1.9%, 15.1% ($\Delta = 15$)

**APPEARS THIS WAY
ON ORIGINAL**

The sponsor stated that (copied from page 32 of the study report):

Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the end of study supported equivalence of the two treatments.

The majority of subjects in both treatment groups were clinical successes (cure + improvement) at both the end of treatment and the end of study (trovafloxacin, 89% and 80%, respectively; clarithromycin, 85% and 74%, respectively).

Medical Officer's Comment:

The MO requested that the FDA statistical reviewer, Dr. Silliman, provide a 95% CI with continuity correction factor for the above. The results were as follows:

EOT: Trovafloxacin versus Clarithromycin: - 3.1%, 11.2% ($\Delta = 15$):

APPEARS THIS WAY
ON ORIGINAL

EOS: Trovafloxacin versus Clarithromycin: -2.5%, 15.7% ($\Delta = 15$)

Based on the FDA analysis, there was therapeutic equivalence between both arms at the EOT and the EOS with trovafloxacin numerically superior to clarithromycin at both timepoints.

For the clinical ITT population, the success rates were 184/208 (88%) for the trovafloxacin-treated patients and 164/199 (82%) for the clarithromycin-treated patients at the EOT (CI: -0.8%, 12.9%). The respective values at the EOS were 145/164 (79%) and 143/199 (72%): 95% CI for this analysis: -1.45, 15.3%. The sponsor stated that this analysis also demonstrated equivalence between the 2 treatment arms.

The sponsor stated that the clinical failure rate was 11% and 15% per arm respectively, at the EOT. At the EOS, 9% and 11% of patients were relapses. Thus as per the MO calculations, the failure rate was 39/197 (20%) on the trovafloxacin arm and 47/178 (27%) on the clarithromycin arm, when failures and relapses were added together, (see introduction re definitions).

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ON ORIGINAL

The sponsor stated that (copied from page 33 of the study report):

Of these subjects, eight trovafloxacin and 12 clarithromycin subjects had pathogens isolated at baseline. In both treatment groups, the most commonly isolated baseline pathogen was *Moraxella catarrhalis*. No pathogen with susceptibility testing done at baseline and follow-up developed resistance to trovafloxacin or clarithromycin during the study.

Clinical Relapse: Among clinically evaluable subjects who were clinical successes at the end of treatment, 17 trovafloxacin subjects and 19 clarithromycin subjects were designated as clinical relapses at the end of study. Of these subjects, eight trovafloxacin and 10 clarithromycin subjects had pathogens isolated at baseline. Among clinically evaluable subjects classified as a clinical relapse at the end of study, the most commonly isolated pathogens at baseline were *Pseudomonas aeruginosa* (3 of the 8 subjects with baseline isolates) for trovafloxacin subjects and *Haemophilus influenzae* (7 of the 10 subjects with baseline isolates) for clarithromycin subjects.

The clinically evaluable subjects with an outcome of failure and a baseline pathogen are listed below: (Outcomes are for EOS only and include patients classified as relapses by the sponsor)

APPEARS THIS WAY
ON ORIGINAL

Trovafloxacin (N = 16):

- #51270420: Failure: *Pseudomonas aeruginosa* at baseline, persistent. Also had *Staphylococcus aureus* which was eradicated.
- 351290382: Failure: *Haemophilus influenzae* at baseline, presumed persistent.
- #51290482: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.
- #51330345: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #51330346: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.

- #51350414: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- 351390399: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #51400357: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #50780322: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #50820093: Failure: *Pseudomonas aeruginosa* at baseline which was persistent.
- #50890170: Failure: *Klebsiella pneumoniae* at baseline which was persistent.
- #50920237: Failure: *Pseudomonas aeruginosa* at baseline, persistent. Also had *Staphylococcus aureus* which was eradicated.
- #51250365: Failure: *Pseudomonas aeruginosa* at baseline which was presumed persistent.
- #51300554: Failure: *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* serologies positive, both classified as presumed persistent.
- #51390447: Failure: *Streptococcus pneumoniae* at baseline which was eradicated.
- #51400467: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.

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ON ORIGINAL

Clarithromycin (N = 22):

- #50050389: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.
- #50720010: Failure: *Serratia marcescens* at baseline which was presumed persistent.
- #50790057: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #50830106: Failure: *Haemophilus parainfluenzae* at baseline which was eradicated.
- #50920197: Failure: *Staphylococcus aureus* at baseline which was eradicated.
- #51270587: Failure: *Staphylococcus aureus* at baseline which was eradicated.
- #51390356: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #51390397: Failure: *Haemophilus influenzae* at baseline which was persistent.
- #51400358: Failure: *Streptococcus pneumoniae* at baseline which was eradicated.
- #51400359: Failure: *Moraxella catarrhalis* at baseline which was eradicated.
- #51400466: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #54990540: Failure: *Haemophilus influenzae* at baseline which was eradicated.
- #50320582: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #50750027: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.

APPEARS THIS WAY
ON ORIGINAL

- #50870145: Failure: *Haemophilus influenzae* at baseline which was eradicated.
- #50929234: Failure: *Pseudomonas aeruginosa* at baseline which was presumed persistent.
- #51270419: Failure: *Haemophilus influenzae* and *Staphylococcus aureus* at baseline which were presumed persistent.
- #51290383: Failure: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #51290481: Failure: *Haemophilus influenzae* at baseline which was eradicated.
- #51300555: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #51300571: Failure: *Haemophilus influenzae* at baseline which was persistent.
- #51400458: Failure: *Xanthomonas maltophilia* at baseline which was presumed persistent.

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Comment: The MO elected to present only those failures and relapses with a baseline pathogen. Overall, the MO did not disagree with the sponsor's determination of outcome. The MO, however, reclassified those patients classified as relapses, into failures.

The most common pathogen associated with failure on the trovafloxacin arm was *Moraxella catarrhalis*, followed by *Pseudomonas aeruginosa*. On the clarithromycin arm, the most common pathogen associated with failure was *Haemophilus influenzae*.

None of the bacterial isolates associated with failure were resistant or developed resistance to either study drug (as per the sponsor).

Clinical response rates for both clinically and bacteriologically evaluable patients can be seen below:

APPEARS THIS WAY
ON ORIGINAL

Table 109.5
Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.3)

Timepoint	Trovafloxacin N= 93	Clarithromycin N = 81
Number of patients evaluated at EOT	93 (100%)	81 (100%)
Cure	46 (49%)	34 (42%)
Improvement	39 (42%)	35 (43%)
Failure	8 (9%)	12 (15%)
Success (Cure + Improvement)	85 (91%)	69 (85%)
Number of patients evaluated at EOS	91(100%)	78 (100%)
Cure	67 (74%)	48 (62%)
Improvement	8 (9%)	8 (10%)
Failure	8 (9%)	12 (15%)
Relapse	8 (9%)	10 (13%)
Success (Cure + Improvement)	75 (82%)	56 (72%)

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Clarithromycin: - 3.4%, 15.8% ($\Delta = 10$)

EOS: Trovafloxacin versus Clarithromycin: - 2.1%, 23.3% ($\Delta = 15$)

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Comment: Trovafloxacin appeared numerically superior to clarithromycin at the MO TOC, the EOS. However, there was no significant difference between the results of this population (clinically and bacteriologically evaluable), and the clinically evaluable population. The FDA-generated 95% CIs (with continuity correction factor) for the above were:

EOT: Trovafloxacin versus Clarithromycin: - 4.6%, 17.0% ($\Delta = 10$)

EOS: Trovafloxacin versus Clarithromycin: - 3.3%, 24.5% ($\Delta = 15$)

Thus, the 2 agents were equivalent at both timepoints.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Response by Baseline Pathogen:

Table 109.6
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3 by MO)

Pathogen		Trovaflaxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	26	24	92.3	18	16	89
	EOS	26	24	92.3	16	7	43.7
<i>Moraxella catarrhalis</i>	EOT	18	14	78	20	16	80
	EOS	17	12	70.5	19	14	73.6
<i>Streptococcus pneumoniae</i>	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
<i>Haemophilus parainfluenzae</i>	EOT	6	6	100	7	6	85.7
	EOS	6	6	100	7	6	85.7
<i>Klebsiella pneumoniae</i>	EOT	5	5	100	7	7	100
	EOS	5	4	80	7	7	100
<i>Pseudomonas aeruginosa</i>	EOT	14	13	92.8	8	8	100
	EOS	14	10	71.4	8	7	87.5
<i>Citrobacter amalonaticus</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Mycoplasma pneumoniae</i>	EOT	6	6	100	2	2	100
	EOS	6	5	83.3	2	2	100
<i>Chlamydia pneumoniae</i>	EOT	9	8	88.8	4	3	75
	EOS	9	6	66.6	4	3	75
<i>Klebsiella spp.</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Neisseria Meningitidis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Pasteurella Multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Proteus Mirabilis</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Proteus spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas putida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Serratia marcescens</i>	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
<i>Staphylococcus aureus</i>	EOT	14	13	92.8	12	10	83.3
	EOS	13	11	84.6	12	9	75
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	EOT	115	106	92.1	101	89	88.1
	EOS	113	94	83.1	98	75	76.5

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Copied below from page 42 of the study report is the sponsor's text:

Among clinically evaluable subjects with the most frequently isolated baseline pathogens, sponsor-defined clinical success rates (cure + improvement) were similar (≤ 10 percentage-point difference) in both treatment groups at the end of treatment and at the end of study, with the following exception: a higher percentage of subjects in the trovafloxacin group with baseline isolates of *Haemophilus influenzae* were clinical successes at the end of study compared to subjects in the clarithromycin group (89%, 16/18 and 44%, 7/16, respectively).

Medical Officer's Comment: *As can be seen from the above, the clinical response by baseline pathogen was numerically superior for the trovafloxacin-treated patients as compared to the clarithromycin at both the EOT and EOS. Confidence intervals were not generated for this variable because this table was baseline pathogen and not patient driven, thus there were patients with more than 1 baseline pathogen. This decision was made in consultation with Dr. Nancy Silliman, FDA statistician.*

For the 3 main pathogens most commonly associated with AECB and for which the sponsor is requesting approval, the MO appended a portion of the above table, below:

**APPEARS THIS WAY
ON ORIGINAL**

Table 109.7
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Main Pathogens Only: Modified 5.3 by MO)

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	26	24	92.3	18	16	89
	EOS	26	24	92.3	16	7	43.7
<i>Moraxella catarrhalis</i>	EOT	18	14	78	20	16	80
	EOS	17	12	70.5	19	14	73.6
<i>Streptococcus pneumoniae</i>	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9

Again, CIs were not applied but it appeared that trovafloxacin was superior to clarithromycin in eradicating Haemophilus influenzae at the EOS. Other than this striking difference, the 2 agents were numerically comparable with trovafloxacin being numerically slightly superior to clarithromycin in patients with Streptococcus pneumoniae and clarithromycin, numerically superior to trovafloxacin in patients with Moraxella catarrhalis. The total eradication rates for the 3 main pathogens were:

*Trovafloxacin EOT: 44/51 (86.2%) and EOS: 42/50 (84%)
Clarithromycin EOT: 42/49 (85.7%) and EOS: 31/46 (67.3%)*

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Signs and Symptoms:
(Copied from page 44 of the study report)

The percentage of clinically evaluable subjects with moderate or severe signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline was comparable between the two treatment groups and was as follows: dyspnea (trovafloxacin: 55%; clarithromycin: 60%), cough (trovafloxacin: 90% and clarithromycin: 99%), lung sounds (trovafloxacin: 62% and clarithromycin: 64%), and increase sputum volume (trovafloxacin: 85% and clarithromycin: 84%). In both treatment groups, the percentage of subjects with signs and symptoms of infection decreased from baseline to the end of treatment and further decreases were observed at the end of study. In general, among the subjects who continued to display these signs or symptoms, the severity was decreased. Similar trends were observed among clinically intent-to-treat subjects. A summary of the percentage of subjects with clinical signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline, end of treatment and end of study is presented in the following table.

Table B. Summary of Clinical Signs and Symptoms						
	Trovafloxacin 100 mg			Clarithromycin 500 mg BID		
	Baseline (N=202)	EOT (N=203)	EOS (N=197)	Baseline (N=187)^a	EOT (N=188)	EOS (N=179)
Sign/Symptom	Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms					
Dyspnea	82%	41%	27%	88%	47%	36%
Cough	100%	78%	52%	100%	78%	58%
Lung Sounds	89%	41%	27%	90%	52%	30%
ISV	100%	54%	30%	100%	56%	34%
	Baseline (N=208)	EOT (N=208)	EOS (N=202)	Baseline (N=199)^a	EOT (N=197)	EOS (N=188)
Sign/Symptom	Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms					
Dyspnea	83%	42%	28%	88%	49%	37%
Cough	100%	79%	53%	100%	78%	58%
Lung Sounds	89%	43%	28%	91%	52%	29%
ISV	100%	55%	31%	100%	57%	35%
EOT= End of Treatment; EOS= End of Study; ISV= Increased Sputum Volume						
a Subject 5138-0593 was not assessed for lung sounds at baseline.						
Ref.: Tables 5.8.1 and 5.8.2						

Medical Officer's Comment: The MO agreed with the sponsor's analysis and verified from the CRFs, that there was indeed a decrease in signs and symptoms as described above.

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Bacteriologic Response:

Sponsor-Defined Pathogen Eradication Rates at EOT and EOS can be seen in Sponsor's Table 5.4.1, copied and modified by the MO:

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Table 109.8
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically evaluable Population: Modified 5.4.1 by MO)

Pathogen		Trovafoxacin			Clarithromycin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	26	24	92.3	16	12	89
	EOS	24	22	92.3	16	10	62.5
<i>Moraxella catarrhalis</i>	EOT	17	13	76	18	17	94
	EOS	16	13	70.5	18	16	89
<i>Streptococcus pneumoniae</i>	EOT	7	6	86	11	11	100
	EOS	7	7	100	11	11	100
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
<i>Haemophilus parainfluenzae</i>	EOT	6	6	100	6	6	100
	EOS	6	6	100	7	7	100
<i>Klebsiella pneumoniae</i>	EOT	5	5	100	7	5	71
	EOS	4	3	75	7	6	83
<i>Pseudomonas aeruginosa</i>	EOT	13	9	69	8	6	75
	EOS	14	9	64	8	6	75
<i>Citrobacter amalonaticus</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Mycoplasma pneumoniae</i>	EOT	6	6	100	2	2	100
	EOS	6	5	83.3	2	2	100
<i>Chlamydia pneumoniae</i>	EOT	9	8	88.8	4	3	75
	EOS	9	6	66.6	4	3	75
<i>Klebsiella spp.</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Neisseria Meningitidis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Pasteurella Multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Proteus Mirabilis</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Proteus spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas putida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Serratia marcescens</i>	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
<i>Staphylococcus aureus</i>	EOT	14	14	92.8	12	12	100
	EOS	13	13	84.6	12	11	92
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	EOT	113	101	89.3	96	85	88.5
	EOS	109	94	86.2	96	81	84.3

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The sponsor's text has been copied from page 45 of the study report below:

Among bacteriologically evaluable subjects, eradication rates for *Haemophilus influenzae* were higher among subjects in the trovafloxacin group compared to clarithromycin group at the end of treatment (92%, 24/26 isolates versus 75%, 12/16 isolates; 95% CI: -6.3, 40.9) and at the end of study (92%, 22/24 isolates versus 63%, 10/16 isolates; 95% CI: 3.0, 55.3). Eradication rates for all other baseline pathogens were comparable between the two treatment groups at both the end of treatment and end of study visits.

Medical Officer's Comment: *As can be appreciated from the sponsor's text, an overall eradication rate was not provided by the sponsor in the study report. Based on the MO's analysis, the 2 agents were numerically comparable at the EOT and EOS.*

The pathogen eradication rates for the 3 main pathogens only were:

*Trovafloxacin EOT: 43/50 (86%) and EOS: 42/47 (89.3%)
Clarithromycin EOT: 40/45 (89%) and EOS: 37/45 (82.2%)*

**APPEARS THIS WAY
ON ORIGINAL**

*Although the MO appreciated the significant decrease in the eradication rate of clarithromycin versus *Haemophilus influenzae* at the EOS, it should be pointed out that a similar albeit slightly smaller decrease occurred for trovafloxacin versus *Moraxella catarrhalis* at the same timepoint.*

Superinfecting Pathogens and Colonizing Organisms:
(Copied from page 46 of the study report)

**APPEARS THIS WAY
ON ORIGINAL**

Superinfecting organisms were isolated from one subject (<1%) in the trovafloxacin group (*Escherichia coli*) and from one subject (<1%) in the clarithromycin group (*Pseudomonas aeruginosa*). Colonizing organisms were isolated from 14 subjects (7%) in the trovafloxacin group and from 27 subjects (14%) in the clarithromycin group.

Medical Officer's Comment: *The MO agreed with the sponsor's determination in all cases after review of the PIDs.*

Cross-tabulation of Sponsor-Defined Clinical Response and Pathogen Outcome:

**APPEARS THIS WAY
ON ORIGINAL**

The sponsor provided only a cross tabulation for the EOT and not the EOS. 26 patients, (11 trovafloxacin and 15 clarithromycin), had clinical responses inconsistent with pathogen outcome. The sponsor's table C has been copied from page 49 of the study report, below and modified to reflect the MO's determination of clinical and bacteriological outcome at the EOS:

**APPEARS THIS WAY
ON ORIGINAL**

Table 109.9
Cross-Tabulation of Clinical and Bacteriological Response at the EOT (as per the Sponsor) and the EOS (as per the MO)

Table C. Summary of Discrepancies Between Sponsor-Defined Clinical Response and Sponsor-Defined Pathogen Outcome at the End of Treatment Bacteriologically Evaluable Subjects					
Subject Number	Baseline Pathogen	Clinical Response		Pathogen Bacteriological Response	
		Sponsor EOT	MO EOS		
Trovafoxacin 100 mg					
5041-0065	<i>Moraxella catarrhalis</i>	Improvement	Cure	Persistent	Pres. Erad.
5041-0069	<i>Moraxella catarrhalis</i>	Improvement	Cure	Persistent	Persistent
5041-0683	<i>Moraxella catarrhalis</i>	Improvement Evaluable	Not	Persistent	-
5092-0237	<i>Pseudomonas aeruginosa</i>	Improvement	Failure	Persistent	Persistent
5125-0365	<i>Pseudomonas aeruginosa</i> ^a	Improvement	Failure	Persistent	Pres. Pers.
5125-0367	<i>Pseudomonas aeruginosa</i>	Improvement	Cure	Persistent	Persistent
5127-0420	<i>Staphylococcus aureus</i>	Failure	Failure	Eradication	Eradicated
5135-0414	<i>Moraxella catarrhalis</i>	Failure	Failure	Eradication	Pres. Pers.
5138-0393	<i>Streptococcus pneumoniae</i>	Improvement	Cure	Persistent	Eradicated
5139-0399	<i>Moraxella catarrhalis</i>	Failure	Failure	Eradication	Eradicated
5140-0357	<i>Moraxella catarrhalis</i>	Failure	Failure	Eradication	Pres. Pers.
Clarithromycin 500 mg BID					
5076-0254	<i>Haemophilus influenzae</i> ^a	Improvement	Cure	Persistent	Pres. Erad.
5079-0057	<i>Moraxella catarrhalis</i>	Failure	Failure	Eradication	Eradicated
5081-0083	<i>Klebsiella pneumoniae</i> ^a	Improvement	Cure	Persistent	Persistent
5083-0106	<i>Haemophilus parainfluenzae</i>	Failure	Failure	Eradication	Eradicated
5092-0197	<i>Staphylococcus aureus</i>	Failure	Failure	Eradication	Eradicated
5092-0234	<i>Pseudomonas aeruginosa</i> ^a	Improvement	Failure	Persistent	Pres. Pers.
5095-0098	<i>Klebsiella pneumoniae</i> ^a	Cure	Cure	Persistent	Pres. Pers.
5125-0366	<i>Pseudomonas aeruginosa</i> ^a	Improvement	Cure	Persistent	Pres. Pers.
5127-0587	<i>Staphylococcus aureus</i>	Failure	Failure	Eradication	Eradicated
5130-0555	<i>Haemophilus influenzae</i>	Improvement	Failure	Persistent	Pres. Pers.
5138-0395	<i>Haemophilus influenzae</i>	Improvement	Cure	Persistent	Pres. Erad.
5139-0356	<i>Moraxella catarrhalis</i>	Failure	Failure	Eradication	Eradicated
5140-0358	<i>Streptococcus pneumoniae</i>	Failure	Failure	Eradication	Eradicated
5140-0359	<i>Moraxella catarrhalis</i>	Failure	Failure	Eradication	Eradicated
5499-0540	<i>Haemophilus influenzae</i>	Failure Evaluable	Not	Eradication	-

a Resistant to study drug at baseline
 Ref.: Table 5.7.1 and Appendix I, Tables 8 and 8a

Medical Officer's Comment: Based on the MO's recreation of this table, 2 patients, one from each arm were unevaluable.

Inconsistency between clinical and bacteriologic outcome persisted in 2 of the original 11 trovafloxacin patients, both clinical cures with documented persistence of the baseline pathogen, (*Moraxella catarrhalis* in 1 case and *Pseudomonas aeruginosa* in the other (neither resistant)).

On the clarithromycin arm, inconsistencies between outcomes were seen in 10 patients, 7 were clinical failures with documented eradication of the baseline pathogen. *Moraxella catarrhalis* was found in 3 of the 7, *Staphylococcus aureus* in 2 and *Haemophilus parainfluenzae* and *Streptococcus pneumoniae* in 1 each. The remaining 3/10 patients were "cures" with "persistence" (1) or "presumed persistence" (2). All 3 of these patients had pathogens resistant to the study drug, (2 isolates *Klebsiella pneumoniae* and 1 *Pseudomonas aeruginosa*).

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There were 5 baseline pathogens resistant to the study drug, all on the clarithromycin arm, 3 failures and 2 cures, (2 isolates each of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, and 1 *Haemophilus influenzae*). There was also 1 resistant baseline *Pseudomonas aeruginosa* on the trovafloxacin arm and this patient was also a failure at the EOS.

The MO deferred to the microbiology reviewer for comment on this phenomenon. However, most isolates associated with AECEB, did not appear to be resistant to trovafloxacin.

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Sponsor's Conclusion: (Copied from the Esub and modified by the MO (in Times New Roman font) to reflect the numerators and denominators):

Four hundred ten (410) subjects were randomized to treatment with trovafloxacin 100 mg once daily (210 subjects) or clarithromycin 500 mg twice daily (200 subjects) for 7 days. The two treatment groups were comparable with respect to characteristics at baseline, medical history, and prior and concomitant medications.

Three hundred ninety one (391) subjects were clinically evaluable (203, trovafloxacin and 188, clarithromycin) and 174 subjects were bacteriologically evaluable (93, trovafloxacin and 81, clarithromycin). All treated subjects were included in the analysis of adverse events.

Comparisons (95% confidence intervals) of the difference between the trovafloxacin and clarithromycin treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the end of study supported equivalence of the two treatments for both clinically evaluable and intent-to-treat subjects.

Success rates among clinically evaluable subjects in the trovafloxacin and clarithromycin groups were 181/103 (89%) and 160/188 (85%), respectively, at the end of treatment and 158/197 (80%) and 131/178 (74%), respectively, at the end of study and those among clinically intent-to-treat subjects were 88% and 82%, respectively, at the end of treatment and 79% and 72%, respectively, at the end of study. These findings were supported by marked decreases in the presence of clinical signs and symptoms of acute bacterial exacerbation of chronic bronchitis from baseline to the end of treatment and to the end of study in both treatment groups.

The eradication rates for *Haemophilus influenzae* was higher for trovafloxacin than for clarithromycin at the end of treatment and at the end of study in both bacteriologically evaluable and intent-to-treat subjects. Eradication rates for all other baseline pathogens were comparable between the two treatment groups at both evaluation timepoints for bacteriologically evaluable and intent-to-treat subjects.

EOT Trovafloxacin (bacteriologically evaluable):

Haemophilus influenzae: 24/26 (92.3%)

Moraxella catarrhalis: 13/17 (76%)

Streptococcus pneumoniae: 6/7 (86%)

EOS Trovafloxacin (bacteriologically evaluable):

Haemophilus influenzae: 22/24 (92.3%)

Moraxella catarrhalis: 13/16 (70.5%)

Streptococcus pneumoniae: 7/7 (100%)

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EOT Clarithromycin (bacteriologically evaluable):

Haemophilus influenzae: 12/16 (89%)

Moraxella catarrhalis: 17/18 (94%)

Streptococcus pneumoniae: 11/11 (100%)

EOS Clarithromycin (bacteriologically evaluable):
Haemophilus influenzae: 10/16 (62.5%)
Moraxella catarrhalis: 16/18 (89%)
Streptococcus pneumoniae: 11/11 (100%)

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Medical Officer's Efficacy Analysis:

In accordance with the evaluability criteria previously described, the MO excluded 19 patients from the sponsor's clinically evaluable population and did not include any of the sponsor-excluded patients. The MO's evaluable population can be seen in table 109.10.

**Table 109.10
Clinically Evaluable Population (as per the MO)**

Reason for exclusion	Trova fl oxacin	Clarithromycin
Total Treated	N=210	N=200
Sponsor Evaluable	203	188
MO Excluded	7	12
No EOS Visit	4	12
Antimicrobial R/x	3	-
Total Evaluated at EOS	196 (93.3%)	176 (88%)

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The numbers of evaluable patients per arm at the EOT was the same as the number at the EOS. The trovafloxacin population represented 47.8% of the randomized patients and the clarithromycin population was 43%.

The MO's bacteriologically evaluable population was a subset of the clinically evaluable.

A by-center breakdown of the MO's evaluable population is presented in Table 109.11:

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**Table 109.11
Clinically Evaluable Population by Center (as per MO)**

Center	Total Randomized N=223 (100%)		Trovafoxacin				Clarithromycin			
			Sponsor Eval. N = 203 (100%)		MO Eval. N= 196		Sponsor Eval. N = 188 (100%)		MO Eval. N= 176	
5005	6	1.5	4	2	4	2	1	0.5	1	0.6
5022	4	1	2	1	2	1	1	0.5	1	0.6
5032	4	1	2	1	2	1	2	1.1	2	1.1
5041	12	2.9	6	2.9	5	2.6	6	3.2	5	2.8
5042	8	2	4	2	3	1.5	4	2.1	4	2.3
5072	12	2.9	6	2.9	6	3.1	6	3.2	5	2.8
5073	1	0.2	1	0.5	1	0.5	0	0	0	0
5074	6	1.5	2	1	2	1	4	2.1	4	2.3
5075	3	0.7	1	0.5	1	0.5	1	0.5	1	0.6
5076	40	9.7	20	9.5	20	10.2	19	10.1	18	10.2
5077	1	0.2	1	0.5	1	0.5	0	0	0	0
5078	36	8.8	18	8.6	17	8.7	18	9.6	18	10.2
5079	7	1.7	4	2	4	2	3	1.6	2	1.1
5080	24	5.8	12	5.7	12	6.1	12	6.4	12	6.8
5081	8	2	4	2	4	2	4	2.1	4	2.3
5082	2	0.5	2	1	1	1	0	0	0	0
5083	6	1.5	3	1.5	3	1.5	3	1.6	3	1.7
5085	2	0.5	1	0.5	1	0.5	1	0.5	1	0.6
5087	2	0.5	1	0.5	1	0.5	1	0.5	1	0.6
5089	3	0.7	1	0.5	1	0.5	2	1.1	2	1.1
5091	8	2	4	2	4	2	4	2.1	3	1.7
5092	16	3.9	8	3.9	7	3.6	7	3.7	7	4
5095	5	1.2	2	1	2	1	2	1.1	2	1.1
5121	3	0.7	1	0.5	1	0.5	2	1.1	1	0.6
5124	1	0.2	1	0.5	1	0.5	0	0	0	0
5125	3	0.7	2	1	2	1	1	0.5	1	0.6
5127	65	15.9	29	14.3	28	14.3	29	15.4	27	15.3
5129	14	3.4	7	3.4	7	3.6	7	3.7	7	4.0
5130	16	3.9	8	3.9	8	4.1	8	4.3	8	4.5
5132	9	2.2	4	2	4	2	5	2.7	5	2.8
5133	3	0.7	2	1	2	1	1	0.5	1	0.6
5134	5	1.2	3	1.5	3	1.5	2	1.1	1	0.6
5135	2	0.5	1	0.5	1	0.5	0	0	0	0
5136	1	0.2	1	0.5	1	0.5	0	0	0	0
5137	8	2	4	2	4	2	4	2.1	3	1.7
5138	7	1.7	3	1.5	3	1.5	4	2.1	4	2.3
5139	16	3.9	8	3.9	8	4.1	8	4.5	8	4.5
5140	21	5.1	9	4.4	8	4.1	10	5.3	9	5.1
5181	3	0.7	1	0.5	1	0.5	0	0	0	0
5213	1	0.2	1	0.5	1	0.5	0	0	0	0
5250	2	0.5	2	1	2	1	0	0	0	0
5499	4	1	2	1	2	1	2	1.1	1	0.6
5743	1	0.2	1	0.5	1	0.5	0	0	0	0
5776	1	0.2	1	0.5	1	0.5	0	0	0	0
5853	8	2	4	2	4	2	4	2.1	4	2.3

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As noted in the sponsor's demographics, no single center enrolled > 20% of the patients. Because the number of patients per center was small, all centers were pooled.

The demographics of the FDA evaluable population can be seen in Table 109.12

Table 109.12
Demographic Characteristics of the FDA Evaluable Population:

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Characteristics	Trovafloxacin	Clarithromycin
	N = 196	N = 176
Sex (Female)	102	97
(Male)	94	79
Age (years) 16 -44	33	30
45 - 64	103	83
≥ 65	60	63
Mean	57.9	58.2
Race: Asian	1	3
Black	16	20
White	169	148
Hispanic	10	4
Polynes.	0	1
Body weight (kg) mean	88.6	82.7

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All 3 arms consisted of a comparable population in terms of weight and age.

Additionally, the MO's population was sufficiently similar to that of the sponsor so that a separate analysis of smokers was not provided.

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Concomitant Medications:

The MO elected (as in the review of study 154-101), not to exclude patients who had been on systemic steroids during this study. The MO's rationale was that not only was the number of evaluable patients per arm on systemic steroids proportionate, but that systemic steroids are often used in patients with CB and at increased doses during acute exacerbations. This implies a standard of care that the MO determined would be appropriate to include in the analysis. The protocol allowed for the inclusion of patients on prednisone, up to 10 mg/day. This low dose was not always adhered to

The MO ascertained through review of the line listings, that 32/196(18.4%) of the MO evaluable trovafloxacin-100 patients, and 40/176 (14.7%) of the MO evaluable clarithromycin patients received systemic steroids during the study.

In accordance with the DAIDP's guidance document, the MO requested that a separate clinical efficacy analysis be performed excluding these patients. These results can be found immediately following the efficacy analyses of all MO evaluable patients.

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EFFICACY:

**Table 109.13
Clinical Response by Patient (as per the MO):**

Timepoint	Trovafoxacin			Clarithromycin		
	N	No. Cured	%	N	No. Cured	%
EOT	196	174	88.8	176	148	84.1
EOS	196	157	80.1	176	129	73.3

The MO applied a 95% CI with continuity correction factor to these results and found the following:

EOT: Trovafoxacin versus Clarithromycin: - 2.8%, 12.2% ($\Delta = 10$)

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EOS: Trovafoxacin versus Clarithromycin: - 2.3%, 15.9% ($\Delta = 15$)

Thus, the MO's results mirrored those of the sponsor in that trovafoxacin was equivalent to clarithromycin at the EOS (MO TOC), for the primary efficacy variable of clinical response. Additionally, trovafoxacin was numerically superior to clarithromycin at the EOT. There were 39 failures on the trovafoxacin arm as compared to 47 on the clarithromycin arm at the EOS, as compared to 22 and 28 per arm respectively, at the EOT.

The following results were obtained when patients on systemic steroids were excluded:

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**Table 109.14
Clinical Response at EOS by Patient Excluding Patients on Systemic Steroids (as per MO):**

Timepoint	Trovafoxacin-100			Clarithromycin		
	N	No. Cured	%	N	No. Cured	%
EOT	164	149	90.8	136	113	83
EOS	164	137	83.5	136	108	79.4

The 95% CI with continuity correction factor was:

EOT: Trovafoxacin versus Clarithromycin: - 6.9%, 7.7% ($\Delta = 10$)

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EOS: Trovafoxacin versus Clarithromycin: - 5.4%, 13.7% ($\Delta = 15$)

Based on this analysis, trovafoxacin was again equivalent to clarithromycin at both timepoints.

20/32 (62.5%) of the trovafoxacin-treated patients on systemic steroids as compared to 21/40 on the clarithromycin arm were clinical cures. Therefore 12 of the 39 (30.7%) failures on the trovafoxacin arm and 19 of the 47 failures (40.4%) on the clarithromycin arm were in patients on systemic steroid therapy.

Clinical response rates were higher on both treatment arms when this subgroup of patients was included in the analysis but the overall result was unchanged.

Clinical Response by Baseline Pathogen:

Table 109.15
Clinical Response by Baseline Pathogen at the EOT and EOS (as per MO)

Pathogen		Trovafoxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	25	23	92	16	14	87.5
	EOS	25	23	92	16	7	43.7
<i>Moraxella catarrhalis</i>	EOT	17	13	76.5	19	15	78.9
	EOS	17	12	70.5	19	14	73.6
<i>Streptococcus pneumoniae</i>	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
<i>Haemophilus parainfluenzae</i>	EOT	6	6	100	7	6	85.7
	EOS	6	6	100	7	6	85.7
<i>Klebsiella pneumoniae</i>	EOT	5	5	100	7	7	100
	EOS	5	4	80	7	7	100
<i>Pseudomonas aeruginosa</i>	EOT	14	13	92.8	8	8	100
	EOS	14	10	71.4	8	7	87.5
<i>Citrobacter amalonaticus</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Mycoplasma pneumoniae</i>	EOT	6	6	100	2	2	100
	EOS	6	5	83.3	2	2	100
<i>Chlamydia pneumoniae</i>	EOT	8	7	87.5	4	3	75
	EOS	8	5	62.5	4	3	75
<i>Klebsiella spp.</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Neisseria Meningitidis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Pasteurella Multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Proteus Mirabilis</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Proteus spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas putida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Serratia marcescens</i>	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
<i>Staphylococcus aureus</i>	EOT	13	12	92.3	12	10	83.3
	EOS	13	11	84.6	12	9	75
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	EOT	111	102	91.8	98	83	84.6
	EOS	111	93	83.7	98	76	77.5

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As can be seen from the above, clinical response by baseline pathogen was numerically superior for the trovafloxacin-treated patients as compared to the clarithromycin both at the EOT and EOS.

For the 3 main pathogens most commonly associated with AECB and for which the sponsor is requesting approval, the MO appended a portion of the above table, below:

Table 109.16
Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Main Pathogens Only: As per MO)

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Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	25	23	92	16	14	87.5
	EOS	25	23	92	16	7	43.7
<i>Moraxella catarrhalis</i>	EOT	17	13	76.5	19	15	78.9
	EOS	17	12	70.5	19	14	73.6
<i>Streptococcus pneumoniae</i>	EOT	7	7	100	11	10	90.9
	EOS	7	6	85.7	11	10	90.9

As above, in this smaller analysis, trovafloxacin was numerically superior to clarithromycin in patients with *Haemophilus influenzae* at baseline, both at the EOT and the EOS. The difference between the 2 agents at the EOS is striking and the MO's analysis confirmed that of the sponsor. Clinical response in patients with *Streptococcus pneumoniae* at baseline was slightly better at the EOT but slightly worse at the EOS with trovafloxacin numerically superior to clarithromycin at the EOT but not the EOS. Clarithromycin was numerically superior to trovafloxacin in patients with *Moraxella catarrhalis* at baseline at both timepoints. The total clinical response rates for the 3 main pathogens were:

Trovafloxacin EOT: 43/49 (87.7%) and EOS: 41/49 (83.6%)
 Clarithromycin EOT: 39/46 (84.7%) and EOS: 31/46 (67.3%)

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Bacteriological Response:

Pathogen Eradication Rates at EOT and EOS as per the MO can be seen table 109.17:

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Table 109.17
Pathogen Eradication Rates at the EOT and EOS (as per the MO)

Pathogen		Trovafoxacin			Clarithromycin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	25	23	92	16	12	89
	EOS	25	22	88	16	10	62.5
<i>Moraxella catarrhalis</i>	EOT	17	13	76.5	18	17	94
	EOS	17	13	76.5	18	16	89
<i>Streptococcus pneumoniae</i>	EOT	7	6	85.7	11	11	100
	EOS	7	7	100	11	11	100
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	3	3	100
	EOS	3	3	100	3	3	100
<i>Haemophilus parainfluenzae</i>	EOT	6	6	100	6	6	100
	EOS	6	6	100	7	7	100
<i>Klebsiella pneumoniae</i>	EOT	5	5	100	7	5	71
	EOS	5	4	80	7	6	83
<i>Pseudomonas aeruginosa</i>	EOT	13	9	69	8	6	75
	EOS	14	9	64	8	6	75
<i>Citrobacter amalonaticus</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Mycoplasma pneumoniae</i>	EOT	6	6	100	2	2	100
	EOS	6	6	100	2	2	100
<i>Chlamydia pneumoniae</i>	EOT	8	7	84.5	4	3	75
	EOS	8	5	62.5	4	3	75
<i>Klebsiella spp.</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Neisseria Meningitidis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Pasteurella Multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Proteus Mirabilis</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Proteus spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas putida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Serratia marcescens</i>	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
<i>Staphylococcus aureus</i>	EOT	13	13	100	12	12	100
	EOS	13	13	84.6	12	11	92
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	0	0
Total	EOT	109	98	90	87	76	87.3
	EOS	111	94	84.6	97	81	83.5

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As can be appreciated from table 109.17, the overall pathogen eradication rates were numerically comparable at the EOT and EOS, with numerical superiority of trovafloxacin versus clarithromycin at both timepoints. The MO's results resemble those of the sponsor, with minor differences. However equivalence was shown between the 2 agents at the EOS for this second primary efficacy variable (as defined in the protocol).

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The pathogen eradication rates for the 3 main pathogens only were:

Table 109.18

Pathogen Eradication Rates at the EOT and EOS (Main pathogens only: as per the MO)

Pathogen		Trovafloxacin			Clarithromycin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	25	23	92	16	12	89
	EOS	25	22	88	16	10	62.5
<i>Moraxella catarrhalis</i>	EOT	17	13	76.5	18	17	94
	EOS	17	13	76.5	18	16	89
<i>Streptococcus pneumoniae</i>	EOT	7	6	85.7	11	11	100
	EOS	7	7	100	11	11	100

Trovafloxacin EOT: 42/49 (85.7%) and EOS: 42/49 (85.7%)
 Clarithromycin EOT: 40/45 (89%) and EOS: 37/45 (82.2%)

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As in the sponsor's analysis, the MO also appreciated the significant decrease in the eradication rate of clarithromycin vs., *Haemophilus influenzae* at the EOS. The lower eradication rate should also be pointed out for trovafloxacin vs. *Moraxella catarrhalis* as compared to clarithromycin at both timepoints.

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Pathogen Eradication Rates and Systemic Steroid Usage:

13 of the baseline pathogens on the trovafloxacin arm and 25 on the clarithromycin arm were from patients on systemic steroids with 10/13 (77%) and 20/25 (80%) eradication per arm respectively, at the EOS.

The 3 persistent organisms on the trovafloxacin arm were one each: *Chlamydia pneumoniae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

The 5 persistent isolates on the clarithromycin arm were 2 *Haemophilus influenzae* and 1 each: *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafloxacin: 81/95 (85.2%)
 Clarithromycin: 61/71 (85.9%)

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Thus, equivalence was again shown between the 2 agents at the EOS. Additionally, the rates are comparable to those attained when the systemic steroid users were included in the analysis.

Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients on systemic steroids were:

Trovafloxacin:
Streptococcus pneumoniae: 6/6 (100%)
Haemophilus influenzae: 22/25 (88%)

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Moraxella catarrhalis: 11/14 (78.5%)

Clarithromycin:

Streptococcus pneumoniae: 9/9 (100%)

Haemophilus influenzae: 8/12 (66.7%)

Moraxella catarrhalis: 11/12 (91.7%)

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These rates were very similar to those obtained when isolates from steroid users were included.

The MO concluded that the exclusion of this patient subgroup had no effect on either overall eradication rates or on eradication rates for the individual pathogens.

Cross-tabulation of Clinical Response and Pathogen Outcome at the EOS (MO Evaluable Population):

On the trovafloxacin arm, there were inconsistent results in 5 patients, (3 clinical successes with persistence of the baseline pathogen and 2 clinical failure with eradication). The clinical successes had 1 each: *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. The clinical failures with eradication both had *Staphylococcus aureus* at baseline.

On the clarithromycin arm, there were 11 patients with inconsistent results (5 patients with clinical success and bacteriologic persistence and 6 with clinical failure and eradication). 2 of the clinical successes had *Haemophilus influenzae* at baseline, 2 had *Klebsiella pneumoniae*, and 1 had *Pseudomonas aeruginosa*. 3 of the clinical failures with eradication had *Haemophilus influenzae*, 2 had *Staphylococcus aureus*, and 1 had *Haemophilus parainfluenzae*.

The MO reviewed the PIDs of these patients previously.

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Safety Review:

85/210 (40%) trovafloxacin subjects and 101/200 (51%) clarithromycin subjects had at least one AE, (all causality). 4/210 (2%) trovafloxacin patients and 8/200 (4%) clarithromycin patients discontinued therapy because of an adverse event. 3 of the discontinuations on the trovafloxacin arm and 6 on the clarithromycin arm were determined to be related to the study drug. An additional clarithromycin patient (#50760221) was discontinued because of an adverse event (atrial fibrillation secondary to exacerbation of CHF) that was not considered to be treatment-related by the investigator and was not included in the summary tables.

The most common adverse events leading to discontinuation on the trovafloxacin arm were related to the gastrointestinal system. 2/210 subjects (1%) were discontinued because of nausea and 1 patient was discontinued because of an event associated with the central nervous and peripheral nervous systems (vertigo). One additional patient discontinued therapy because of an exacerbation of COPD (#51810561)

On the clarithromycin arm the system most affected and leading to discontinuation was the gastrointestinal with 5/200 (3%) discontinued because of nausea, vomiting, and diarrhea). 2 of these 5 also had "other" events, 1 with taste perversion and 1 with an injury. In addition, 1 subject each was discontinued because of respiratory decompensation, generalized pain, and urticarial rash.

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

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Table 109.19
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloracin	Clarithromycin
Number of Subjects Treated	210 (100%)	200 (100%)
Subject-Days of Exposure	1440	1339
Subjects With At Least One Event	85 (40%)	101 (51%)
Number of Adverse Events	145	205
Subjects with Serious Adverse Events	1 (<1%)	6 (3%)
Subjects with Severe Adverse Events	5 (2%)	13 (7%)
Subjects Discontinued Due to Adverse Events	4 (2%)	8 (4%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0
Subjects Discontinued Due to Objective Test Findings	1 (<1%)	2 (1%)
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

Table 109.20
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Trovafloracin	Clarithromycin
Evaluable for Adverse Events	210 (100%)	200 (100%)
Subjects With At Least One Event	85 (40%)	101 (51%)
Subjects Discontinued due to Adverse Event	4 (2%)	8 (4%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	5 (2%)	6 (3%)
Cardiovascular	1 (<1%)	7 (4%)
Centr. & Periph. Nerv.	36(17%)	23 (12%)
Gastrointestinal	26(12%)	47 (24%)
General	9 (4%)	13 (7%)
Hematopoietic	2 (1%)	1(< 1%)
Musculoskeletal	2 (3%)	0
Other Adverse Events	2 (3%)	1(< 1%)
Psychiatric	1(<1%)	0
Metabolic	9 (4%)	17 (9%)
Respiratory	0	1 (<1%)
Skin/ Appendages	20 (10%)	17 (9%)
Special Senses	8 (4%)	11 (6%)
Insertion site	10 (5%)	32 (16%)
Urinary Tract	0	1 (<1%)
	3 (1%)	0

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Table 109.21
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin	Clarithromycin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	210 (100%)	200 (100%)
Subjects With At Least One Event	42 (20%)	76 (38%)
Subjects Discontinued due to Adverse Event	3 (1%)	6 (6%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	4 (2%)	4 (2%)
Cardiovascular	-	1 (<1%)
Centr. & Periph. Nerv.	18 (9%)	12 (6%)
Gastrointestinal	15 (7%)	40 (20%)
General	2 (<1%)	5 (3%)
Psychiatric	7 (3%)	7 (4%)
Skin/ Appendages	2 (<1%)	5 (3%)
Special Senses	4 (2%)	31 (16%)

Overall, and as noted in previous trials, the most frequent treatment-related AEs were from the CNS and GI systems. The % of nervous system AEs was higher for the trovafloxacin patients as compared to the clarithromycin patients; however, the incidence of GI events was higher on the clarithromycin arm.

The further breakdown of these events can be found in the MO's Table 109.22

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Table 109.22
Most Common CNS and GI AEs/Treatment-related/All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin N = 210		Clarithromycin N = 200	
	42	20%	76	38%
Nervous system				
Headache	7	3%	2	1%
Dizziness	6	3%	5	3%
Vertigo	3	1%	4	2%
GI System				
Nausea	11	5%	18	9%
Vomiting	-	-	5	3%
Constipation	-	-	5	3%
Diarrhea	1	<1%	16	8%

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Other events of note included:

Dry mouth in 1 (<1%) trovafloxacin patient and 3 (2%) of the clarithromycin patients.

Insomnia in 5 (3%) of the clarithromycin and 2 (<1%) of the trovafloxacin patients.

Taste perversion on 4 (2%) of the trovafloxacin and 31 (16%) of the clarithromycin patients.

Moniliasis in 1 (<1%) trovafloxacin patient and 4 (2%) clarithromycin patients.

Serious Adverse Events:

3 trovafloxacin-treated subjects and 11 clarithromycin-treated subjects had serious adverse events.

Listed below are the severe adverse events that were considered treatment-related:

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Trovafloxacin (N= 3):

- #50820089: post-treatment (day 16), exacerbation of COPD, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #50950097: post-treatment (day 21), exacerbation of bronchitis with bronchospasm, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51810561: exacerbation of COPD day 3, patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.

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Clarithromycin (N = 11):

- #50050391: acute pneumothorax study day 1 secondary to underlying bullous lung disease. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- #50220524: respiratory failure day 2, secondary to pneumonia. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- #50790061: nausea and vomiting, day 6, related to the study drug. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- #50760221: atrial fibrillation day 3 secondary to underlying CHF. Patient was hospitalized and study medication stopped. Event was considered unrelated to the study medication and resolved with therapy.
- # 50950098: post-treatment (day 31), exacerbation of COPD, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51300377: exacerbation of angina day 6. Patient was hospitalized and study medication continued. Event was considered unrelated to the study medication and resolved with therapy.
- #51320375: Aspiration and death secondary to cardiac arrest day 104 (97 days after therapy). Considered unrelated to the study drug.
- #51370426: post-treatment (day 10), exacerbation of bronchitis with bronchospasm, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51390397: post-treatment (day 11), exacerbation of bronchitis with bronchospasm, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51380397; post-treatment fever (day 23). No etiology, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.

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- #51390445: post-treatment (day 31), exacerbation of bronchitis and depression, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #54990540: cerebral vascular accident day 20. Patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.

Deaths: There was one death on the clarithromycin arm, patient #51320375: a 76 YO male with a history of cardiovascular disease, sinus infections, peptic ulcer disease, and AECB. Developed pulmonary aspiration and death, 97 days post-therapy. No further information was provided and the event appeared unrelated to the study drug, clarithromycin.

There were no deaths on the trovafloxacin arm of this study.

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Clinical Laboratory Abnormalities:

The sponsor submitted tables 4.1, 4.2, 6.1, and 3.3, all of which contain listings of patients who discontinued therapy because of abnormalities.

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The sponsor's text has been copied from page 55 of the study report:

One subject in each treatment group was discontinued from treatment due to abnormal laboratory results (objective test finding), as summarized in the following narratives.

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Trovafloxacin 100 mg Group

Subject 5042-0165, a 40 year-old white female with a history of non-thrombocytopenic purpuras, non-infectious gastroenteritis/colitis, rheumatism, and involuntary movements of limbs, received trovafloxacin 100 mg daily for 3 days (Days 1 - 3) for acute bacterial exacerbation of chronic bronchitis. On Day 1, the subject was diagnosed with severe thrombocytopenia (platelets: _____).

_____ at which time the subject was discontinued from treatment, and at the follow-up visit on Day 30 _____ This subject's thrombocytopenia was determined to have an unknown etiology.

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Clarithromycin 500 mg BID Group

Subject 5095-0101, a 47 year-old white female with a history of hypertension, received clarithromycin 500 mg twice daily for 2 days (Days 1 and 2) and once daily for 1 day (Day 3) for acute bacterial exacerbation of chronic bronchitis. On Day 1, the subject had elevated SGOT _____, SGPT _____, and alkaline phosphatase _____ levels.

On Day 3, the subject was discontinued from treatment due to these abnormal laboratory values. Each of these laboratory parameters was within the normal range on Day 8 (SGOT _____; SGPT, _____; alkaline phosphatase, _____) and at the follow-up visit on Day 31 (SGOT, _____; SGPT, _____; alkaline phosphatase, _____). This subject's laboratory abnormalities were determined to have an unknown etiology.

Clinically significant post-baseline laboratory abnormalities were observed for 14% (28/204) of subjects in the trovafloxacin group and 13% (25/189) of subjects in the clarithromycin group.

No subject in either group had a clinically significant alanine aminotransferase value (SGPT).

No subject in either treatment group had a clinically significant creatinine value.

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The MO did not consider any other laboratory abnormalities found, to be related to the study drugs.

Conclusions:**As per the Sponsor:**

The main portion of the sponsor's conclusion can be found at the conclusion of the sponsor's efficacy analysis. The sponsor concluded:
(Copied from page 57 of the study report):

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Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to clarithromycin 500 mg twice daily for 7 days for clinical success rates at the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis.

Pathogen eradication rates for *Haemophilus influenzae* at both the end of treatment and the end of study were higher in the trovafloxacin group compared to the clarithromycin group (end of treatment: 92% versus 75%, respectively; end of study: 92% versus 63%, respectively).

The overall incidence of all and treatment-related adverse events was lower among subjects in the trovafloxacin group as compared to subjects in the clarithromycin group (40% and 20% versus 51% and 38%, respectively). The percentage of subjects with adverse events leading to discontinuation was comparable between the two treatment groups (2% and 4%, respectively). Subjects in the trovafloxacin group had lower frequencies of gastrointestinal system (12% versus 24%) and special senses (5% versus 16%) adverse events and a higher frequency of central and peripheral nervous system (17% versus 12%) adverse events compared to subjects in the clarithromycin group. The frequency and type of clinically significant laboratory abnormalities were comparable between the two treatment groups.

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Reviewer's Conclusions:

In this pivotal study comparing trovafloxacin and clarithromycin in the treatment of AECB for 7 days, the sponsor was able to demonstrate equivalence of trovafloxacin to clarithromycin.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 157/196 (80.1%) for the trovafloxacin-treated patients, and 129/176 (73.3%) for the clarithromycin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 2.3%, 15.9% ($\Delta = 15$), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 174/196 (88.8%) for the trovafloxacin-treated patients versus 148/176 (84.1%) for the clarithromycin-treated patients. A 95% CI also determined equivalence between the 2 arms at this earlier timepoint.

When patients receiving systemic steroids were excluded, the following results were obtained at the EOS: 137/164 (83.5%) trovafloxacin versus 108/136 (79.4%) clarithromycin. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 5.4%, 13.7% ($\Delta = 15$), trovafloxacin was again equivalent to clarithromycin for the primary efficacy variable of clinical response.

The bacteriologic efficacy analysis yielded the following pathogen eradication rates:

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EOT: trovafloxacin 98/109 (90%) versus clarithromycin 76/87 (87.3%)
EOS: trovafloxacin 94/111 (84.6%) versus clarithromycin 81/87 (83.5%)

If only the 3 main pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 42/49 (85.7%) versus clarithromycin 40/45 (89%)
EOS: trovafloxacin 42/49 (85.7%) versus clarithromycin 37/45 (82.2%)

Specific pathogen eradication rates for the three main pathogens, were as follows:

Table 109.18
Bacteriologic Eradication Rates (as per the MO)

Pathogen	Trovafoxacin-100		Clarithromycin	
	EOT	EOS	EOT	EOS
<i>Haemophilus influenzae</i>	23/25 (92%)	22/25 (88%)	12/16 (100%)	10/16 (62.5%)
<i>Moraxella catarrhalis</i>	13/17 (88%)	13/17 (76.5%)	17/18 (94%)	16/18 (89%)
<i>Streptococcus pneumoniae</i>	6/7 (85.7%)	7/7 (100%)	11/11 (100%)	11/11 (100%)

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafoxacin: 81/95 (85.2%)
Clarithromycin: 61/71 (85.9%)

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Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients on systemic steroids were:

Trovafoxacin:
Streptococcus pneumoniae: 6/6 (100%)
Haemophilus influenzae: 22/25 (88%)
Moraxella catarrhalis: 11/14 (78.5%)

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Clarithromycin:
Streptococcus pneumoniae: 9/9 (100%)
Haemophilus influenzae: 8/12 (66.7%)
Moraxella catarrhalis: 11/12 (91.7%)

These rates were the same as or very similar to those obtained when isolates from steroid users were included.

The MO concluded that the exclusion of this patient subgroup had no effect on either overall eradication rates or on eradication rates for the individual pathogens.

The MO determined that the sponsor's and MO's pathogen eradication rates were very similar for all subgroups. By the EOS, trovafoxacin had higher eradication rates (88% versus 63%), than did clarithromycin for *Haemophilus influenzae*.

The adverse events seen in this study, were similar to those noted in previous studies, with a lower overall incidence of adverse events in the trovafoxacin-treated patients (42/210: 20%) as compared to the clarithromycin-treated patients (76/200: 38%)

The most common complaints were from the gastrointestinal tract, with 5% (11/210) of trovafoxacin patients having nausea that was treatment related. As seen previously, there were also complaints of dizziness and headache. In this trial, 6/210 (3%) of the episodes of dizziness and 7/210 (3%) of the episodes of headache were determined to be treatment-related.

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There were no significant laboratory abnormalities.

In conclusion, trovafoxacin appeared safe and effective in the treatment of AECB caused by the three main pathogens and was equivalent to the approved comparator, clarithromycin.

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Based on the above, trovafloxacin 100 mg PO for 7 days was equivalent to clarithromycin in the treatment of AECB caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

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Study 154-141

TITLE:

A RANDOMIZED, DOUBLE BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND CIPROFLOXACIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

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Study Dates: December 21, 1994 - September 21, 1995

Objective: The objective of this study was to compare the safety and efficacy of trovafloxacin with ciprofloxacin in the treatment of subjects with acute exacerbation of chronic bronchitis.

List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5015	Sanford Chodosh, MD
	5017	John Gezon, MD
	5078	C. Andrew Deabate, MD
	5096	Jeffrey Adelglass, MD
	5144	Kirk Jacobson, MD
	5145	Stephen Kraus, MD
	5147	Alex Pareigis, MD
	5148	Stan Parman, MD
	5149	Gary Ruoff, MD
	5150	Irwin Spim, MD
	5151	Keith Vanzandt, MD
	5152	Lawrence Alwine, DO
	5153	Spencer Coleman, MD
	5154	John Estess, MD
	5156	Andrew Hughes, MD
	5157	Mark Lamos, MD
5159	Onelio Perdomo, MD	
5160	Thomas Saddoris, II, MD	
5161	Sandra Willsie, DO	
5210	Thomas Nolen, MD	
6579	William Gray, MD	
Costa Rica	5034	Guillermo Rodriguez Gomez, MD

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Study Design: Study 154-141 was a Phase III, randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg daily as a single dose in the morning), versus ciprofloxacin (500 mg twice daily), administered orally for 7 days for the treatment of AECB.

Protocol Overview:

Copied below from the electronic submission, appendix A of the study report is the sponsor's schedule of visits and procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number	1	2	3	4
Study day:	Day 1	Day 4	Day 8	Day 28
Allowable Window:	-48 hours	Day 3-5	Day 7-9	Day 25-31
Treatment Period	Day 1 to Day 7			
Follow-up period	Day 8 to Day 31			
Informed consent	X			
Demographic Information	X			
Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record			X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X			
Microbiology				
Sputum Gm stain	X	X	X	X
culture & sensitivity	X	X	X	X
serology	X			X
Safety laboratory tests				
hematology	X		X	abn
biochemistry	X		X	abn
urinalysis	X		X	abn
Pregnancy test*	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's evaluation				
clinical		X	X	X

abn= abnormal at previous visit or clinically significant adverse event

*to be done by local site for women of child bearing potential

As noted from the above schedule, all baseline assessments were performed within the 48 hours prior to the start of the study.

At the baseline visit (V1, Day 1), all subjects had to have a clinical picture characterized by the following criteria:

- Clinical signs and symptoms of chronic bronchitis defined by the presence of cough, dyspnea, lung sounds (rales and rhonchi), and excessive secretion of mucus. Subjects were to have coughed up sputum on most days during three consecutive months for two or more successive years.
- Signs and symptoms characteristic of acute bacterial exacerbation, including increased dyspnea and increased sputum volume and purulence.
- Purulent sputum was to be present and defined by Gram stain showing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification field (LPF) [10X].
- The absence of pneumonia on chest x-ray.

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Those patients who met the above definition and who gave informed consent were eligible for randomization, if they fulfilled the inclusion and exclusion criteria. Baseline visit assessments also included collection of demographic information, concurrent disease, medical history and physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature).

The clinical assessment of signs and symptoms of AECB included sputum characteristics, cough, dyspnea, lung sounds, and chest x-ray (unless one had been taken within 48 hours of the baseline assessment).

Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per LPF, squamous epithelial cells per LPF), of sputum were performed. Subjects with inadequate sputum specimens were not randomized and no further evaluation was performed. Hematology, serum chemistry, and urinalysis determinations were performed and serum was obtained at baseline for the determination of antibodies to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Susceptibility to the study drugs, trovafloxacin and ciprofloxacin, was determined from bacterial isolates grown from adequate sputum specimens. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. However, if no pathogen was detected on baseline culture, the continuation of the study drug was at the discretion of the investigator. If a pathogen was resistant to study medication, study treatment could continue at the investigator's discretion, only if there was evidence of clinical improvement.

At Visits 2 (V2: Day 4) and 3 (V3: Day 8; EOT), a determination of clinical efficacy was performed. These determinations included clinical assessments of signs and symptoms of AECB and adequate sputum samples for culture and sensitivity to assess bacteriological response to study therapy. Safety was assessed through the recording of concomitant medication, vital signs, study drug dosing, and adverse events. At Visit 3, hematology, chemistry, and urinalysis tests were performed.

At Visit 4 (V4: Day 28; EOS), efficacy and safety observations were again performed as in V2 and V3 with the exception of the laboratory analyses which were only performed if a clinically significant abnormality was present at V3 (Day 8) or if the subject was experiencing a clinically significant adverse event. Final serology was performed at this visit and the investigator provided a final evaluation of clinical response.

Compliance:

This study was conducted in compliance with a local or central Institutional Review Board (IRB) and informed consent regulations.

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Concomitant Illnesses and Medications:

The investigator documented all concomitant medication usage at each visit. This included any therapeutic interventions. No other antimicrobials were allowed. If another antimicrobial was used, the patient was classified as a treatment failure.

The concomitant use of systemic corticosteroids was allowed in the form of 10 mg of prednisone or less daily. The use of other (non-anti-infective), medications was limited to those essential to the care of the subject. The use of any other investigational drug was prohibited. Mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing.

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Discontinuation of Study Therapy:

Discontinuations were allowed at the discretion of the investigator only if the patient showed no signs of clinical improvement or worsening before the EOT (V3).

Additionally, patients could discontinue therapy if they developed an adverse event or a clinically significant laboratory abnormality.

The reason for discontinuation was recorded on the CRF and the patient followed through the EOS, if possible. The investigator made a final evaluation at the time of discontinuation.

Protocol Amendments:

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This protocol was amended once on October 13, 1994, as detailed below:

- Study drug administration for ciprofloxacin was changed from one 500 mg capsule twice daily to two 250 mg capsules twice daily. This was done in order to increase the number of placebo tablets to 2, in order to accommodate the double-dummy study design.
- Monitoring procedures for subjects who took theophylline during the study were specified.

Precautions:

Because ciprofloxacin can affect theophylline levels, all subjects on concomitant theophylline had serum levels monitored periodically at a local laboratory.

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Study Population:

Approximately 250 subjects with acute exacerbation of chronic bronchitis were expected to be randomized to one of the treatment groups. Each study site attempted to enrol at least 10 patients.

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Inclusion and Exclusion Criteria:

Medical Officer's Comment: Overall, the MO agreed with the inclusion and exclusion criteria which were the same as those in study 154-109. Therefore, all the MO's comments are unchanged.

Randomization and Blinding:

Study numbers were sequentially assigned to the patients by the investigator as they were determined to be eligible for treatment. The study number was entered onto the patient's CRF and the patient received

study medication with the corresponding number. Study medication was blinded by a double-dummy technique.

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Dosage Form and Administration:

Study drug was in the form of tablets and packaged in blister cards using a double dummy technique to maintain blinding. The study drug administration schedule provided one of the following two doses of study drug, dependent on the random assignment:

	<u>AM Administration</u>	<u>PM Administration</u>
Trovafloxacin (100 mg/d)	2-placebo for Ciprofloxacin 1-Trovafloxacin x 100 mg	2-placebo for Ciprofloxacin
Ciprofloxacin (1,000 mg/d)	2-Ciprofloxacin 250 mg 1-placebo for Trovafloxacin	2-Ciprofloxacin 250 mg

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The blister cards contained sufficient supplies for a 7 day course of treatment, and were given to the subjects at V1. Subjects began study drug medication with the morning dose (even if it was not the morning) and completed a full day of medication on Day 1. The subjects were informed that compliance with taking all tablets as instructed was imperative.

Note: The concomitant use of systemic corticosteroids was allowed in patients receiving chronic, low dose oral steroids (10 mg prednisone daily or less).

To ensure adequate records of disposition of unused supplies at the study site and to facilitate the final drug accountability process a Drug Inventory Record was maintained by the investigator.

Compliance:

Patients were informed that compliance with taking all tablets as instructed was imperative. Outpatients were asked to bring all unused medication and empty containers to the first follow-up visit. All doses taken were charted in the case report form.

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Microbiologic Methods:

Bacteriologic response was assessed at V3 (EOT) and V4 (EOS). Only those sputum specimens that were adequate, as defined previously, were cultured. If there was no obtainable "adequate" specimen, at the EOT or EOS, and the patient was cured or improved, a presumptive assignment of eradication was made.

All specimens were initially sent to the local laboratory for culture. Isolates considered significant were sent to the central laboratory where susceptibility testing was performed. Local susceptibility data was used only if the central laboratory's data was missing.

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 11 of the study report)

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Criteria	Trovafoxacin*		Ciprofloxacin+	
	Zone size(mm) 5µg disc	MIC µg/ml	Zone Size(mm) 5 µg disc	MIC µg/ml
Susceptible	≥15	≤2	≥21	≤1
Intermediate	11-14	4	16-20	—
Resistant	≤10	≥8	≤15	≥4

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Clinical Response:

Clinical response was determined by the sponsor and evaluated at the EOT: V3 (Day 8), and at the EOS: V4 (Day 28), or at the time of discontinuation from the study. Clinical response was primarily based on the global assessment of the clinical presentation of the subject at the evaluation time point.

Clinical or global assessment was based upon resolution or improvement of clinical laboratory signs of infection such as, disappearance or decreased purulent sputum production, changes in dyspnea and cough, and stabilization in general physical condition. Supporting data to evaluate clinical response included reduction in leukocytosis. Clinical response was classified as cure, improvement, failure, or indeterminate as defined in the introduction of the MOR.

Medical Officer's Comment: For the MO's comment on both clinical and bacteriologic response, see the MOR of study 154-101. The MO points out that in this study as in study 154-109, the determination of clinical response was made by the sponsor and not by the investigator (154-101). The sponsor's TOC visit was the EOT but as noted previously, assessments could be made at either visit. Therefore, the sponsor's population was not static but contained patients with an assessment at either visit and not necessarily both.

Safety Assessments:

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Adverse Events:

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the CRF. Following resolution of the adverse event or at the EOS, the investigator's judgment of causality of the adverse event was recorded.

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the sponsor project clinician immediately by telephone. In the case of death, a summary of available autopsy findings was submitted as soon as possible to the sponsor.

In addition, physical examination was performed at baseline (V1). Concomitant medication use and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) were evaluated at V1 and at V2, V3 (EOT), and V4 (EOS).

Clinical Laboratory Tests:

Hematology, coagulation, serum chemistry, and urinalysis determinations were performed at baseline (V1), and at V2 and V3. At V4, hematology, coagulation, serum chemistry, and urinalysis were only performed if a clinically significant abnormality was present at V3.

Data Analysis:

See the introduction to the MOR for a review of the sponsor's subsets and their definitions.

Clinical Evaluability Criteria:

See the Introduction to the MOR for a review of the sponsor's criteria.

Criteria for Bacteriological Evaluability:

See the introduction of a review of the sponsor's criteria.

Primary and Secondary Endpoints for Efficacy:

Primary efficacy endpoints were:

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- Sponsor-defined subject clinical response at the EOT and;
- Pathogen eradication rates at the EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at the EOS;
- Investigator-defined subject clinical response at the EOT, and sponsor-defined and investigator-defined subject clinical response at the EOS.

Medical Officer's Comment: *As stated in the introduction, the MO applied the TOC to the later EOS visit, therefore the primary endpoint for the MO's analysis was clinical response at that timepoint. This study is the same as study 154-109 and the MO's management of the data was unchanged.*

Definitions of Response:

Please refer to the introduction of the MOR for the sponsor's definitions.

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Interim Analyses:

No interim analyses were performed.

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Demographics:

As per the sponsor, 256 patients were randomized and treated (131 subjects to receive trovafloxacin (51.2%), and 125 to receive ciprofloxacin (48.8%)).

Of the treated patients, 235 completed treatment (121/131 (92.3%) trovafloxacin-treated patients and 114/125 (91.2%) ciprofloxacin-treated patients). 21 patients were withdrawn from treatment, (10 trovafloxacin, and 11 ciprofloxacin), but 10 of these completed the study. In addition to these 11 (7 trovafloxacin and 4 ciprofloxacin patients) withdrawn during the treatment, an additional 1 trovafloxacin and 1 ciprofloxacin patient were withdrawn during follow-up, thus 13 patients were withdrawn from the study (8 trovafloxacin and 5 ciprofloxacin).

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The MO has recreated sponsor’s Table 1.1, the Disposition of Enrolled subjects.

Table 141.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin 100 mg	Ciprofloxacin 500 mg bid
Subjects with Signed Consent	261		
Withdrawn Prior to Randomization	5		
Randomized		131	125
Randomized, But Not Treated		0	0
All Treated Subjects		131 (100%)	125 (100%)
Withdrawn During Treatment		10 (8%)	11 (9%)
Completed Treatment		121 (92%)	114 (91%)
Withdrawn During Follow-up		1 (<1%)	1 (<1%)
Completed Study		123 (94%)	120 (96%)
Completed Treatment and Study		120 (92%)	113 (90%)
Withdrawn During Treatment and Study		7 (5%)	4 (3%)

Medical Officer’s Comment: A comparable number of patients was withdrawn from both arms.

Copied and modified below is sponsor’s Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

Table 141.2
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)

Center	Total Randomized N = 256 (100%)		Trovafloxacin		Ciprofloxacin	
			Randomized and Treated N = 131	100%	Randomized and Treated N = 125	100 %
5015	26	10.1	13	9.9	13	10.4
5017	7	2.7	3	2.3	4	3.2
5034	19	7.4	9	6.9	10	8.0
5078	47	18.3	24	18.3	23	18.4
5096	3	1.1	2	1.5	1	0.8
5144	7	2.7	3	2.3	4	3.2
5145	11	4.2	5	3.8	6	4.8
5149	5	1.9	3	2.3	2	1.6
5150	5	1.9	2	1.5	3	2.4
5151	3	1.1	2	1.5	1	0.8
5152	4	1.5	2	1.5	2	1.6
5153	13	5.0	7	5.3	6	4.8
5154	4	1.5	2	1.5	2	1.6
5156	54	21.0	28	21.3	26	20.8
5157	1	0.3	1	0.7	0	-
5159	7	2.7	4	3.0	3	2.4
5160	27	10.5	13	9.9	14	11.2
5161	3	1.1	2	1.5	1	0.8
5210	10	3.9	6	4.5	4	3.2

Medical Officer’s Comment: There were 19 centers, all of which enrolled patients. There was 1 center (5156) with > 20% of the patients. Additionally center 5078 had approximately 18%. Therefore these 2 centers enrolled 39.3% of the patients.

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Copied below is the sponsor's table of all randomized patients and the study evaluation groups:

Table 141.3
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

	Trovafloxacin	Ciprofloxacin
	100 mg	500 mg bid
All Randomized Subjects	131 (100%)	125 (100%)
All Treated Subjects	131 (100%)	125 (100%)
Subjects with Inappropriate Baseline Diagnosis	6 (5%)	4 (3%)
Clinically Intent-to-Treat Subjects	125 (95%)	121 (97%)
Clinically Evaluable Subjects	116 (89%)	115 (92%)
Clinically evaluable with baseline pathogen	63 (48%)	71 (57%)
Clinically Not Evaluable Subjects	9 (7%)	6 (5%)
Insufficient Therapy	7 (5%)	5 (4%)
No post-baseline clinical assessment	5 (4%)	5 (4%)
Prior Antibiotic therapy	1 (<1%)	1 (<1%)
Concomitant Antibiotic therapy	3 (2%)	0
No post-baseline clinical assessment in evaluable analysis window	5 (4%)	5 (4%)
Clinically evaluable at EOS	110 (84%)	102 (82%)
Clinically evaluable at EOS with baseline pathogen	59 (45%)	65 (52%)
Bacteriologically Evaluable Subjects	60 (46%)	69 (55%)
Bacteriologically Not Evaluable Subjects	56 (43%)	46 (37%)
No Baseline Pathogen	52 (40%)	44 (35%)
Baseline culture Outside Window	1 (<1%)	0
No post-baseline cultures	3 (2%)	2 (2%)
Bacteriologically Evaluable at EOS	55 (42%)	61 (49%)
Analyzed for Safety		
Adverse Events	131 (100%)	125 (100%)
Laboratory Data	124 (95%)	118 (94%)

* Subjects may have had more than one reason to have been unevaluable

Medical Officer's Comment: 21 of the randomized and treated subjects were not clinically evaluable, (11/131 11.9%) trovafloxacin-treated subjects and 10/125 (8%) ciprofloxacin-treated subjects).

The bacteriologically evaluable population was a subset of the clinically evaluable population and the bacteriological ITT population, which were both subsets of the clinical ITT population.

There were a total of 10/131 (8%) trovafloxacin-treated patients who discontinued therapy. 3 of these patients continued the study and were clinically evaluable. The remaining 7 did not complete the study and were not evaluable.

On the ciprofloxacin arm, 11/125 (9%) patients discontinued treatment. 7 of these patients continued the study and 6 of these patients were clinically evaluable. The remaining 4 did not complete the study and were not evaluable.

All patients who discontinued treatment were reviewed (see below):

Trovafloxacin (N = 10):

- #50340411: 47 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. This patient had Haemophilus influenzae in the initial sputum culture and was not clinically or bacteriologically evaluable at either timepoint. Reviewer agreed because the patient did not receive an adequate course of therapy. *

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- #50340415: 85 YO withdrawn from treatment on day 5 because of insufficient response. This patient completed the study and was clinically and bacteriologically evaluable. *Haemophilus influenzae* was isolated in the initial sputum as well as in the EOT and EOS specimens. The patient was classified as a failure with persistence and received amoxicillin therapy. Reviewer agreed.
- #50780224: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #50780229: 44 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #50780232: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #50780250: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #51530035: 63 YO withdrawn from treatment on day 2 for multiple adverse events including theophylline toxicity, nausea, hypochloremic acidosis, and respiratory failure. The patient did not complete the study and was hospitalized and treated with a number of intravenous antimicrobials active against the initial isolate, *Moraxella catarrhalis*. This patient was neither clinically nor bacteriologically evaluable. Reviewer agreed because the patient did not receive the minimum number of doses to be considered an evaluable failure. *
- #51530204: 67 YO withdrawn from treatment on day 3 because of an adverse event. The patient completed the study and was clinically and bacteriologically evaluable. *Escherichia coli* and *Klebsiella pneumoniae* were isolated from the initial specimen and were presumed eradicated at the EOT and EOS. The patient was classified as a clinical cure. Reviewer disagreed because although the patient did not receive an alternative antimicrobial, she did not receive the minimum duration of therapy necessary to be evaluable as a cure.
- #51560214: 70 YO withdrawn on day 4 because she withdrew consent despite an initial improvement. The patient did not complete the study and was not bacteriologically evaluable but was clinically evaluable as per the sponsor as an improvement. The patient had *Staphylococcus aureus* and *Streptococcus pneumoniae* at baseline and at day 4 and received Cefprozil®. This patient was excluded from the Reviewer's analysis because she had no EOS visit, although she was included in the sponsor's analysis as an improvement.
- #52100181: 50 YO withdrawn from treatment after 2 days of therapy because of chest tightness and blurry vision. The patient continued the study but was neither clinically nor bacteriologically evaluable. Reviewer agreed because the patient did not receive the minimum number of doses to be considered evaluable. *

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Ciprofloxacin (N=11):

- #50150143: 64 YO withdrawn from treatment on day 6 because of adverse events including shakiness, lightheadedness, and anxiety. The patient completed the study and was clinically and bacteriologically evaluable as an improvement with eradication of the baseline pathogen, *Xanthomonas maltophilia*. Reviewer agreed.

- #50170072: 66 YO withdrawn from treatment on day 1 because of adverse events including nausea, vomiting, and hives. The patient completed the study but was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #50780231: 40 YO was lost to follow-up after 1 day of therapy. The patient discontinued both the study and treatment. The patient was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #50780286: 47 YO withdrawn on day 5 because of an increase in LFTs. The patient completed the study and was clinically but not bacteriologically evaluable. No baseline pathogen was isolated. Reviewer agreed.
- #51440068: 74 YO withdrawn from treatment on day 1 because of an adverse event (bitter taste in mouth). The patient did not complete the study and was neither clinically nor bacteriologically evaluable. Reviewer agreed. *
- #51450094: 62 YO withdrawn from treatment on day 4 because of an adverse event, (diarrhea). The patient completed the study and was clinically and bacteriologically evaluable. This patient was categorized as an improvement at the EOT and a relapse at the EOS. Initial sputum isolate was *Klebsiella pneumoniae*, eradicated at the EOT but recultured at the EOS. The patient was treated with Bactrim® from study days 10- 24. Reviewer agreed.
- #51560076: 84 YO withdrawn from treatment on day 7 because of an adverse event (diverticulitis). The patient completed the study and was clinically but not bacteriologically evaluable. Reviewer agreed.
- #51560159: 70 YO withdrawn from treatment on day 1 because of an adverse event, (nausea and vomiting). The patient did not complete the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. *
- #51560169: 50 YO withdrawn from treatment and the study on day 1 because he withdrew consent. The patient did not complete the study and was neither clinically or bacteriologically evaluable. Reviewer agreed. *
- #51560216: 83 YO withdrawn on day 3 because of adverse events including dizziness, insomnia and shaking. The patient completed the study and was carried forward as an evaluable cure because she did not receive any alternative antimicrobial therapy. This patient had *Staphylococcus aureus* isolated at baseline which was presumed eradicated. Reviewer disagreed and excluded this patient from the FDA evaluable population because the patient did not receive the minimum duration of therapy necessary to be classified as a cure.
- #51610090: 48 YO withdrawn from treatment on day 7 because of insufficient response. The patient completed the study and was clinically and bacteriologically evaluable. The patient was classified as an evaluable failure with presumed persistence of the baseline pathogen, *Chlamydia pneumoniae*. Bactrim® r/x was prescribed from day 7 – 21. Reviewer agreed.

Although the 10 trovafloxacin and 11 ciprofloxacin patients listed above, represent discontinuations from therapy or the study, only those patients with a * are those patients who were excluded from the sponsor's clinical efficacy analysis (trovafloxacin (7) and ciprofloxacin (5)). An additional 8 trovafloxacin-treated patients and 5 ciprofloxacin-treated patients were clinically unevaluable as per the sponsor. The most common reason for exclusion was inappropriate baseline diagnosis, (6 trovafloxacin, and 4 ciprofloxacin). This determination was made based on the patients' response to a questionnaire

regarding the existence of symptoms of AECEB as outlined in the inclusion criteria. If the patient answered no to any question, the sponsor automatically excluded them. This was done retrospectively and in most cases the patients received 7 days of therapy and would have been classified as cures.

All clinically unevaluable patients (as per the sponsor), not listed above, are reviewed below:

Trovafloxacin (N = 8)

- #50150118: *Inappropriate baseline diagnosis: Haemophilus influenzae isolated at baseline. Reviewer agreed.*
- #50150119: *Inappropriate baseline diagnosis: Haemophilus influenzae isolated at baseline. Reviewer agreed.*
- #50170071: *Inappropriate baseline diagnosis: Haemophilus influenzae and Streptococcus pneumoniae isolated at baseline and eradicated at EOT and EOS. Reviewer agreed.*
- #50340414: *Prior antibiotic therapy: Bactrim® up until day -1. Streptococcus pneumoniae isolated at baseline and at the EOS. Would have been a clinical cure with persistence at the EOS. Reviewer agreed.*
- #51490101: *Inappropriate baseline diagnosis: Streptococcus pneumoniae isolated at baseline. Reviewer agreed.*
- #51560172: *Inappropriate baseline diagnosis: Haemophilus influenzae at baseline. Classified as a clinical cure with presumed eradication at the EOS. Reviewer agreed.*
- #51600173: *Inappropriate baseline diagnosis: sputum culture performed 72 hours prior to baseline assessment. Reviewer agreed.*
- #51600207: *Concomitant antimicrobial therapy: ciprofloxacin days 4 – 14 for a sinus headache. All sputum specimens were inadequate.*

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ON ORIGINAL**

Ciprofloxacin (N =5):

- #50150012: *Inappropriate baseline diagnosis: Moraxella catarrhalis isolated at baseline. Reviewer agreed.*
- #50170188: *Prior antimicrobial therapy: Doxycycline from day - 11 to start. Reviewer agreed.*
- #51440066: *Inappropriate baseline diagnosis: Haemophilus influenzae isolated at baseline but no Gram stain. Reviewer agreed.*
- #51560180: *Inappropriate baseline diagnosis: Haemophilus influenzae at baseline which was eradicated but patient developed a septic arthritis on day 4 and received intravenous cefazolin. Reviewer agreed.*
- #51590024: *Inappropriate baseline diagnosis: Inadequate sputum production at all timepoints. Reviewer agreed.*

Based on the above listings, and in conjunction with the study report, the MO found that the sponsor's clinically evaluable trovafloxacin population consisted of 116 patients and the ciprofloxacin of 115. The bacteriologically evaluable population consisted of 60 trovafloxacin and 69 ciprofloxacin patients. The

most common reason for exclusion from the bacteriologically evaluable population was "no baseline pathogen" in 52 trovafloxacin and 44 ciprofloxacin patients. Other reasons included "baseline culture outside of window" and "no post-baseline cultures."

The sponsor provided the Reviewer with a listing of patients that were clinically evaluable as per the sponsor but who had no EOS evaluation. This listing included the following patients:

Trovafloxacin (N = 6):

- #50340405: *Cure at EOT.*
- #50780235: *Cure at EOT.*
- #50780253: *Cure at EOT.*
- #51440065: *Improvement at EOT.*
- #51560214: *Improvement at EOT.*
- #51560111: *Improvement at EOT.*

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Ciprofloxacin (N =13)

- #50340404: *Cure at EOT.*
- #50340412: *Improvement at EOT*
- #50780252: *Cure at EOT.*
- #50780256: *Cure at EOT.*
- #50780286: *Improvement at EOT.*
- #50780310: *Cure at EOT.*
- #50780311: *Cure at EOT.*
- #51520002: *Cure at EOT*
- #51520003: *Improvement at EOT.*
- #51540039: *Improvement at EOT.*
- # 51560076: *Improvement at EOT.*
- #51600124: *Improvement at EOT.*
- #51600176: *Improvement at EOT.*

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The MO excluded all of the above patients who did not have an EOS visit because the MO TOC was applied to the EOS. The above listing excluded failures, which were always carried forward.

Baseline Characteristics:

The 2 groups were comparable in terms of age, race, weight, sex, and smoking history. The distribution of smokers was similar between the trovafloxacin and ciprofloxacin groups (33% and 43% ex-smokers, 16% and 15% non-smokers, and 51% and 42% smokers, respectively.)

76 of the trovafloxacin patients were male with a mean age of 58.2 and 62% were white.
55 of the trovafloxacin patients were women with a mean age of 57.5 and 76% were white.

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77 of the ciprofloxacin patients were male with a mean age of 58.5 and 60% were white.
48 of the ciprofloxacin patients were women with a mean age of 58.2 and 75% were white.

The median duration since the onset of the underlying primary diagnosis of CB was not provided.

The median duration since the onset of the present episode was 6 days for both treatment groups

The respective means were 9.8 days for the trovafloxacin patients and 8.2 days for the ciprofloxacin patients.

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Duration of Treatment:

The median duration of treatment was 7 days for subjects in the both treatment groups.

Concomitant Medications:

The majority of patients were on concomitant medications during therapy. The most commonly used medications were bronchodilators (98 and 106 patients per arm respectively) (b)(4)

Systemic steroids were taken by 42 (21%), of the trovafloxacin-treated patients and 49 (28%), of the ciprofloxacin-treated patients. However, based on line listings provided by the sponsor, the MO found that 15/116 (13%), of the clinically evaluable (as per the sponsor), trovafloxacin patients and 18 (15.6%), of the clinically evaluable ciprofloxacin patients were on systemic steroids.

Medical Officer's Comment: *The MO did not exclude patients taking steroids in studies 154-101 and 154-109, but instead, provided separate analyses of clinical and bacteriological response with and without these patients in the MO's efficacy analyses. The MO elected to do the same for this study. The rationale was that there was no major difference in efficacy with or without these patients. The MO found that 34 of the sponsor's clinically evaluable trovafloxacin patients and 42 ciprofloxacin patients received systemic steroids.*

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Concomitant Antimicrobials:

Of the treated patients, 22 trovafloxacin-treated patients and 26 ciprofloxacin-treated patients received concomitant antimicrobials for the following reasons:

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(Copied from page 29 of the study report)

During the study, 22 trovafloxacin and 26 ciprofloxacin subjects received antibiotics other than study drug for the following reasons: inadequate response (14 subjects in each group), side effects (2 subjects in each group), as prior or concomitant medications (trovafloxacin, 2), and other reasons (trovafloxacin 4; ciprofloxacin, 10). All subjects with an appropriate baseline diagnosis who received concomitant medication for inadequate response were evaluable; all other subjects who received concomitant antibiotics were considered to be clinically not evaluable

(This information was located in sponsor's table 2.4, appendix 1).

- inadequate response: 14 trovafloxacin and 14 ciprofloxacin (all carried forward as evaluable failures)
- other reasons: 8 trovafloxacin and 12 ciprofloxacin patients.

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The other category was compromised of the following patients:

Trovafloxacin (N = 8):

- #50150080: Other/relapse: ampicillin day 29, classified as a failure. Reviewer agreed.
- #51530035: Other/early discontinuation because of adverse events day 2 (see above). Reviewer agreed.
- #51560168: Other/exacerbation of COPD on days 22 and 26. Patient was treated with cefotaxime and cephalixin. Carried forward as a failure. Reviewer agreed.
- #51560214: Other/withdrew consent: Cefprozil® day 4. Patient would have been excluded from MO analysis because of a missing EOS visit.
- #51600111: Other/sinusitis: amoxicillin day 21. Classified as a cure per the sponsor but patient would have been excluded from MO analysis because of a missing EOS visit.
- #51600175: Other/sinusitis: ciprofloxacin day 25. Classified as a cure per the sponsor. Reviewer disagreed and patient was included in the MO's analysis as an evaluable failure at the EOS.
- #51600207: Other/sinusitis: ciprofloxacin day 3. Reviewer agreed to exclusion because of apparent misdiagnosis and inadequate sputum samples (see above).
- #52100181: Other/adverse events: day 12. Reviewer agreed.

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Ciprofloxacin (N= 12):

- #50170072: Other/adverse event: azithromycin day 4, sponsor unevaluable because of inappropriate baseline diagnosis. Reviewer agreed.
- #50340412: Other/surgical prophylaxis: cephalixin and gentamicin days 11-16 and 19 - 25. Classified as an improvement at EOT. The patient was excluded from the MO evaluable population because there was no EOS visit.
- #50780286: Other/elevated LFTs day 6. Classified as an improvement at the EOT. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #51450094: Other/adverse events, Bactrim® days 10 - 24. Classified as a failure. Reviewer agreed.
- #51520002: Other/sinusitis: Ceclor® day 8, classified as a cure. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #51520003: Other/surgical prophylaxis: vancomycin and cefazolin days 7 - 14, classified as a cure. The patient was excluded from the MO's evaluable population because of a missing EOS visit.
- #51560076: Other/diverticulitis: ciprofloxacin days 5 - 16, classified as a cure. Reviewer agreed but the patient was excluded from the MO population because there was no EOS visit.

- #51560165: Other/pharyngitis: Ceclor®, erythromycin day 14, classified as a failure. Reviewer agreed.
- #51560180: Other/septic arthritis (see above): sponsor and Reviewer unevaluable.
- #51560210: Other/rhinitis: Cefuroxime® day 25. Classified as a cure by the sponsor. Reviewer disagreed and reclassified as a failure at the EOS.
- #51600124: Other/lung abscess: amoxicillin and Cefixime® days 12 –32. Sponsor classified as improved. The patient was excluded from the MO’s evaluable population because of a missing EOS visit.
- #51600176: Other/patient took doxycycline on her own from days 13 –36, sponsor classified as improved. The patient was excluded from the MO’s evaluable population because of a missing EOS visit.

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Protocol Deviations:

(Copied from page 29 of the study report)

Deviations from protocol were noted for 23 subjects, one of whom had more than one deviation, during the study. These deviations were categorized as follows:

- Inclusion criteria deviations included subjects <40 years of age (3 subjects), subjects with an inappropriate diagnosis due to insufficient symptoms or inappropriate sputum histology (10 subjects), and a subject for whom a Gram stain was not performed (1 subject);
- Other (study procedure) deviations included randomized out of order (8 subjects) and baseline physiological examination performed outside of the 48-hour window prior to treatment initiation (1 subject);
- Deviations that involved taking medications in amounts greater than specified by protocol (prednisone >10 mg/day) (1 subject).

Subjects with an inappropriate baseline diagnosis were not included in the clinical and bacteriological intent-to-treat and evaluable analyses. All other deviations did not effect evaluability. Subjects with protocol deviations are listed in the following table.

Table A. Summary of Protocol Deviations	
(All Randomized Subjects)	
Inclusion	5015-0012; 5015-0118; 5015-0119; 5017-0071; 5078-0222; 5144-0066; 5149-0101; 5152-0004; 5156-0172; 5156-0180; 5159-0024; 5160-0124; 5160-0173
Other (randomized out of order or baseline visit outside window)	5017-0188; 5078-0326; 5160-0109; 5160-0111; 5160-0121; 5160-0176; 5160-0191; 5160-0207; 5160-0227
Taking Medications Not Specified by Protocol or Taking an Allowed Medication in Amounts Greater Than Specified by Protocol	5154-0040

Medical Officer's Comment: *The MO reviewed all deviations and agreed with the sponsor's judgement. Notable was the exclusion of the patient on higher systemic steroid doses than those allowed for in the protocol as compared to study 154-109 where such patients were included.*

Medical Officer's Comment: *Based on the above demographic information, the MO determined that:*

- *Patients receiving steroid therapy (trovafloxacin: 14 sponsor-evaluable (12 FDA-evaluable), and ciprofloxacin: 18 sponsor-evaluable (15 FDA-evaluable), should be evaluated in a separate analysis in order to ascertain if their inclusion in the evaluable population affected outcome.*
- *Patients who received concomitant antimicrobials (2 patients, 1 each arm), should be carried forward as failures.*
- *Patients who did not have an EOS visit (19), should be excluded from the MO evaluable population.*
- *Patients who did not receive the previously specified minimum duration of therapy to be evaluable as cures should be excluded. (2 from MO review)*

Overall, there was concordance between the MO and the sponsor in terms of outcome assessments and evaluability.

Sponsor's Efficacy Analysis:

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Sponsor-Defined Clinical Response:

Table 141.4
Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)

Timepoint	Trovafloxacin N= 131	Ciprofloxacin N = 125
Number of patients evaluated at EOT	116 (100%)	115 (100%)
Cure	47 (41%)	47 (41%)
Improvement	64 (55%)	59 (51%)
Failure	5 (4%)	9 (8%)
Success (Cure + Improvement)	111 (96%)	106 (92%)
Number of patients evaluated at EOS	110(100%)	102 (100%)
Cure	87 (79%)	62 (61%)
Improvement	8 (7%)	19 (19%)
Failure	5 (5%)	9 (9%)
Relapse	10 (9%)	12 (12%)
Success (Cure + Improvement)	95 (86%)	81 (79%)

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Ciprofloxacin: - 2.6%, 9.7% ($\Delta = 10$)

EOS: Trovafloxacin versus Ciprofloxacin: - 3.2%, 17.1% ($\Delta = 15$)

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The sponsor stated that (copied from page 32 of the study report):

Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the

end of study supported equivalence of the two treatments. At the end of study, the distribution of clinical cure, improvement, failure, and relapse (trovafloxacin, 79%, 7%, 5%, and 9%, respectively; ciprofloxacin, 61%, 19%, 9%, and 12%, respectively) showed a statistically significant ($p=0.005$) advantage for trovafloxacin.
(Mandel-Haentzel-Cochran)

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Medical Officer's Comment:

The MO requested that the FDA statistical reviewer, Dr. Silliman, provide a 95% CI with continuity correction factor for the above. The results were as follows:

EOT: Trovafloxacin versus Ciprofloxacin: - 3.5%, 10.5% ($\Delta = 10$):

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EOS: Trovafloxacin versus Ciprofloxacin: -4.1%, 18.0% ($\Delta = 15$)

Based on the FDA analysis, there was therapeutic equivalence between both arms at the EOT and the EOS with trovafloxacin numerically superior to ciprofloxacin at both timepoints.

As per the sponsor, for the clinical ITT population, the success rates were 114/125 (91%) for the trovafloxacin-treated patients and 107/121 (88%) for the ciprofloxacin-treated patients at the EOT (CI: - 4.8%, 10.3%). The respective values at the EOS were 104/125 (83%) and 95/121 (79%): 95% CI for this analysis: - 5.1, 14.5%. The sponsor stated that this analysis also showed equivalence between the 2 treatment arms, with a statistically significant advantage for trovafloxacin ($p = 0.035$) at the EOS.

The sponsor stated that the clinical failure rate was 9% and 12% per arm respectively, at the EOT. At the EOS, 8% and 10% of patients were relapses. Thus as per the MO calculations, the failure rate was 21/125 (17%) on the trovafloxacin arm and 26/121 (22%) on the ciprofloxacin arm, when failures and relapses were added together, (see introduction re definitions).

The clinically evaluable subjects with an outcome of failure at the EOT (5 trovafloxacin and 9 ciprofloxacin) or relapse at the EOS (10 trovafloxacin and 12 ciprofloxacin) and a baseline pathogen (EOT 4 per arm respectively, and EOS 8 and 9 respectively), are listed below:
(Outcomes are for EOS only and include patients classified as relapses by the sponsor)

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Trovafloxacin (N = 12):

- #50150080: Failure: *Haemophilus influenzae* at baseline, eradicated. Also had *Streptococcus pneumoniae* which was persistent.
- #50170070: Failure: *Chlamydia pneumoniae* titer positive. Classified as presumed persistent.
- #50340415: Failure: *Haemophilus influenzae* at baseline which was presumed persistent.
- #51560114: Failure: *Staphylococcus aureus* at baseline which was presumed persistent.
- #50150009: Relapse: *Staphylococcus aureus* at baseline which was eradicated.
- #50150011: Relapse: *Moraxella catarrhalis* at baseline which was persistent.
- #50150079: Relapse: *Streptococcus pyogenes* at baseline which was presumed persistent.
- #50150144: Relapse: *Pseudomonas aeruginosa* at baseline which was persistent. Also had *Mycoplasma pneumoniae* which was presumed persistent.

- #51560074: Relapse: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #51560177: Relapse: *Haemophilus influenzae* at baseline which was persistent.
- #51600123: Relapse: *Pseudomonas aeruginosa* at baseline which was presumed persistent.
- #52100182: Relapse: *Haemophilus influenzae* at baseline which was eradicated.

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Ciprofloxacin (N = 13):

- #50150120: Failure: *Haemophilus influenzae* and *Moraxella catarrhalis* at baseline. Both eradicated
- #50170185: Failure: *Haemophilus influenzae* and *Staphylococcus aureus* at baseline which were presumed persistent.
- #51500031: Failure: *Haemophilus parainfluenzae* at baseline which was presumed persistent
- #51610090: Failure: *Mycoplasma pneumoniae* at baseline which was presumed persistent.
- #50150077: Relapse: *Haemophilus influenzae* at baseline which was eradicated. Also had *Streptococcus pneumoniae* which was persistent.
- #50150117: Relapse: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #50150142: Relapse: *Streptococcus pneumoniae* at baseline which was eradicated.
- #50150147: Relapse: *Haemophilus influenzae* at baseline which was persistent.
- #50780251: Relapse: *Haemophilus parainfluenzae* and *Streptococcus pneumoniae* at baseline were eradicated.
- #51450094: Relapse: *Klebsiella pneumoniae* at baseline which was presumed persistent.
- #51560088: Relapse: *Moraxella catarrhalis* at baseline which was presumed persistent.
- #516001091: Relapse: *Pseudomonas aeruginosa* at baseline which was persistent.
- #521000058: Relapse: *Haemophilus influenzae* at baseline which was persistent.

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Medical Officer's Comment: The MO elected to present only those failures and relapses with a baseline pathogen. Overall, the MO did not disagree with the sponsor's determination of outcome. The MO, however, reclassified those patients classified as relapses, into failures.

The most common pathogen associated with failure on the trovafloxacin arm was *Haemophilus influenzae* followed by *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. On the ciprofloxacin arm, the most common pathogen associated with failure was *Haemophilus influenzae*.

None of the bacterial isolates associated with failure were resistant or developed resistance to either study drug (as per the sponsor).

Clinical response rates for both clinically and bacteriologically evaluable patients can be seen below:

Table 141.5
Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.3)

Timepoint	Trovafloxacin N= 60	Ciprofloxacin N = 69
Number of patients evaluated at EOT	60 (100%)	69 (100%)
Cure	29 (48%)	35 (51%)
Improvement	27 (45%)	30 (43%)
Failure	4 (7%)	4 (6%)
Success (Cure + Improvement)	56 (93%)	65 (94%)
Number of patients evaluated at EOS	57(100%)	64 (100%)
Cure	44 (77%)	41 (64%)
Improvement	1 (2%)	10 (16%)
Failure	4 (7%)	4 (6%)
Relapse	8 (14%)	9 (14%)
Success (Cure + Improvement)	45 (79%)	51 (72%)

The sponsor provided the following 95% CIs, without continuity correction factor:

EOT: Trovafloxacin versus Ciprofloxacin: - 9.3%, 7.5% ($\Delta = 10$)

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EOS: Trovafloxacin versus Ciprofloxacin: - 15.2%, 13.7% ($\Delta = 20$)

Medical Officer's Comment: Trovafloxacin appeared numerically superior to ciprofloxacin at the MO TOC, the EOS. However, there was no significant difference between the results of this population (clinically and bacteriologically evaluable), and the clinically evaluable population. The FDA-generated 95% CIs (with continuity correction factor) for the above were:

EOT: Trovafloxacin versus Ciprofloxacin: - 10.8%, 9.1% ($\Delta = 10$)

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EOS: Trovafloxacin versus Ciprofloxacin: - 16.9%, 15.4% ($\Delta = 20$)

Thus, the 2 agents were marginally equivalent at the EOT, but equivalence was demonstrated at the MO TOC, the EOS.

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Clinical Response by Baseline Pathogen:

Table 141.6
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3 by MO)

Pathogen		Trovafloracin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	17	15	88	20	18	90
	EOS	16	12	75	19	14	74
<i>Moraxella catarrhalis</i>	EOT	13	13	100	13	12	92
	EOS	13	11	85	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	5	4	80	9	9	100
	EOS	4	3	75	8	5	63
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	6	6	100
	EOS	2	2	100	6	6	100
<i>Haemophilus parainfluenzae</i>	EOT	7	7	100	12	11	92
	EOS	6	6	100	10	8	80
<i>Klebsiella pneumoniae</i>	EOT	4	4	100	5	5	100
	EOS	4	4	100	5	4	80
<i>Pseudomonas aeruginosa</i>	EOT	3	3	100	6	6	100
	EOS	3	1	33	5	4	80
<i>Mycoplasma pneumoniae</i>	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
<i>Chlamydia pneumoniae</i>	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
<i>Neisseria meningitidis</i>	EOT	-	-	-	2	2	100
	EOS	-	-	-	1	1	100
<i>Pasteurella multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Staphylococcus aureus</i>	EOT	13	12	92	10	9	90
	EOS	11	9	82	9	8	89
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Total	EOT	74	69	93.2	91	85	93.4
	EOS	68	54	79.4	83	66	79.5

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Copied below from page 40 of the study report is the sponsor's text:

Among clinically evaluable subjects with the most frequently isolated baseline pathogens, sponsor-defined clinical success rates (cure + improvement) were similar (≤ 10 percentage-point difference) in both treatment groups at the end of treatment and at the end of study.

Medical Officer's Comment: *The clinical response by baseline pathogen was proportionately the same for the trovafloxacin-treated patients as compared to the ciprofloxacin-treated patients at both the EOT and EOS. Confidence intervals were not generated for this variable because this table was baseline*

pathogen and not patient driven, thus there were patients with more than 1 baseline pathogen. This decision was made in consultation with Dr. Nancy Silliman, FDA statistician.

For the 3 main pathogens most commonly associated with AECB and for which the sponsor is requesting approval, the MO appended a portion of the above table, below:

Table 141.7
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Main Pathogens Only: Modified 5.3 by MO)

Pathogen		Trovafoxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	17	15	88	20	18	90
	EOS	16	12	75	19	14	74
<i>Moraxella catarrhalis</i>	EOT	13	13	100	13	12	92
	EOS	13	11	85	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	5	4	80	9	9	100
	EOS	4	3	75	8	5	63

Again, CIs were not applied but it appeared that trovafoxacin was equivalent to ciprofloxacin in eradicating *Haemophilus influenzae* at the EOS, and numerically slightly superior versus the other 2 main pathogens. The total cure/eradication rates for the 3 main pathogens were:

Trovafoxacin EOT: 32/35 (91.4 %) and EOS: 26/33 (78.7%)
 Ciprofloxacin EOT: 39/42 (92.8%) and EOS: 28/39 (71.7%)

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Thus the response for both agents for this variable match the clinical response for all evaluable patients.

Signs and Symptoms:
 (Copied from page 42 of the study report)

**APPEARS THIS WAY
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The percentage of clinically evaluable subjects with moderate or severe signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline was comparable between the two treatment groups and was as follows: dyspnea (trovafoxacin: 65%; ciprofloxacin: 66%), cough (trovafoxacin: 96%; ciprofloxacin: 97%), lung sounds (trovafoxacin: 78%; ciprofloxacin: 77%), and increased sputum volume (trovafoxacin: 96%; ciprofloxacin: 95%).

In both treatment groups, the percentage of subjects with signs and symptoms of infection decreased from baseline to the end of treatment and further decreases were observed at the end of study. In general, among the subjects who continued to display these signs or symptoms, the severity was decreased. Similar trends were observed among clinically intent-to-treat subjects. A summary of the percentage of subjects with clinical signs and symptoms of acute bacterial exacerbation of chronic bronchitis at baseline, end of treatment and end of study is presented in the following table.

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Table B. Summary of Clinical Signs and Symptoms						
	Trovafloxacin 200 mg			Ciprofloxacin 500 mg BID		
	Baseline (N=114)	EOT (N=116)	EOS (N=112)	Baseline (N=114)	EOT (N=115)	EOS (N=110)
Sign/Symptom^a	Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms					
Dyspnea	99%	39%	26%	98%	44%	29%
Cough	100%	78%	50%	100%	78%	59%
Lung Sounds	94%	34%	20%	96%	37%	26%
ISV	100%	42%	22%	100%	50%	35%
	Baseline (N=124)	EOT (N=120)	EOS (N=116)	Baseline (N=121)	EOT (N=117)	EOS (N=115)
Sign/Symptom^a	Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms					
Dyspnea	99%	40%	26%	98%	45%	30%
Cough	100%	78%	51%	100%	79%	58%
Lung Sounds	94%	37%	21%	95%	38%	25%
ISV	100%	42%	23%	100%	51%	36%
EOT=End of Treatment; EOS=End of Study; ISV=Increased Sputum Volume						
a Not all subjects were evaluated for all signs/symptoms at all timepoints						
Ref.: Tables 5.8.1 and 5.8.2						

Medical Officer's Comment: *The MO agreed with the sponsor's analysis and verified from the CRFs, that there was indeed a decrease in signs and symptoms as described above.*

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Bacteriologic Response:

Sponsor-Defined Pathogen Eradication Rates at EOT and EOS can be seen in Sponsor's Table 5.4.1, copied and modified by the MO:

**APPEARS THIS WAY
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Table 141.8
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically evaluable Population: Modified 5.4.1 by MO)

Pathogen		Trovafoxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	16	15	94	19	18	95
	EOS	15	13	87	16	13	81
<i>Moraxella catarrhalis</i>	EOT	12	12	100	12	12	100
	EOS	12	10	83	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	3	2	67	9	8	89
	EOS	3	2	67	8	7	88
<i>Haemophilus parahaemolyticus</i>	EOT	3	3	100	6	6	100
	EOS	2	2	100	6	6	100
<i>Haemophilus parainfluenzae</i>	EOT	7	7	100	12	11	92
	EOS	6	6	100	10	9	90
<i>Klebsiella pneumoniae</i>	EOT	3	2	67	5	5	100
	EOS	3	3	100	5	4	80
<i>Pseudomonas aeruginosa</i>	EOT	2	1	50	6	5	83
	EOS	2	0	0	5	4	80
<i>Mycoplasma pneumoniae</i>	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
<i>Chlamydia pneumoniae</i>	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
<i>Neisseria meningitidis</i>	EOT	-	-	-	2	2	100
	EOS	-	-	-	1	1	100
<i>Pasteurella multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Staphylococcus aureus</i>	EOT	12	11	92	9	8	89
	EOS	11	10	91	8	7	88
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
Total	EOT	67	61	91	88	82	93.1
	EOS	63	52	82.5	78	66	84.6

The sponsor's text has been copied from page 43 of the study report below:

Among bacteriologically evaluable subjects with the most frequently isolated baseline pathogens, sponsor-defined pathogen eradication rates were similar (≤ 10 percentage-point difference) in both treatment groups at the end of treatment and at the end of study.

Medical Officer's Comment: As can be appreciated from the sponsor's text, an overall eradication rate was not provided in the study report. Based on the MO's analysis, the 2 agents were numerically comparable at the EOT and EOS, with ciprofloxacin being slightly numerically superior. For the 3 main pathogens however, there was a slight numerical difference in favor of trovafloxacin (EOS).

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The pathogen eradication rates for the 3 main pathogens only were:

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Trovafloxacin EOT: 29/31 (93.5%) and EOS: 25/30 (83.3%)
Ciprofloxacin EOT: 38/40 (95%) and EOS: 29/36 (80.5%)

Based on the above, ciprofloxacin was slightly numerically inferior to trovafloxacin at the EOS with regards to overall bacteriological eradication rate versus the 3 main pathogens associated with AECB. CIs were not applied as discussed previously.

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Superinfecting Pathogens and Colonizing Organisms:
(Copied from page 44 of the study report)

Superinfecting organisms were not isolated from any subject in the trovafloxacin or ciprofloxacin treatment groups. Colonizing organisms were isolated from 4 subjects (3%) in the trovafloxacin group and from 2 subjects (2%) in the ciprofloxacin group.

Medical Officer's Comment: The MO agreed with the sponsor's determination in all cases after review of the PIDs.

Cross-tabulation of Sponsor-Defined Clinical Response and Pathogen Outcome:

The sponsor provided only a cross tabulation for the EOT and not the EOS. 6 patients, (3 trovafloxacin and 3 ciprofloxacin), had clinical responses inconsistent with pathogen outcome. The sponsor's table C has been copied from page 46 of the study report, below and modified to reflect the MO's determination of clinical and bacteriological outcome at the EOS:

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Table 141.9

Cross-Tabulation of Clinical and Bacteriological Response at the EOT (as per the Sponsor) and the EOS (as per the MO)

Table C. Summary of Discrepancies Between Sponsor-Defined Clinical Response and Pathogen Outcome at the End of Treatment (Bacteriologically Evaluable Subjects)					
Subject Number	Baseline Pathogen	Clinical Response		Pathogen Bacteriological Response	
Trovafloxacin 100 mg					
5045-0080	<i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i>	Failure	Failure	Eradicated	Eradicated
5145-0017	<i>Klebsiella pneumoniae</i>	Improvement	Cure	Persistent	Pres.pers.
5160-0123	<i>Pseudomonas aeruginosa</i>	Improvement	Failure	Persistent	Persistent
Ciprofloxacin 500 mg BID					
5015-0077	<i>Streptococcus pneumoniae</i>	Cure	Failure	Persistent	Persistent
5015-0120	<i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i>	Failure	Failure	Eradicated	Eradicated
5160-0191	<i>Pseudomonas aeruginosa</i>	Improvement	Failure	Persistent	Persistent
Ref.: Table 6.7.1 and Appendix I, Table 8					

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Medical Officer's Comment:

Inconsistency between clinical and bacteriologic outcome persisted in 2 of the original 3 trovafloxacin patients, one a clinical cure with presumed persistence of the baseline pathogen, *Klebsiella pneumoniae*, and the other was a clinical failure with documented eradication of one of the baseline pathogens, *Haemophilus influenzae*, but with persistence of the other, *Streptococcus pneumoniae*.

Sponsor's Conclusion: (Copied from the Esub and modified by the MO in Times New Roman font to reflect the numerators and denominators):

Two hundred fifty-six (256) subjects were randomized to treatment with trovafloxacin 100 mg once daily (131 subjects) or ciprofloxacin 500 mg twice daily (125 subjects) for 7 days. The two treatment groups were comparable with respect to characteristics at baseline, medical history, and prior and concomitant medications.

Two hundred thirty one (231) subjects were clinically evaluable (116, trovafloxacin and 115, ciprofloxacin) and 129 subjects were bacteriologically evaluable (60, trovafloxacin and 69, ciprofloxacin). All treated subjects were included in the analysis of adverse events.

Comparisons (95% confidence intervals) of the difference between the trovafloxacin and ciprofloxacin treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the end of study supported equivalence of the two treatments for both clinically evaluable and intent-to-treat subjects.

Success rates among clinically evaluable subjects in the trovafloxacin and ciprofloxacin groups were 111/116 (96%) and 106/115 (92%), respectively, at the end of treatment and 95/110 (86%) and 81/102 (79%), respectively, at the end of study and those among clinically intent-to-treat subjects were 91% and 88%, respectively, at the end of treatment and 83% and 79%, respectively, at the end of study. These findings were supported by marked decreases in the presence of clinical signs and symptoms of acute bacterial exacerbation of chronic bronchitis from baseline to the end of treatment and to the end of study in both treatment groups.

At the end of study, the distribution of clinical cure, improvement, failure, and relapse (trovafloxacin, 79%, 7%, 5%, and 9%, respectively; ciprofloxacin, 61%, 19%, 9%, and 12%, respectively) showed a statistically significant ($p=0.005$) advantage for trovafloxacin.

Sponsor-defined pathogen eradication rates were similar between the two treatments in both bacteriologically evaluable and intent-to-treat subjects.

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Table 141.10
Sponsor Bacteriologic Eradication Rates (as per the MO)

Pathogen	Trovafloxacin-100		Ciprofloxacin	
	EOT	EOS	EOT	EOS
<i>Haemophilus influenzae</i>	15/16 (94%)	13/15 (87%)	18/19 (95%)	13/16 (81%)
<i>Moraxella catarrhalis</i>	12/12 (100%)	10/12 (83%)	12/12 (100%)	9/12 (75%)
<i>Streptococcus pneumoniae</i>	2/3 (67%)	2/3 (67%)	8/9 (89%)	7/8 (88%)

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Medical Officer's Efficacy Analysis:

In accordance with the evaluability criteria previously described, the MO excluded 21 patients from the sponsor's clinically evaluable population and did not include any of the sponsor-excluded patients. The MO's evaluable population can be seen in table 141.11

**Table 141.11
Clinically Evaluable Population (as per the MO)**

Reason for exclusion	Trovafloxacin	Ciprofloxacin
	N= 131	N = 125
Total Treated	116	115
Sponsor Evaluable	7	14
MO Excluded	6	13
No EOS Visit	1	1
Antimicrobial R/x		
Total Evaluated at EOS	109 (83.2%)	101 (81%)

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The numbers of evaluable patients per arm at the EOT was the same as the number at the EOS. The trovafloxacin population represented 42.5% of the randomized patients and the ciprofloxacin population was 39.4%.

The MO's bacteriologically evaluable population was a subset of the clinically evaluable.

A by-center breakdown of the MO's evaluable population is presented in Table 141.12:

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**Table 141.12
Clinically Evaluable Population by Center (as per MO)**

Center	Total Randomized N = 256 (100%)		Trovafloxacin		Ciprofloxacin	
			N = 131	100%	N = 125	100%
5015	26	10.1	11	10.1	12	11.9
5017	7	2.7	2	1.8	2	2.0
5034	19	7.4	6	5.5	8	7.9
5078	47	18.3	18	16.5	17	16.8
5096	3	1.1	2	1.8	1	1.0
5144	7	2.7	2	1.8	2	2.0
5145	11	4.2	5	4.6	6	5.9
5149	5	1.9	2	1.8	2	2.0
5150	5	1.9	2	1.8	3	3.0
5151	3	1.1	2	1.8	1	1.0
5152	4	1.5	2	1.8	0	0
5153	13	5.0	5	4.6	6	5.9
5154	4	1.5	2	1.8	1	1.0
5156	54	21.0	26	23.9	21	20.8
5157	1	0.3	1	0.9	0	-
5159	7	2.7	4	3.7	2	2.0
5160	27	10.5	10	9.2	12	11.9
5161	3	1.1	2	1.8	1	1.0
5210	10	3.9	5	4.6	4	4.0

As noted in the sponsor's demographics, center #5156 enrolled > 20% of the patients.

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The demographics of the FDA evaluable population can be seen in Table 141.13.

**Table 141.13
Demographic Characteristics of the FDA Evaluable Population:**

Characteristics	Trovafloxacin	Ciprofloxacin
	N = 109	N = 101
Sex (Female)	45	38
(Male)	64	63
Age (years) 16 -44	22	16
45 - 64	52	52
≥ 65	35	33
Mean	58.3	58.5
Race: Asian	0	1
Black	26	20
White	77	71
Hispanic	6	8
Polynes.	0	1
Body weight (kg) mean	79.5	80.8

Both arms consisted of a comparable population in terms of weight and age.

Concomitant Medications:

The MO elected (as in the review of study 154-101), not to exclude patients who had been on systemic steroids during this study. The MO's rationale was that not only was the number of evaluable patients per arm on systemic steroids proportionate, but that systemic steroids are often used in patients with CB and at increased doses during acute exacerbations. This implies a standard of care that the MO determined would be appropriate to include in the analysis. The protocol allowed for the inclusion of patients on prednisone, up to 10 mg/day. This low dose was adhered to.

The MO ascertained through review of the line listings, that 12/109 (11%) of the MO evaluable trovafloxacin patients, and 15/101 (15.8%) of the MO evaluable ciprofloxacin patients received systemic steroids during the study.

In accordance with the DAIDP's guidance document, the MO requested that a separate efficacy analysis be performed excluding these patients. These results can be found immediately following the efficacy analyses of all MO evaluable patients.

EFFICACY:

**Table 141.14
Clinical Response by Patient (as per the MO):**

Timepoint	Trovafloxacin			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	109	104	95.4	101	92	91.1
EOS	109	93	85.3	101	79	78.2

The MO applied a 95% CI with continuity correction factor to these results and found the following:

EOT: Trovafloxacin versus Ciprofloxacin: - 3.4%, 12.1% ($\Delta = 10$)
 EOS: Trovafloxacin versus Ciprofloxacin: - 4.3%, 18.5% ($\Delta = 15$)

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Thus, the MO's results mirrored those of the sponsor in that trovafloxacin was equivalent to ciprofloxacin at the EOS (MO TOC), for the primary efficacy variable of clinical response. Additionally, trovafloxacin was numerically superior to ciprofloxacin at both timepoints. There were 16 failures on the trovafloxacin arm as compared to 22 on the ciprofloxacin arm at the EOS, as compared to 5 and 9 per arm respectively, at the EOT.

The following results were obtained when patients on systemic steroids were excluded:

Table 141.15
Clinical Response at EOS by Patient Excluding Patients on Systemic Steroids (as per MO):

Timepoint	Trovafloxacin-100			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	97	94	96.9	86	81	94.2
EOS	97	87	89.7	86	73	84.9

The 95% CI with continuity correction factor was:

EOT: Trovafloxacin versus Ciprofloxacin: - 4.4%, 9.8% ($\Delta = 10$)
 EOS: Trovafloxacin versus Ciprofloxacin: - 6.0%, 15.6% ($\Delta = 15$)

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Based on this analysis, trovafloxacin was again equivalent to ciprofloxacin at both timepoints but with an approximately 5% point difference in response rates as compared to the clinically evaluable population as a whole.

6/12 (50%) of the trovafloxacin-treated patients on systemic steroids as compared to 6/15 (40%) on the ciprofloxacin arm were clinical cures. Therefore 6 of the 16 (37.5%) failures on the trovafloxacin arm and 6 of the 22 failures (27.2%) on the ciprofloxacin arm were seen in patients on systemic steroid therapy.

Clinical response rates were higher on both treatment arms when this subgroup of patients was excluded from the analysis but the overall result was unchanged.

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Clinical Response by Baseline Pathogen:

Table 141.16
Clinical Response by Baseline Pathogen at the EOT and EOS (as per MO)

Pathogen		Trovafoxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	16	14	87.5	19	17	89.9
	EOS	16	12	75	19	13	69
<i>Moraxella catarrhalis</i>	EOT	13	13	100	12	11	91.6
	EOS	13	10	76.9	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	4	3	75	8	8	100
	EOS	4	3	75	8	5	63
<i>Haemophilus parahaemolyticus</i>	EOT	2	2	100	6	6	100
	EOS	2	2	100	6	6	100
<i>Haemophilus parainfluenzae</i>	EOT	6	6	100	10	9	90
	EOS	6	6	100	10	8	80
<i>Klebsiella pneumoniae</i>	EOT	3	3	100	5	5	100
	EOS	3	3	100	5	4	80
<i>Pseudomonas aeruginosa</i>	EOT	3	3	100	5	5	100
	EOS	3	1	33	5	4	80
<i>Mycoplasma pneumoniae</i>	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
<i>Chlamydia pneumoniae</i>	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
<i>Neisseria meningitidis</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pasteurella multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Staphylococcus aureus</i>	EOT	11	10	90.9	8	7	87.5
	EOS	11	9	82	8	7	87.5
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
Total	EOT	67	62	92.5	82	76	92.6
	EOS	67	52	77.6	82	64	78

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As can be seen from the above, clinical response by baseline pathogen was essentially the same for the trovafloxacin-treated patients as compared to the ciprofloxacin both at the EOT and EOS.

For the 3 main pathogens most commonly associated with AECB and for which the sponsor is requesting approval, the MO appended a portion of the above table, below:

Table 141.17
Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically Evaluable Population/Main Pathogens Only: As per MO)

Pathogen		Trovafoxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	16	14	87.5	19	17	89.9
	EOS	16	12	75	19	13	69
<i>Moraxella catarrhalis</i>	EOT	13	13	100	12	11	91.6
	EOS	13	10	76.9	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	4	3	75	8	8	100
	EOS	4	3	75	8	5	63

As above, in this smaller analysis, trovafloxacin was numerically superior to ciprofloxacin in patients with *Haemophilus influenzae* at baseline, at the EOS. Clinical response in patients with *Streptococcus pneumoniae* at baseline was worse at the EOT but superior at the EOS. The total clinical response rates for the 3 main pathogens were:

Trovafoxacin EOT: 30/33 (90.9%) and EOS: 25/33 (75.7%)
 Ciprofloxacin EOT: 36/39 (92.3%) and EOS: 27/39 (69.2%)

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Once again the MO's results mirror those of the sponsor, in that although the 2 agents appear equivalent at the EOT, trovafloxacin appears to be numerically superior at the EOS.

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Bacteriological Response:

Pathogen Eradication Rates at EOT and EOS as per the MO can be seen table 141.17:

Table 141.18**Pathogen Eradication Rates at the EOT and EOS (as per the MO)**

Pathogen		Trovafloracin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	15	14	93.3	18	17	94.4
	EOS	16	14	87.5	18	14	77.8
<i>Moraxella catarrhalis</i>	EOT	12	12	100	12	12	100
	EOS	13	10	76.9	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	3	2	67	8	7	87.5
	EOS	3	2	67	8	7	88
<i>Haemophilus parahaemolyticus</i>	EOT	2	2	100	6	6	100
	EOS	2	2	100	6	6	100
<i>Haemophilus parainfluenzae</i>	EOT	6	6	100	10	9	90
	EOS	6	6	100	10	9	90
<i>Klebsiella pneumoniae</i>	EOT	2	1	50	5	5	100
	EOS	2	2	100	5	4	80
<i>Pseudomonas aeruginosa</i>	EOT	2	1	50	5	4	80
	EOS	2	0	0	5	4	80
<i>Mycoplasma pneumoniae</i>	EOT	2	2	100	1	0	0
	EOS	2	1	50	1	0	0
<i>Chlamydia pneumoniae</i>	EOT	6	5	83	3	3	100
	EOS	6	5	83	3	3	100
<i>Neisseria meningitidis</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pasteurella multocida</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Staphylococcus aureus</i>	EOT	11	10	90.9	7	6	85.7
	EOS	11	10	91	7	6	85.7
<i>Streptococcus pyogenes</i>	EOT	1	1	100	1	1	100
	EOS	1	0	0	1	1	100
<i>Xanthomonas maltophilia</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
Total	EOT	64	58	90.6	80	74	92.5
	EOS	62	50	80.6	79	66	83.5

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As can be appreciated from table 141.17, the overall pathogen eradication rates were numerically comparable at the EOT and EOS. The MO's results resemble those of the sponsor, with minor differences.

The pathogen eradication rates for the 3 main pathogens only were:

Table 141.19

Pathogen Eradication Rates at the EOT and EOS (Main pathogens only: as per the MO)

Pathogen		Trovafoxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	15	14	93.3	18	17	94.4
	EOS	16	14	87.5	18	14	77.8
<i>Moraxella catarrhalis</i>	EOT	12	12	100	12	12	100
	EOS	13	10	76.9	12	9	75
<i>Streptococcus pneumoniae</i>	EOT	3	2	67	8	7	87.5
	EOS	3	2	67	8	7	88

Trovafoxacin EOT: 28/30 (93.3%) and EOS: 26/32 (81.2%)
 Ciprofloxacin EOT: 36/38 (94.7%) and EOS: 30/38 (78.9%)

The pathogen eradication rates for the 3 main pathogens only, are similar to those for all organisms as well as to the sponsor's results.

Pathogen Eradication Rates and Systemic Steroid Usage:

6 of the baseline pathogens on the trovafoxacin arm and 10 on the ciprofloxacin arm were from patients on systemic steroids with 4/6 (67%), and 3/10 (30%), eradications per arm respectively, at the EOS.

The 2 persistent organisms on the trovafoxacin arm were one each: *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

The 7 persistent isolates on the ciprofloxacin arm were 2 each *Haemophilus influenzae* and *Moraxella catarrhalis*, and 1 each *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Mycoplasma pneumoniae*.

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafoxacin: 48/58 (82.7%)
 Ciprofloxacin: 64/70 (91.4%)

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Thus, when the baseline pathogens belonging to patients on systemic steroids were excluded, the overall bacteriologic eradication rate was numerically better for ciprofloxacin as compared to trovafoxacin.

Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients on systemic steroids were:

Trovafoxacin:
Streptococcus pneumoniae: 2/3 (67%)
Haemophilus influenzae: 12/14 (85.7%)
Moraxella catarrhalis: 9/12 (75%)

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Ciprofloxacin:
Streptococcus pneumoniae: 7/8 (87.5%)
Haemophilus influenzae: 13/15 (86.7%)
Moraxella catarrhalis: 9/10 (90%)

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These rates were very similar to those obtained when isolates from steroid users were included.

The MO concluded that the exclusion of this patient subgroup had no effect on either overall eradication rates or on eradication rates for the individual pathogens.

Cross-tabulation of Clinical Response and Pathogen Outcome at the EOS (MO Evaluable Population):

On the trovafloxacin arm, there were inconsistent results in 3 patients. All 3 were clinical failures with eradication of the baseline pathogen. The isolates associated with these results were 2 *Haemophilus influenzae* and 1 *Staphylococcus aureus*.

On the ciprofloxacin arm, there were 7 patients with inconsistent results (6 patients with clinical failure and bacteriologic eradication and 1 with clinical success and persistence). 2 of the clinical failures had *Haemophilus influenzae* at baseline, 2 had *Streptococcus pneumoniae*, and 1 each had *Haemophilus parainfluenzae* and *Moraxella catarrhalis*. The clinical success with persistence had *Moraxella catarrhalis*. The MO reviewed the PIDs of these patients previously.

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Safety Review:

51/131 (39%) trovafloxacin subjects and 50/125 (40%) ciprofloxacin subjects had at least one AE, (all causality). 3/131 (2%) trovafloxacin patients and 7/125 (6%) ciprofloxacin patients discontinued therapy because of an adverse event. 1 of the discontinuations on the trovafloxacin arm and 5 on the ciprofloxacin arm were determined to be related to the study drug.

The most common adverse events leading to discontinuation on the trovafloxacin arm were related to the gastrointestinal system. 2/131 subjects (1%) were discontinued because of nausea, vomiting, abdominal pain, and gastroenteritis. Other events that led to discontinuation included abnormal vision, drug reactions, chest pain, and respiratory insufficiency.

On the ciprofloxacin arm the systems most affected and leading to discontinuation were the gastrointestinal and central and peripheral nervous systems, with 4/125 (3%) discontinued because of nausea, vomiting, and diarrhea and 2/125 (2%) discontinued because of dizziness and tremor. Other events that led to discontinuation, included anxiety, insomnia, pruritus, and paresthesias.

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

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Table 141.20
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloxacin	Ciprofloxacin
Number of Subjects Treated	131 (100%)	125 (100%)
Subject-Days of Exposure	873	834
Subjects With At Least One Event	51 (39%)	50 (40%)
Number of Adverse Events	93	91
Subjects with Serious Adverse Events	1 (<1%)	4 (3%)
Subjects with Severe Adverse Events	1 (<1%)	5 (4%)
Subjects Discontinued Due to Adverse Events	3 (2%)	7 (6%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0
Subjects Discontinued Due to Objective Test Findings	1 (<1%)	0
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

Table 141.21
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Trovafloxacin	Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	131 (100%)	125 (100%)
Subjects With At Least One Event	51 (39%)	50 (40%)
Subjects Discontinued due to Adverse Event	3 (2%)	7 (6%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	4 (3%)	0
Cardiovascular	4 (3%)	1 (<1%)
Centr. & Periph. Nerv.	10 (8%)	14 (11%)
Gastrointestinal	25 (19%)	27 (22%)
General	5 (4%)	6 (5%)
Hematopoietic	0	2 (2%)
Musculoskeletal	5 (4%)	3 (2%)
Other Adverse Events	2 (3%)	1 (<1%)
Psychiatric	1 (<1%)	4 (3%)
Skin/ Appendages	4 (3%)	3 (2%)
Special Senses	6 (5%)	3 (2%)
Reproductive	1 (<1%)	2 (2%)
Metabolic	1 (<1%)	0
Respiratory	5 (4%)	4 (3%)

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Table 141.22
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin	Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	131 (100%)	125 (100%)
Subjects With At Least One Event	25 (19%)	27 (22%)
Subjects Discontinued due to Adverse Event	1 (<1%)	5 (4%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	2 (2%)	0
Musculoskeletal	1 (<1%)	0
Centr. & Periph. Nerv.	3 (2%)	6 (5%)
Gastrointestinal	17 (13%)	19 (15%)
General	1 (<1%)	1 (<1%)
Psychiatric	5 (4%)	4 (3%)
Skin/ Appendages	0	1 (<1%)
Special Senses	2 (2%)	1 (<1%)
Reproductive	1 (<1%)	1 (<1%)
Respiratory	1 (<1%)	0

Overall, and as noted in previous trials, the most frequent treatment-related AEs were from the CNS and GI systems. The % of nervous system AEs was higher for the ciprofloxacin patients as compared to the trovafloxacin patients and the incidence of GI events was higher on the ciprofloxacin arm.

The further breakdown of these events can be found in the MO's Table 141.22

Table 141.23
Most Common CNS and GI AEs/Treatment-related/All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin N = 131		Ciprofloxacin N = 125	
	51	39%	50	40%
Nervous system				
Headache	5	4%	7	6%
Dizziness	5	4%	4	3%
GI System				
Nausea	11	8%	13	10%
Abdominal Pain	4	3%	2	2%
Constipation	4	3%	1	< 1%
Diarrhea	4	4%	6	5%
Dyspepsia	1	< 1%	4	3%

Other events of note included:

Insomnia in 5 (4%) of the ciprofloxacin and the trovafloxacin patients.

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Serious Adverse Events:

4 trovafloxacin-treated subjects and 9 ciprofloxacin-treated subjects had serious adverse events.

Listed below are the severe adverse events that were considered treatment-related:

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Trovafloxacin (N= 4):

- #50340405: post-treatment (day 27), acute MI in a 75 YO Costa Rican male with a history of hypertension, patient was hospitalized. Event was considered unrelated to the study medication but led to death.
- #51530035: theophylline toxicity day 2 of therapy. Therapy was permanently discontinued and the event resolved. This event was considered related to the study drug.
- #51560074: post-treatment (day 32), supraventricular tachycardia in an 80 YO male with a history of atherosclerosis and palpitations, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51560168: post-treatment (day 22), acute exacerbation of COPD in a 66 YO male with a history of COPD, patient was hospitalized. Event was considered unrelated to the study drug but related to the underlying disease process.

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Ciprofloxacin (N = 9):

- #50150117: post-treatment (day 16), acute exacerbation of COPD in a 70 YO male with a history of COPD, patient was hospitalized. Event was considered unrelated to the study drug but related to the underlying disease process.
- #50340412: bronchospasm day 6, secondary to underlying disease process. Patient was hospitalized and study medication continued. Event resolved with therapy.
- #50780255: gun shot wound day 29. Patient was hospitalized. Event was considered unrelated to study medication and resolved with therapy.
- #50780255: exacerbation of cellulitis day 38. Patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- # 51520003: superficial femoral arterial occlusion day 5, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.
- #51560076: exacerbation of diverticulitis day 2. Patient was hospitalized and study medication discontinued. Event was considered unrelated to the study medication and resolved with therapy.
- #51560085: pneumonia day 36, considered unrelated to the study drug. Patient was hospitalized and event resolved.
- #51560180: post-treatment (day 8), exacerbation of osteoarthritis, patient was hospitalized. Event was considered unrelated to the study medication and resolved with therapy.

Deaths: There was one death on the trovafloxacin arm, patient #50340405: a 75 YO male with a history of COPD, HTN, and CHF. Developed an acute MI and death, 27 days post-therapy. The death was attributed to the underlying HTN and appeared unrelated to the study drug, trovafloxacin.

There were no deaths on the ciprofloxacin arm of this study.

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Clinical Laboratory Abnormalities:

The sponsor has submitted tables 4.1, 4.2, 6.1, and 3.3, all of which contained listings of patients who discontinued therapy because of abnormalities. All of the above were reviewed and the MO came to the following conclusions:

Clinically significant laboratory abnormalities were observed for 16% (20/124) of subjects in the trovafloxacin group and 14% (17/118) of subjects in the ciprofloxacin group.

No subject on the trovafloxacin arm had a clinically significant SGPT or SGOT.

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No subject in either treatment group had a clinically significant creatinine value.

The MO did not consider any other laboratory abnormalities found, to be related to the study drugs.

Conclusions:

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As per the Sponsor:

(Copied from page 54 of the study report)

Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to that of ciprofloxacin 500 mg twice daily for 7 days for clinical success rates in subjects with acute bacterial exacerbation of chronic bronchitis. Sponsor-defined pathogen eradication rates were similar between the two treatment groups. The overall incidence of adverse events for subjects in the trovafloxacin group was comparable to that of subjects in the ciprofloxacin group (39% and 40%, respectively), as was the frequency of treatment-related adverse events (19% and 22%, respectively) and adverse events leading to discontinuation (2% and 6%, respectively). The most commonly reported adverse event in both treatment groups was nausea. The frequency and type of adverse laboratory events were comparable between the two treatment groups.

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As per the Reviewer:

In this pivotal study comparing trovafloxacin and ciprofloxacin in the treatment of AECB for 7 days, the sponsor was able to demonstrate equivalence between the 2 antimicrobial agents.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 93/109 (85.3%) for the trovafloxacin-treated patients, and 79/101 (78.2%) for the ciprofloxacin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 4.3%, 15.9% ($\Delta = 15$), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 104/109 (95.4%) for the trovafloxacin-treated patients versus 92/101 (91.1%) for the ciprofloxacin-treated patients. A 95% CI determined equivalence between the 2 arms at this earlier timepoint.

When patients receiving systemic steroids were excluded, the following results were obtained at the EOS: 87/97 (89.7%) trovafloxacin versus 81/86 (94.2%) ciprofloxacin. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 5.9%, 15.6% ($\Delta = 15$), trovafloxacin was again equivalent to ciprofloxacin for the primary efficacy variable of clinical response.

The overall bacteriologic efficacy analysis yielded the following by-pathogen eradication rates:

EOT: trovafloxacin 58/64 (90.6%) versus ciprofloxacin 74/80 (92.5%)

EOS: trovafloxacin 50/62 (80.6%) versus ciprofloxacin 66/79 (83.5%)

If only the 3 main pathogens were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 28/30 (93.3%) versus ciprofloxacin 36/38 (94.7%)

EOS: trovafloxacin 26/32 (81.2%) versus ciprofloxacin 30/38 (78.9%)

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Specific pathogen eradication rates for the three main pathogens, were as follows:

**Table 141.24
Bacteriologic Eradication Rates (as per the MO)**

Pathogen	Trovafloxacin-100		Ciprofloxacin	
	EOT	EOS	EOT	EOS
<i>Haemophilus influenzae</i>	14/15 (93.3%)	14/16 (87.5%)	17/18 (94.4%)	14/18 (77.8%)
<i>Moraxella catarrhalis</i>	12/12 (100%)	10/13 (76.9%)	12/12 (100%)	9/12 (75%)
<i>Streptococcus pneumoniae</i>	2/3 (67%)	2/3 (67%)	7/8 (87.5%)	7/8 (87.5%)

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafloxacin: 48/58 (82.7%)

Ciprofloxacin: 64/70 (91.4%)

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Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients receiving systemic steroids were:

**Table 141.25
Bacteriologic Eradication Rates Excluding Patients on Systemic Steroids (as per the MO)**

Pathogen	Trovafloxacin-100	Ciprofloxacin
	EOS	EOS
<i>Haemophilus influenzae</i>	12/14 (85.7%)	13/15 (86.7%)
<i>Moraxella catarrhalis</i>	9/12 (75%)	9/10 (90%)
<i>Streptococcus pneumoniae</i>	2/3 (67%)	7/8 (87.5%)

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These rates were the same as or very similar to those obtained when isolates from steroid users were included.

The MO concluded that the exclusion of this patient subgroup had marginal (5% lower efficacy) effect on either overall eradication rates or on eradication rates for the individual pathogens.

The MO determined that the sponsor's and MO's clinical response and pathogen eradication rates were very similar for all subgroups.

The adverse events seen in this study, were similar to those noted in previous studies, with a similar overall incidence of adverse events in the trovafloxacin-treated patients (51/131: 39%) as compared to the ciprofloxacin-treated patients (50/125: 40%)

The most common complaints were from the gastrointestinal tract, with 8% (11/131) of trovafloxacin patients having nausea that was treatment-related. As seen previously, there were also complaints of dizziness and headache. In this trial, 5/131 (4%) of the episodes of dizziness and 5/125 (4%) of the episodes of headache were determined to be treatment-related.

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There were no significant laboratory abnormalities.

In conclusion, trovafloxacin 100 mg PO for 7 days, was effective in the treatment of AEBC caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* and was equivalent to the approved comparator, ciprofloxacin.

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Reviewer's Overall Conclusion for the Indication of Acute Exacerbation of Chronic Bronchitis:
 In support of this indication, the sponsor submitted 1 phase II and 2 phase III double-blind, comparative trials. Please see MO table 141.23 for an overview.

**Table 141.26
 Overview of AECB (As per the MO)**

Study #	154-101 Phase II, DB	154-109 Phase III, DB, pivotal	154-141 Phase III, DB, pivotal
Comparator	Ofloxacin	Clarithromycin	Ciprofloxacin
Location	US and Costa Rica (1 center)	US	US and Costa Rica (1 center)
Treatment Arms	Trovafloxacin 100 mg qd Trovafloxacin 300 mg qd Ofloxacin 400 mg bid	Trovafloxacin 100 mg qd Clarithromycin 500 mg bid	Trovafloxacin 100 mg qd Ciprofloxacin 500 mg bid
Duration of therapy	10 days	7 days	7 days
# Randomized	223	410	256
# MO Evaluable at EOS	65 54 61	196 176	109 101
# MO Evaluable on Steroids	12 5 9	32 40	12 15
# MO Evaluable w/o Steroids	53 49 52	164 136	97 86
Clinical Efficacy EOS	57/65 (87.2%) 52/54 (96.3%) 57/61 (93.4%)	157/196 (80.1%) 129/176 (73.3%)	93/109 (85.3%) 79/101 (78.2%)
Clinical efficacy EOS (excluding steroid-users)	49/53 (92.5%) 47/49 (95.9%) 51.52 (98.1%)	137/164 (83.5%) 108/136 (79.4%)	87/97 (89.7%) 73/86 (84.9%)
By-patient Bacteriologic Eradication EOS	10/12 (83.3%) 6/6 (100%) 5/5 (100%)	22/25 (88%) 10/16 (62.5%)	14/16 (87.5%) 14/18 (77.8%)
<i>Haemophilus influenzae</i>	6/6 (100%) 2/2 (100%) 8/8 (100%)	13/17 (76.5%) 16/18 (89%)	10/13 (76.9%) 9/12 (75%)
<i>Moraxella catarrhalis</i>	2/3 (67%) 4/4 (100%) 3/3 (100%)	7/7 (100%) 11/11 (100%)	2/3 (67%) 7/8 (88%)
<i>Streptococcus pneumoniae</i>	3/73 (4%) 24/75 (37%) 7/73 (10%)	9 (4%) 9 (5%)	5 (4%) 4 (3%)
Adverse Events (Treatment-Related) (Dizziness)			
Comment	Underpowered pilot, dose-finding study. Trovafloxacin-100 was not equivalent to trovafloxacin-300 or ofloxacin. Trovafloxacin-300 was equivalent to ofloxacin. The use of systemic steroids did not alter these results.	2 primary efficacy variables. Trovafloxacin equivalent to comparator for both. The use of systemic steroids did not alter results (max. allowed: 10 mg). Trovafloxacin had higher efficacy relative to comparator for <i>Haemophilus influenzae</i> .	2 primary efficacy variables. Trovafloxacin equivalent to comparator for both. The use of systemic steroids did not alter results (max. allowed: 10 mg).

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From the first study, 154-101, a double-blind, phase II trial comparing trovafloxacin-100, trovafloxacin-300, and ofloxacin in the treatment of AECB for 10 days, few conclusions could be drawn.

Only the trovafloxacin-300 arm was equivalent to the comparator agent, ofloxacin, with EOS clinical response rates of 57/65 (87.6%) for the trovafloxacin-100 patients, 52/54 (96.3%) for the trovafloxacin-300 patients, and 57/61 (93.4%) for the ofloxacin patients. Based on a 95% CI, trovafloxacin-300 was equivalent to both comparator arms and ofloxacin was superior to the trovafloxacin-100 arm.

When patients receiving systemic steroids were excluded, the clinical response at the EOS was 49/53 (92.4%) for the trovafloxacin-100 patients, 47/49 (95.9%) for the trovafloxacin-300 patients, and 51/52 (94.4%) for the ofloxacin patients. Based on a 95% CI, trovafloxacin-300 was superior to both comparators and ofloxacin was superior to trovafloxacin-100.

The bacteriologic efficacy analysis yielded the following at the EOT, 29/29 (100%) for the trovafloxacin-100 arm, as compared to 20/20 (100%) and 21/22 (95.4%) for the trovafloxacin-300 and ofloxacin arms respectively.

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Numerically all 3 arms were comparable at the EOT.

At the EOS, the pathogen eradication rate decreased to 25/39 (86.2%) on the trovafloxacin-100 arm, but remained the same for the trovafloxacin-300 and ofloxacin arms. This decrease in eradication rate was also seen in the sponsor's analysis. Statistical significance could not be drawn from these results, as the number of bacterial isolates was very small.

Specific pathogen eradication rates for the three main pathogens (at the MO TOC, the EOS), were as follows:

Table 141.27
Bacteriologic Eradication Rates (as per the MO)

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Pathogen	Trovafloxacin-100	Trovafloxacin-300	Ofloxacin
	EOS	EOS	EOS
<i>Haemophilus influenzae</i>	10/12 (80%)	5/5 (100%)	5/5 (100%)
<i>Moraxella catarrhalis</i>	6/6 (100%)	2/2 (100%)	8/8 (100%)
<i>Streptococcus pneumoniae</i>	2/3 (67%)	4/4 (100%)	3/3 (100%)

The primary adverse events were from the central and peripheral nervous systems, and consisted on multiple complaints of dizziness, visual disturbances, and headache. The trovafloxacin-300 arm had a much higher number of treatment-related adverse events from these systems, 34/75 (45%) as compared to the trovafloxacin-100 arm 3/73 (4%). Additionally, there was a higher incidence of GI complaints on the trovafloxacin-300 arm 24/75 (32%) as compared to the trovafloxacin-100 arm, 4/73 (5%).

There were no significant laboratory abnormalities.

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In conclusion, trovafloxacin appeared effective in the treatment of AECB caused by the three main pathogens; however, marginal equivalence was shown only for the trovafloxacin-300 arm versus the approved comparator, ofloxacin.

From the second study, 154-109, a phase III, pivotal trial comparing trovafloxacin and clarithromycin in the treatment of AECB for 7 days, the sponsor was able to demonstrate equivalence between the 2 antimicrobial agents.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 157/196 (80.1%) for the trovafloxacin-treated patients, and 129/176 (73.3%) for the clarithromycin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 2.3%, 15.9% ($\Delta = 15$), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 174/196 (88.8%) for the trovafloxacin-treated patients versus 148/176 (84.1%) for the clarithromycin-treated patients. A 95% CI determined equivalence between the 2 arms at this earlier timepoint.

When patients on systemic steroids were excluded, the following results were obtained at the EOS: 137/164 (83.5%) trovafloxacin versus 108/136 (79.4%) clarithromycin. Based on a 95% CI (EOS: Trovafloxacin versus Clarithromycin: - 5.4%, 13.7% ($\Delta = 15$), trovafloxacin was again equivalent to clarithromycin for the primary efficacy variable of clinical response.

The bacteriologic efficacy analysis yielded the following pathogen eradication rates:

EOT: trovafloxacin 98/109 (90%) versus clarithromycin 76/87 (87.3%)
 EOS: trovafloxacin 94/111 (84.6%) versus clarithromycin 81/87 (83.5%)

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If only the 3 main pathogens were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 42/49 (85.7%) versus clarithromycin 40/45 (89%)
 EOS: trovafloxacin 42/49 (85.7%) versus clarithromycin 37/45 (82.2%)

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Specific pathogen eradication rates for the three main pathogens (at the MO TOC, the EOS), were as follows:

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Table 141.28
Bacteriologic Eradication Rates (as per the MO)

Pathogen	Trovafloxacin	Clarithromycin
	EOS	EOS
<i>Haemophilus influenzae</i>	22/25 (88%)	10/16 (62.5%)
<i>Moraxella catarrhalis</i>	13/17 (76.5%)	16/18 (89%)
<i>Streptococcus pneumoniae</i>	7/7 (100%)	11/11 (100%)

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Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

Trovafloxacin: 81/95 (85.2%)
 Clarithromycin: 61/71 (85.9%)

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Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients receiving systemic steroids were:

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Table 141.29
Bacteriologic Eradication Rates excluding patients on Systemic Steroids (as per the MO)

Pathogen	Trovafloxacin	Clarithromycin
	EOS	EOS
<i>Haemophilus influenzae</i>	22/25 (88%)	8/12 (66.7%)
<i>Moraxella catarrhalis</i>	11/14 (78.5%)	11/12 (91.7%)
<i>Streptococcus pneumoniae</i>	6/6 (100%)	9/9 (100%)

The adverse events seen in this study were similar to those noted in previous studies. The most common complaints were from the gastrointestinal tract, with 5% (11/210) of trovafloxacin patients having nausea that was treatment related. As seen previously, there were also complaints of dizziness and headache. In this trial, 6/210 (3%) of the episodes of dizziness and 7/210 (3%) of the episodes of headache were determined to be treatment-related.

In conclusion, trovafloxacin appeared effective in the treatment of AECB caused by the three main pathogens and was equivalent to the approved comparator, clarithromycin.

In the third study, 154-141, the sponsor compared trovafloxacin 100 mg daily to ciprofloxacin 500 mg bid in the treatment of AECB for 7 days, and was able to demonstrate equivalence between the 2 antimicrobial agents.

Amongst the FDA clinically evaluable population, the MO found that clinical response, (the primary efficacy variable), at the EOS, (the MO TOC), was 93/109 (85.3%) for the trovafloxacin-treated patients, and 79/101 (78.2%) for the ciprofloxacin-treated patients. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 4.3%, 15.9% ($\Delta = 15$), trovafloxacin was equivalent to the comparator.

The clinical response at the EOT was 104/109 (95.4%) for the trovafloxacin-treated patients versus 92/101 (91.1%) for the ciprofloxacin-treated patients. A 95% CI determined equivalence between the 2 arms at this earlier timepoint.

When patients receiving systemic steroids were excluded, the following results were obtained at the EOS: 87/97 (89.7%) trovafloxacin versus 81/86 (94.2%) ciprofloxacin. Based on a 95% CI (EOS: Trovafloxacin versus Ciprofloxacin: - 5.9%, 15.6% ($\Delta = 15$), trovafloxacin was again equivalent to ciprofloxacin for the primary efficacy variable of clinical response.

The bacteriologic efficacy analysis yielded the following pathogen eradication rates:

EOT: trovafloxacin 58/64 (90.6%) versus ciprofloxacin 74/80 (92.5%)
 EOS: trovafloxacin 50/62 (80.6%) versus ciprofloxacin 66/79 (83.5%)

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If only the 3 main pathogens were included, the overall pathogen eradication rates were:

EOT: trovafloxacin: 28/30 (93.3%) versus ciprofloxacin 36/38 (94.7%)
 EOS: trovafloxacin 26/32 (81.2%) versus ciprofloxacin 30/38 (78.9%)

Specific pathogen eradication rates for the three main pathogens (at the MOT TOC, EOS), were as follows:

Table 141.30
Bacteriologic Eradication Rates (as per the MO)

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Pathogen	Trovafloxacin	Ciprofloxacin
	EOS	EOS
<i>Haemophilus influenzae</i>	14/16 (87.5%)	14/18 (77.8%)
<i>Moraxella catarrhalis</i>	10/13 (76.9%)	9/12 (75%)
<i>Streptococcus pneumoniae</i>	2/3 (67%)	7/8 (87.5%)

Overall pathogen eradication rates at the EOS for the bacteriologically evaluable population minus the systemic steroid users were:

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Trovafloxacin: 48/58 (82.7%)
 Ciprofloxacin: 64/70 (91.4%)

Pathogen eradication rates at the EOS for the 3 main pathogens, excluding those patients receiving systemic steroids were:

Table 141.31
Bacteriologic Eradication Rates Excluding Patients on Systemic Steroids (as per the MO)

Pathogen	Trovafloxacin	Ciprofloxacin
	EOS	EOS
<i>Haemophilus influenzae</i>	12/14 (85.7%)	13/15 (86.7%)
<i>Moraxella catarrhalis</i>	9/12 (75%)	9/10 (90%)
<i>Streptococcus pneumoniae</i>	2/3 (67%)	7/8 (87.5%)

The adverse events seen in this study were similar to those noted in previous studies. The most common complaints were from the gastrointestinal tract, with 8% (11/131) of trovafloxacin patients having nausea that was treatment-related. As seen previously, there were also complaints of dizziness and headache. In this trial, 5/131 (4%) of the episodes of dizziness and 5/125 (4%) of the episodes of headache were determined to be treatment-related.

In all three trials, the MO determined that there were no significant laboratory abnormalities.

In conclusion, trovafloxacin appeared effective in the treatment of AECB caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* and was equivalent to the approved comparators, clarithromycin and ciprofloxacin. The clinical response and pathogen eradication rates were within 5% points difference when patients on systemic steroids were included. This decrease in efficacy was seen in both pivotal trials and was consistent on both arms.

The MO concluded that the exclusion of this patient subgroup had a consistent effect (increase) on clinical response and on overall eradication rates as well as on eradication rates for the individual pathogens thereby indicating that the use of systemic steroids has an effect on clinical response in AECB.

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Overall pathogen eradication rates at the EOS were:

Streptococcus pneumoniae: 11/13 (89.6%)
Haemophilus influenzae: 46/58 (79.3%)
Moraxella catarrhalis: 29/36 (80.5%)
Staphylococcus aureus: 23/24 (95.8%)
Klebsiella pneumoniae: 10/11 (90.9%)
Haemophilus parainfluenzae: 14/14 (100%)

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For comparative purposes, the MO provided data pertaining to this indication, from recently approved quinolone agents.

NDA 20 - 677/Sparfloxacin: The sponsor submitted one large pivotal trial in support of this indication. The reviewing MO found an EOS clinical response rate of 244/279 (87.5%) sparfloxacin, as compared to 245/276 (88.8%) ofloxacin. Bacteriologic response by pathogen revealed the following eradication rates: *Haemophilus influenzae* 51/57 (89.5%) sparfloxacin versus 61/65 (93.8%) ofloxacin, *Moraxella catarrhalis* 36/38 (94.7%) sparfloxacin versus 33/34 (97.1%) ofloxacin, *Streptococcus pneumoniae* 30/34 (88.25%) sparfloxacin versus 20/22 (90.9%) ofloxacin, *Klebsiella pneumoniae*: 15/15 (100%) sparfloxacin versus 15/17 (88.2%) ofloxacin, *Staphylococcus aureus*: 16/19 (84.2%) versus ofloxacin 13/14 (92.9%), and *Haemophilus parainfluenzae*: 115/126 (91.3%) sparfloxacin versus ofloxacin 96/108 (88.9%). This trial was similar in design to that under review and based on the above, sparfloxacin was approved for the indication of AECB caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Chlamydia pneumoniae*. (The MOR did not discuss whether *Staphylococcus aureus* had a sole pathogen in order to be considered evaluable.)

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NDA 20 – 634/Levofloxacin: The sponsor submitted 2 US pivotal studies (an open-label, multicenter trial with cefaclor as the comparator, and the other, an open study with cefuroxime as the comparator.) Additionally, a supportive double-blind foreign study was also submitted with amoxicillin as the comparator. As per the reviewing MO, the clinical cure rate of levofloxacin (280/291:98%) met the 95% CI versus the approved comparators, cefaclor (123/127:97%) and cefuroxime 188/203 (93%). By pathogen eradication rates were: *Haemophilus influenzae* 47/52 (90%) versus combined comparators (cefaclor/cefuroxime 36/46 (78%), *Moraxella catarrhalis*, 30/30 (100%) versus 26/29 (90%) combined comparators, *Streptococcus pneumoniae* 16/18 (89%) versus 15/15 (100%) combined comparators, and *Haemophilus parainfluenzae*, 27/32 (84%) versus 28/39 (72%) combined comparators. Based on the above, an approval was granted for levofloxacin in this indication. The sponsor also requested approval for AECB caused by *Staphylococcus aureus*. This approval was granted by the MTL. The eradication rates were 9/12 (75%) versus comparator 31/34 (91%). Although the 95% CI was met, the reviewing MO recommended that approval should not be granted because of the low numbers of individual isolates and the inability to calculate valid CIs around the difference in eradication rates. Additionally, the decision to not grant approval was based on concerns about the development of resistance and the MO recommended that if approval was granted, that a rigorous subsequent study be imposed to further characterize the microbiology of clinical and microbiological failures. Eradication rates for other organisms were not addressed in the conclusion of the review. An eradication rate was provided for levofloxacin versus *Klebsiella pneumoniae* in 1 study alone: 13/13 (100%).

The clinical success rates for trovafloxacin (both pivotal studies combined), were 250/305 (82%) for all patients and 224/261 (85.9%), when patients receiving systemic steroids were excluded. The MO determined that both the clinical success rates and the pathogen eradication rates were comparable between trovafloxacin and those reported in recent fluoroquinolone NDAs.

RECOMMENDED REGULATORY ACTION:

The following statement can be added to the labeling:

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Orig. NDA #20-759

Orig. NDA #20-760

HFD-590

HFD-590/Div. Dir./MGoldberger

HFD-590/Dep. Dir./RALbrecht

HFD-590/MTL/BLeiss

HFD-590/MO/RAlivisatos

HFD-590/CSO/PFogarty

HFD-725/Biostat/Silliman

HFD-344/Thomas

/S/

12.19.98

Regina Alivisatos, MD
Medical Officer, DSPIDPs

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/S/ 12/17/97

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Addendum to MOR of NDA 20 – 759/Acute Exacerbations of Chronic Bronchitis

On November 14, 1997, (Telecon), the sponsor's representatives made a request to add *Haemophilus parainfluenzae* and *Staphylococcus aureus* to the list of requested pathogens for this indication.

This request was made because the sponsor wanted their label to be consistent with those of previously approved quinolones. Specifically, these organisms are included in the AECB indication of both sparfloxacin and levofloxacin.

As noted in the conclusion of the MOR for AECB, the bacteriologic response by pathogen for these organisms was:

Sparfloxacin: *Staphylococcus aureus*: 18/22 (84%)
Haemophilus parainfluenzae: 115/126 (91.3%)

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Levofloxacin: *Staphylococcus aureus*: 9/12 (75%)
Haemophilus parainfluenzae: 32/32 (100%)

As noted in the overall conclusion of the MOR of NDA 20 – 759/AECB, there were 279 clinically evaluable sparfloxacin patients in NDA 20 – 677 and 291 in the levofloxacin NDA 20 – 634. Neither approval of *Staphylococcus aureus* (22 and 12 isolates respectively), was based on the number of isolates representing 10% of the evaluable isolates. Rather, approval was granted based on the number of these isolates exceeding 10 (alternative interpretation of the PTC Rule of 10).

A review of these organisms in the original submission revealed the following bacteriologic eradication rates (EOS/MO TOC):

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Table 1

Bacteriologic Eradication Rates of *Staphylococcus aureus* and *Haemophilus influenzae* (as per MO)

Study	Drug Regimen	<i>Staphylococcus aureus</i>	<i>Haemophilus parainfluenzae</i>
154-101	Trovafloxacin-100	-	2/2 (100%)
	Trovafloxacin-300	-	3/3 (100%)
	Ofloxacin	-	4/4 (100%)
154-109	Trovafloxacin	11/13 (84.6%)	6/6 (100%)
	Clarithromycin	9/12 (75%)	6/7 (85.7%)
154-141	Trovafloxacin	10/11 (91%)	6/6 (100%)
	Ciprofloxacin	6/7 (85.7%)	9/10 (90%)
Total	Trovafloxacin-100	23/24 (95.8%)	14/14 (100%)

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The following can be stated:

In study 154-101, the eradication rates for *Haemophilus parainfluenzae* alone were equal between the arms.

In study 154-109, there was numerical superiority of trovafloxacin versus the comparator for both organisms.

In study 154-141, there was numerical superiority of trovafloxacin versus the comparator for both organisms.

Total trovafloxacin, 100 mg PO qd, (EOS) pathogen eradication rates for these isolates were:

Staphylococcus aureus: 23/24 (95.8%)
Haemophilus parainfluenzae: 14/14 (100%)

The inclusion of *Haemophilus parainfluenzae* in the labeling for AECB is acceptable to the MO. The sponsor was able to show equivalent efficacy for this organism which is well recognized as a pathogen in this disease. Additionally, the eradication rate was numerically superior to those of previously approved agents. The number of isolates did not meet the standard of the PTC Rule of 10 in terms of percentage of isolates (14/202 (6.9%)), however it did meet the standard of at least 10 evaluable isolates.

The issue of the inclusion of *Staphylococcus aureus* was discussed in the MOR of AECB. At this time there is no clear standard as to the evaluability criteria necessary to be met in terms of sputum quality or organism quantity that can be adhered to. The approval for this organism in the sparfloxacin NDA 20-677 was granted without the application of specific criteria. It was the current MO's determination that based on numbers alone, it was highly unlikely that the evaluable by the RMO isolates were sole pathogens.

In the 11/14/97, the MO requested that Pfizer provide additional data pertaining to the quality of the specimens as well as to document the presence of *Staphylococcus aureus* as a sole pathogen in as many evaluable cases as possible. It was determined that although this information would be helpful in strengthening the sponsor's case, it was not imperative given recent regulatory precedence. However, the resubmitted data was intended to reset this precedence if possible and to impose a new standard to which other agents need apply given the issue of potential development of resistance.

This data are reviewed below:

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The sponsor submitted (FAX/November 20, 1997), clinical response and bacteriologic eradication tables for all patients with *Staphylococcus aureus* isolated either as a sole pathogen or as a co-pathogen (patient line listings were also provided). Please note that the primary determinant of efficacy for this indication was clinical response at the EOS, as opposed to bacteriologic eradication (see Introduction to MOR of AECEB). Additionally, the MO extrapolated bacteriological response from the clinical response unless there was an EOS culture result. This method of assessment differed from that of previously reviewed NDAs, where bacteriologic response was assessed separately.

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Also of note is that the total number of evaluable *Staphylococcus aureus* isolates (24) represented 11.9% of the total number of evaluable pathogens (202/all studies). However as no *Staphylococcus aureus* was isolated in study 101, the total number of isolates from the 2 pivotal studies (109 and 141) was 173. Thus the 24 isolates of *Staphylococcus aureus* represented 13.9% of the evaluable isolates and when only those isolates that were sole pathogens were taken into account, 13, they represented 7.5% of the total number of isolates,

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All of the sputum specimens evaluated in both studies were of good quality, as per protocol, consisting of > 25 WBCs/HPF and < 10 epithelial cells/HPF. Further information with regards to a predominant morphology on Gram stain could not be obtained from this submission. In the CRFs, the reporting of Gram stain bacterial morphology was performed erratically with some investigators reporting this information whereas others merely documented the adequacy of the specimen.

The MO elected to present bacteriological eradication rates as well as clinical response rates by study below:

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Table 2
Study 154 – 109

Staphylococcus aureus Bacteriologic Eradication and Clinical Response at the EOS (as per the MO)

	Trovafloxacin	Clarithromycin
Clinical Response (success)		
Sole pathogen	4/4 (100%)	7/9 (77.8%)
Co-infection	7/9 (77.8%)	2/3 (66.7%)
Total	11/13 (84.6%)	9/12 (75%)
Bacteriologic Response (Eradication)		
Sole Pathogen	4/4 (100%)	9/9 (100%)
Co-infection	9/9 (100%)	2/3 (66.7%)
Total	13/13 (100%)	11/12 (91.7%)

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In both trovafloxacin-treated patients where *Staphylococcus aureus* was mixed with another isolate, *Pseudomonas aeruginosa* was the co-pathogen. In both of these cases, the *Staphylococcus aureus* was eradicated but the *Pseudomonas aeruginosa* was not, thus the patients were assigned an outcome of failure as per the MO (according to the clinical outcome).

Table 3
Study 154 – 141
***Staphylococcus aureus* Bacteriologic Eradication and Clinical Response at EOS (as per the MO)**

	Trovafloxacin	Ciprofloxacin
Clinical Response (success)		
Sole pathogen	7/9 (77.8%)	7/8 (87.5%)
Co-infection	2/2 (100%)	5/5 (100%)
Total	9/11 (81.8%)	12/13 (92.3%)
Bacteriologic Response (Eradication)		
Sole Pathogen	8/9 (88.9%)	5/5 (100%)
Co-infection	2/2 (100%)	1/2 (50%)
Total	10/11 (90.9%)	6/7 (85.7%)

In both instances of clinical failure in the trovafloxacin-treated patients, *Haemophilus influenzae* was the co-pathogen.

Table 4
Combined Results (studies 154-109 and 154-141)
***Staphylococcus aureus* Bacteriologic Eradication and Clinical Response at EOS (as per the MO)**

	Trovafloxacin	Comparators
Clinical Response (success)		
Sole pathogen	11/13 (84.6%)	14 /17 (82.3%)
Co-infection	9/11 (81.8%)	7/8 (87.5%)
Total	20/24 (83.3%)	21/25 (84%)
Bacteriologic Response (Eradication)		
Sole Pathogen	12/13 (92.3%)	14/14 (100%)
Co-infection	11/11 (100%)	3/5 (60%)
Total	23/24 (95.8%)	17/19 (89.4%)

From the above, it became apparent that trovafloxacin was as effective in the eradication of *Staphylococcus aureus* (either as a sole pathogen or as a co-pathogen), versus not only the comparator agents but also versus sparfloxacin and levofloxacin. The MO determined that the sponsor met the "Rule of 10" in terms of 10% of the evaluable isolates when all isolates were taken into account and additionally, that at least 10 isolates (sole isolates n = 13) were provided. Although the MO recognizes that as recommended in PTC, the greater of the 2 should be met and that the sponsor does not meet this goal based on "sole isolates" only, regulatory precedence indicates that the sponsor provided greater information than that contained in previous applications receiving approval. Additionally, the sponsor provided valuable information with regards to clinical response in either setting. This information cannot be compared to that in previously reviewed NDAs because the sponsors of those NDAs did not provide these data.

The MO determined that the information provided was adequate to recommend an approval for trovafloxacin in the treatment of AECB caused by *Staphylococcus aureus*, either as a sole pathogen or as a co-pathogen. However, the real value in this submission lies in the resetting of regulatory precedence in that other submissions should also provide adequate information with regards to the number of isolates that occurred as sole pathogens as well as their eradication rates and the clinical response rates associated with them.

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RECOMMENDED REGULATORY ACTION:

The following statement can be added to the labeling:

Trovafloxacin is indicated for the treatment of Acute Exacerbation of Chronic Bronchitis caused by *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* at a dose of 100 mg PO daily for 7 - 10 days.

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12/17/97

Regina Alivisatos, MD
Medical Officer, DSPIDPs

Orig. NDA #20-759

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HFD-725/Biostat/Silliman

HFD-344/Thomas

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Nosocomial Pneumonia

The proposed indication as it will appear in the labeling if approved is:

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Nosocomial pneumonia caused by *Escherichia coli*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

The sponsor has also appended the following statement to the draft labeling for this indication:

“As with other antibiotics, treatment of nosocomial infections due to *Pseudomonas aeruginosa* infections, may require combination therapy.”

The proposed dose is alatrofloxacin 300 mg IV daily → trovafloxacin 200 mg PO daily for 10 – 14 days total.

In support of this indication, the sponsor has submitted one double-blind, comparative trial of the efficacy and safety of alatrofloxacin/trovafloxacin at the proposed dose compared to ciprofloxacin 400 mg IV BID → ciprofloxacin 750 mg PO BID for 10 – 14 days total (study 154-113), and one open, randomized trial of the efficacy and safety of alatrofloxacin/trovafloxacin at the proposed dose compared to ceftazidime 2 gm (maximum) BID IV → ciprofloxacin 750 mg BID for 10 – 14 days total (study 154-137).

Also contained within the electronic submission were documents related to the pharmacokinetics and microbiological properties of trovafloxacin and the requested indication. These were summarized in the MOR of AECB and will briefly be mentioned here.

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Antimicrobial Agents Currently Approved for this Indication:

Zosyn®: moderate to severe nosocomial pneumonia caused by beta-lactamase producing strains of *Staphylococcus aureus*. “Initial presumptive treatment of patients with NP should start with Zosyn® at a dosage of 3.375 gm q 6 hours PLUS AN AMINOGLYCOSIDE. Treatment with the aminoglycoside should be continued in patients from whom *Pseudomonas aeruginosa* is isolated. If *Pseudomonas aeruginosa* is not isolated than the aminoglycoside may be discontinued at the discretion of the treating physician.”

Ciprofloxacin: Mild/moderate/severe nosocomial pneumonia caused by *Haemophilus influenzae* or *Klebsiella pneumoniae* at a dose of 400 mg IV q8h.

Medical Officer's Comment: All other agents listed below are approved for the indication of LRTI (lower respiratory tract infections).

Ciprofloxacin: (LRTI: mild to moderate): *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.)

Ceclor®: (LRTI and pneumonia: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*.)

Cefizox®: (LRTI: *Klebsiella* spp., *Proteus mirabilis*, *Escherichia coli*, *Serratia* spp., *Enterobacter* spp., *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus* spp. including *Streptococcus pneumoniae* but excluding *Enterococcus*)

Cefotan®: (LRTI: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, and *Serratia marcescens*)

Ceptaz®: (LRTI: *Pseudomonas aeruginosa*, other *Pseudomonas* spp., *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, *Serratia* spp., *Citrobacter* spp., and *Staphylococcus aureus*)

Claforan®: (LRTI: *Haemophilus influenzae*, *Streptococcus pneumoniae*, other *Streptococcal* spp excluding Enterococci, *Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, *Serratia marcescens*, *Proteus* spp. and *Proteus mirabilis*, *Staphylococcus aureus*, *Pseudomonas* spp. including *aeruginosa*.)

Cleocin®: (LRTI: *Streptococcus pneumoniae* and other Streptococci excluding Enterococci, *Staphylococcus aureus*)

Flagyl®: (LRTI including pneumonia: *Bacteroides fragilis* group)

Rortaz®: (LRTI: *Pseudomonas aeruginosa*, other *Pseudomonas* spp., *Haemophilus influenzae* *Streptococcus pneumoniae*, *Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, *Serratia* spp., *Proteus mirabilis*, *Citrobacter* spp., and *Staphylococcus aureus*.)

Lorabid®: (Pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae*).

Spectobid®: (LRTI: *Haemophilus influenzae*, *Streptococcus pneumoniae*, beta-hemolytic Streptococci, and non-penicillinase producing Staphylococci)

Tazicef®: (LRTI: *Pseudomonas aeruginosa*, *Haemophilus influenzae* *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Escherichia coli*, *Serratia* spp., *Proteus mirabilis*, *Citrobacter* spp., and *Staphylococcus aureus*.)

Tazidime®: (LRTI: *Pseudomonas aeruginosa*, *Haemophilus influenzae* *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Escherichia coli*, *Serratia* spp., *Proteus mirabilis*, *Citrobacter* spp., and *Staphylococcus aureus*.)

Zinacef®: LRTI: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella* spp., *Escherichia coli*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Escherichia coli*)

Zithromax®:

Rocephin®: (LRTI: *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus mirabilis*, and *Serratia marcescens*.)

Primaxin®: (LRTI: *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Acinetobacter* spp., *Enterobacter* spp., *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, and *Serratia marcescens*.)

Pipracil®: (LRTI: *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Enterobacter* spp., *Bacteroides* spp. and anaerobic cocci, *Klebsiella* spp., *Escherichia coli*, *Staphylococcus aureus*, and *Serratia* spp.)

Amoxil®: (indicated for the therapy of infections due to susceptible strains of the following Gram (+) cocci: *Streptococci* and *Streptococcus pneumoniae* and gram (-) organisms: *Haemophilus influenzae*, *Escherichia coli* and *Proteus mirabilis*).

Augmentin®: (LRTI: beta-lactamase producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*).

Azactam®: LRTI: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Serratia marcescens*.)

Ilosone/Ilotycin®: (LRTI: *Streptococcus* spp.)

Kefurox®: (LRTI: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus pyogenes*)

Mandol®: (LRTI: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella* spp., *Staphylococcus aureus*, *Proteus mirabilis* and beta-hemolytic Streptococci)

Mefoxin®: LRTI: *Streptococcus pneumoniae* and other Streptococci excluding Enterococcus, *Klebsiella* spp., *Escherichia coli*, *Haemophilus influenzae*, and *Bacteroides* spp.)

Mezlin®: (LRTI: *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Pseudomonas* spp., *Bacteroides* spp. including *fragilis*, *Klebsiella* spp., and *Escherichia coli*)

Nebcin®: (LRTI, serious: *Klebsiella* spp., *Escherichia coli*, *Enterobacter* spp., *Proteus mirabilis*, and *Staphylococcus aureus*)

Netromycin®: (LRTI including pneumonia and bronchitis: *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Proteus mirabilis*, *Proteus* spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Serratia marcescens*.)

PCE Dispertab®: (LRTI: mild to moderate: *Streptococcus pneumoniae* and *Streptococcus* spp.)

Abbreviations used in this section:

Ceftaz = Cefazidime

URTI = upper respiratory tract infection
 LRTI = lower respiratory tract infection
 URT = upper respiratory tract
 LRT = lower respiratory tract
 COPD = chronic obstructive pulmonary disease
 Cipro = ciprofloxacin
 Trovafloxacin = trovafloxacin
 V1 = visit one or baseline visit on study day 1
 V2 = visit 2, window study days 3 -7
 V3 = visit 3
 V4 = visit 4
 EOT = End of Therapy
 EOS = End of Study
 TOC = Test of Cure
 AE = Adverse Event
 PTC = Points to Consider
 ELF = epithelial lining cells
 MSSA = methicillin-sensitive *Staphylococcus aureus*
 MRSA = methicillin-resistant *Staphylococcus aureus*
 PMN = polymorphonuclear
 AC = advisory committee
 AE = adverse event
 NP = nosocomial pneumonia
 CAP = community acquired pneumonia
 Bronch = bronchoscopy
 VAP = ventilator associated pneumonia

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Materials Reviewed for this Indication:

Electronic submission/December 29, 1996
 FAX/September 23, 1997 containing tables pertaining to studies 154-113 and 154-137

Background:

The lower respiratory tract clinical syndrome of pneumonia can be divided into to broad categories: community-acquired pneumonias (CAP) and nosocomial pneumonias (NP).

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Nosocomial pneumonia is a clinical syndrome, characterized by the presence of a new infiltrate on CxR, as well as at least 2 of the following: cough, the production of sputum or a change in the character of the sputum, auscultatory findings and/or evidence of pulmonary consolidation, dyspnea, tachypnea, fever, and leucocytosis. Additionally, an organism consistent with a respiratory pathogen must be isolated from an appropriately obtained specimen.

The term NP is utilized in patients who acquire this clinical picture while in the hospital setting (> 48 hours after admission), or in nursing home patients. This differentiation, based on time of acquisition, is necessary in order to separately evaluate those patients with CAP who not only may be treated as out-patients but additionally present with a different microbial etiologies. Additionally, this differentiation has prognostic significance because patients in a hospital setting have increased mortality.

Risk factors for the development of NP include advanced age, severity of the underlying disease, intubation, use of respiratory equipment, use of a naso-gastric tube, altered mental status, and previous antimicrobial usage. Approximately 60% of the cases of NP are associated with Gram (-) bacilli including *Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, *Enterobacter* spp., and *Pseudomonas* spp. *Haemophilus influenzae* is also thought to be a pathogen especially in patients who have been hospitalized for a brief duration.

Staphylococcus aureus accounts for approximately 20% of the cases in contrast to *Streptococcus pneumoniae* which accounts for only Anaerobic bacteria are often isolated (35%) but are thought to account for only 5% of the cases. *Legionella* spp. has also been reported as the cause of sporadic outbreaks.

Some debate exists over the most appropriate method for obtaining sputum samples and thus a microbiologic diagnosis. Methods that can be employed include expectorated sputum, transtracheal aspiration, bronchial brushings, biopsy materials, pleural fluid, blood cultures, and surrogate markers (detection of antigen or specific nucleic acid by non-culture methods)

There appears to be concurrence between the FDA Guidance document, the IDSA Guidelines as well as various medical texts, that the use of expectorated or endotracheally aspirated sputum is acceptable as long as the specimen is screened for suitability (presence of > 25 PMNs and < 10 squamous epithelial cells/low magnification field [x 10]).

An appropriate specimen and a microbiologic diagnosis should be made within 24 –72 hours of starting therapy. All isolates should be sensitive to both the test drug and the comparator.

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General guidelines for the duration of therapy vary from 10 – 14 days. The type of therapy selected depends on several issues including the location of the patients within the hospital setting (ICU), the presence of a ventilator, the use of previous antimicrobial therapy which might have led to the selection of resistant pathogens, the site of the infiltrate, and many other factors. All of the above will ultimately help determine a microbial differential diagnosis and aid in the development of an empiric regimen. The use of an extended spectrum penicillin or a third generation cephalosporin is generally advocated. Unresolved issues include the need for the addition of anaerobic coverage or not, that is clindamycin or metronidazole as well as the addition of an aminoglycoside or aztreonam when *Pseudomonas aeruginosa* is suspected or documented. The emergence of MRSA has also led to the increasing use of vancomycin in the empiric treatment of this disease.

Above reference: Mandell, Douglas and Bennett's principles and Practice of Infectious Diseases, Fourth edition, pages 608 - 612.

The FDA PTC states that one well-controlled trial that establishes clinical efficacy (95%CI) or general equivalence (difference in success rate no greater than 5%) to an approved comparator is required for approval.

Current IDSA Guidelines for the evaluation of anti-infective drug products, Vol. 15, suppl. 1, Nov. 1992, pages S80 – S87, suggest the following:

The minimal diagnostic criteria permitting the inclusion of patients in clinical trials are:

- Patients must have signs and symptoms consistent with bacterial pneumonia as described above.
- Patients must have a new infiltrate on CxR within 48 hours of institution of therapy.
- Suitable specimens for microbiologic evaluation must be obtained. This includes purulent expectorated sputum, transtracheal aspirates, specimens obtained by bronchial lavage or biopsy, pleural fluid aspirates, blood cultures, and surrogate markers.
- Patients must be adults, > 18 years of age.
- Pregnant or lactating women as well as patients with severe underlying diseases must be excluded.
- Patients who received prior antimicrobial therapy for $\geq$ 24 hours should be excluded.
- The study design should be randomized, prospective, and double blind.

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- A separate analysis of ventilator-associated pneumonia (VAP) should be provided.
- The duration of treatment varies but it may be desirable to treat until the patient has been afebrile for 7 - 10 days.
- Conversion from the intravenous to the oral route can occur after an evaluation between days 3 - 7 of the study.
- Clinical evaluation is based on the resolution or improvement of the clinical and laboratory signs of infection such as fever, leucocytosis, purulent sputum production, and radiographic lung infiltrates.
- Hospitalized patients should be assessed every day during treatment and within 5 - 7 days after completion.
- Sputum samples should be collected at entry and at regular intervals.
- A CxR should be obtained 3 days after initiation of therapy and at any other time the investigator deems necessary.
- A post-therapy evaluation is necessary to determine response.
- Patients who have received at least 5 days of therapy and at least 80% of the study medication will have an assessment of clinical response.

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In addition to the above, patients who worsen or who do not improve after 2 - 3 days should be removed from the study and classified as clinical failures. The addition of an antimicrobial that is not a study drug should also result in the designation of clinical failure.

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The definitions of clinical response are as follows:

- **Clinical cure:** the complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on CxR.
- **Clinical failure:** the lack of any resolution in the signs and symptoms of pneumonia or persistence or progression of these after 3-5 days of therapy; the development of new pulmonary or extrapulmonary clinical findings consistent with active infection; persistence or progression of radiographic abnormalities; death due to pneumonia; or an inability to complete the study because of adverse effects.
- **Indeterminate:** must be substantiated by stated reasons.

The definitions of microbiologic response include:

- Eradication
- Persistence
- Relapse
- Reinfection
- Superinfection.

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The current guidance for evaluability criteria of the DAIDP recently addressed the indication of pneumonia (CAP and NP). Amongst the points that were stressed, were:

- The differentiation of a CAP as opposed to a NP, and within the category of NP, the subsetting of those patients with VAP.
- The need for those patients with NP to have both fever and leucocytosis as well as least 1 of the other symptoms (cough, purulent sputum, auscultatory findings, dyspnea, tachypnea, hypoxemia, and an organism consistent with a respiratory pathogen.)
- A CxR within 48 hours of initiation of therapy that reveals the presence of a new or progressive infiltrate.
- The lack of consensus in the literature on the criteria for interpretation of the culture and Gram stain results of specimens obtained from patients with VAP.
- The prerequisite of 80 – 120% of therapy for evaluability
- The “optional” EOT visit, as this visit cannot be used as the TOC
- The “required” TOC visit at least 1 week after completion of therapy
- Clinical outcome as the primary efficacy variable

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The DAIDP advisory committee agreed to all of the above.

Previous Recent Regulatory History:

Ofloxacin: NDA 19-735/S-029 and NDA 20-087/S-009: submitted in February 1993 for the indications of NP and severe CAP. The applicant submitted the data from 1 controlled and 1 uncontrolled study in support of this indication. Ceftazidime was the comparator agent in both trials. In the controlled trial, the efficacy of ofloxacin was inferior to that of the comparator. Multiple problems existed with the submission including: the lack of the specification of the timing of the acquisition of the NP in hospitalized patients, thus making the differentiation between patients with NP and those with CAP difficult. Additionally, the duration of therapy ranged from 7 – 14 days which again made the evaluation of the patients difficult. A severity scoring system was not provided and although sputum samples were collected, no guidelines as to the characterization of an acceptable specimen were provided, thus making the differentiation between colonization and true infection impossible. This application was denied.

Ciprofloxacin: NDA 19-847/S-008, NDA 19-857/S-008, NDA 19-858/S-008: submitted January 1993 for the indication of severe LRTI including NP. The applicant submitted one well designed, controlled, third party blinded, randomized trial comparing the efficacy and safety of ciprofloxacin with intravenous imipenem in patients with severe pneumonia. Additionally, data from supportive studies was also submitted. The MO utilized clinical response as the primary efficacy variable as compared to the applicant who used bacteriologic response. All other parameters in this submission were similar to those of the current submission. Clinical cure rates at the EOS were 59.2% for the ciprofloxacin-treated patients and 39.5% for the imipenem-treated patients. The MO recommended approval for this indication, but only for *Haemophilus influenzae* (14/19 eradicated) and *Klebsiella pneumoniae* (8/9 eradicated). Approval was not recommended for the requested pathogens: *Staphylococcus aureus* (8/14 eradicated) and *Pseudomonas aeruginosa* (18/29 eradicated) in severe disease although there was pre-existing approval for *Pseudomonas aeruginosa* in mild to moderate disease.

Medical Officer's Comment: *The original RMO determined that there was concurrence from all sources as to the criteria utilized in the diagnosis of NP as well as in the design and implementation of clinical trials to assess the efficacy and safety of new agents for this entity. Additionally, the RMO found that the sponsor had adhered to the FDA Guidance document in the design and implementation of these clinical trials for the indication of NP.*

The MO made the following determinations with regards to evaluability criteria:

- The diagnosis of NP must be well established. This included the development of the signs and symptoms consistent with NP at least 48 hours after admission to the hospital for a non-respiratory diagnosis. The exception to this was the acceptance of non-ambulatory nursing home patients admitted for a possible Gram (-) pneumonia.

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The sponsor has adequately provided this information. A review of the CRFs revealed that the investigators not only had to verify the presence of increased cough, sputum production, increased purulence, dyspnea, fever, and leucocytosis, but additionally had to obtain a CxR to verify the presence of a new infiltrate as well as a sputum culture to assess not only for purulence but also for a predominant organism. Blood cultures were also obtained on all patients.

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- The MO carried forward any patient who received any additional antimicrobials not prespecified in the protocol, during the study as an evaluable failure. The only exception to this was in patients who received an antimicrobial that was clearly utilized for another infectious process and that had no activity against the designated pathogen. Failure was determined after 1 full day of therapy. This was consistent with the sponsor's evaluation of the data which was done in a blinded ad hoc manner because the duration of therapy necessary before a patient could be called a failure was not pre-determined by protocol. Although the MO determined that 1 day of therapy was not enough to fairly categorize a patient as a failure attributable to the study drug, the MO decided to re-evaluate this issue if it appeared that there were significant numbers of patients that fell into this category from either treatment arm.
- The MO did not consider evaluable those patients who received an alternative antimicrobial within 24 hours of the start of the study, unless the prerequisite clinical and microbiologic criteria were present (that is the isolation of a predominate pathogen on culture in association with the clinical picture of NP).
- The MO provided separate analyses of clinical response for those patients with ventilator-associated pneumonia and requested that the sponsor provide similar analyses of their data.
- The MO adhered to the categories of clinical and microbiologic assessment as described above in the IDSA Guidelines. This included the use of the primary efficacy variable of clinical response as a determinate of microbiologic outcome for each pathogen. That is, a patient who was cured was assumed to have "eradication/presumed eradication" of the primary pathogen or alternatively, a patient who failed was assumed to have "persistence/presumed persistence" of the primary pathogen.
- The MO assessed cure and improvement together in order to provided a dichotomous "cure/fail" analysis.
- The MO determined that the TOC should be applied to the EOS visit. This determination differs from that of the sponsor where the primary efficacy variable, clinical response, was applied to the EOT. The logical continuation of this argument was that a patient who was not seen at the later follow-up visit was not evaluable. If, however, the sponsor excluded a patient because they were not seen at the EOT but were seen at the later visit, the MO determined that this patient was evaluable. All failures were carried forward.
- Patients were eligible for classification as clinical cures if they received of the
study drug.
- The windows of evaluability provided for by the sponsor were not changed for the EOS (days 28 –35) as the MO TOC was at the EOS and therefore sufficiently far out from therapy that the presence of active drug or post-antibiotic effect could be excluded.

- In both the double-blind trial (154-113) and the open trial (154-137), where ciprofloxacin and ceftazidime/ciprofloxacin were the respective comparator agents, the sponsor allowed for the use of either clindamycin or metronidazole, at the investigator's discretion, to provide broader anaerobic coverage. The MO elected to accept this concomitant antimicrobial usage. Additionally, both studies allowed for the addition of vancomycin in the presence of MRSA. If *Pseudomonas aeruginosa* was isolated, study 113 allowed for the addition of aztreonam and study 137 for the addition of gentamicin. The MO requested that the sponsor provide a separate analysis of the data with regards to these patients who received additional Gram (-) coverage.

The MO reviewed the sponsor's evaluability criteria and general approach in this introduction. Both studies (154-113 and 154-137) were similar with only minor differences between them and these were pointed out in this section. Subsequent to the introduction, each study was reviewed separately and the MO referred back to this introductory section.

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Microbiology:

In support of the effectiveness of trovafloxacin against the requested pathogens, the sponsor submitted, (microbiology section of the electronic submission), the results of microbiology studies of trovafloxacin versus the requested pathogens. These MIC-90 results are summarized below:
(Copied from page 10, section H.3.A of the Esub)

Pathogen	MIC ₉₀ (µg/mL)
<i>Streptococcus pneumoniae</i> (including penicillin resistant)	0.12
<i>Staphylococcus aureus</i>	0.06
<i>Haemophilus influenzae</i>	0.015
<i>Moraxella catarrhalis</i>	0.03
<i>Escherichia coli</i>	0.06
<i>Klebsiella pneumoniae</i>	0.12
<i>Pseudomonas aeruginosa</i>	1.0
<i>Enterobacter cloacae</i>	1.6
<i>Proteus mirabilis</i>	0.5
<i>Enterococcus faecalis</i>	2.0
<i>Serratia marcescens</i>	1.0
<i>Morganella morganii</i>	0.5
ATYPICAL	
<i>Legionella pneumoniae</i>	0.008
<i>Mycoplasma pneumoniae</i>	0.25
<i>Chlamydia pneumoniae</i>	1.0
ANAEROBES	1.0

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Pharmacokinetics:

The MO reviewed the 2 studies submitted by the sponsor assessing the penetration of orally administered trovafloxacin into the bronchial tree (studies 154-016: an open study to assess concentrations of trovafloxacin in bronchial washings and serum after administration of a single dose to subjects undergoing bronchoscopy and 154-020: an open study to assess the concentration of trovafloxacin in bronchial mucosa, epithelial lining fluid, and alveolar macrophages compared to that of serum after administration of single and multiple oral 200 mgm doses to subjects undergoing fiber-optic bronchoscopy), in the MOR pertaining to AECB.

The results of these studies are provided below (copied from the electronic submission):

154-016	26	Bronchial epithelial cells/macrophages	2.9 (4-6 hr postdose) 7.3 (18-24 hr postdose)
154-020	5	Lung mucosa (single dose)	1.1 (6 hr postdose)
	9	Lung mucosa (multiple dose)	1.1 (6 hr postdose)
154-020	5	Lung epithelial lining fluid (single dose)	2.3 (6 hr postdose)
	7	Lung epithelial lining fluid (multiple dose)	5.8 (6 hr postdose)
154-020	5	Alveolar macrophages (single dose)	13.3 (6 hr postdose)
	8	Alveolar macrophages (multiple dose)	24.1 (6 hr postdose)

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Medical Officer's Comment: These results showed that trovafloxacin was well distributed to bronchial mucosal tissue, ELF and macrophages following single and multiple 200 mg doses. In addition, the concentrations obtained were well above the MIC-90s of pathogens responsible for lower respiratory tract infections, including those associated with NP. The sponsor stated that:
(Copied from page 10, section H.3.A of the Esub)

The mean peak blood levels (C_{max}) of the 200 mg trovafloxacin oral dose (used for community-acquired pneumonia and sinusitis) and 300 mg alatrofloxacin IV dose (trovafloxacin equivalent dose; used for nosocomial pneumonia) are 2.5 ug/mL and 4.5 ug/mL, respectively, with a half life of 10-12 hours. Trovafloxacin has been found to be well distributed to bronchial mucosa, epithelial lining fluid (ELF) and alveolar macrophages following single and multiple 200 mg doses. Lung levels of trovafloxacin are 2-8 fold higher than serum levels giving levels in the lung and blood with once daily oral dosing that are many fold higher than the respiratory pathogen MIC_{90S}. Animal experiments (including models of meningitis) have confirmed potent *Streptococcus pneumoniae* activity in experiments where common quinolones have failed. In *in vitro* and animal models of legionellosis, trovafloxacin is more potent than any of the currently marketed azalides, macrolides, or quinolones.

Medical Officer's Comment: The MO defers to the PK reviewer for further comment.

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General Approach to Evaluation:

Copied below from page 9 of section H.3.A, is the sponsor's table of the studies performed in support of this indication:

Nosocomial Pneumonia					
154-113	Alatrofloxacin 300 mg ^d QD IV → trovafloxacin 200 mg QD PO (10 to 14 days total)	12 9	Ciprofloxacin 400 mg BID IV → ciprofloxacin 750 mg BID PO (10 to 14 days total)	138	Phase III DB
154-137	Alatrofloxacin 300 mg ^d QD IV → trovafloxacin 200 mg QD PO (10 to 14 days total)	13 5	Ceftazidime 2 gm (max.) BID IV → ciprofloxacin 750 mg BID (10 to 14 days total)	140	Phase III Open Randomized

Medical Officer's Comment: Study 154-137 was identical to 113 with the exception that it was an open study due to the difficulties in blinding ceftazidime because of its color.

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Definitions:

The sponsor's definition of NP has been copied below from page 11, section H.3.A of the Esub:

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- new infiltrate on chest x-ray;
- at least one of the following: cough or increasing severity of coughing, acute changes in the quality of sputum, oral temperature $>38^{\circ}\text{C}$ (100.4°F) or $<36.1^{\circ}\text{C}$ (97°F) or documented fever or hypothermia within the last 24 hours, auscultatory findings such as rales or evidence of pulmonary consolidation, or leukocytosis (blood leukocyte count $>10000/\text{mm}^3$ or $>15\%$ bands);
- requirement for hospitalization and initial intravenous therapy;
- absence of cavitary lung disease, known lung cancer, cystic fibrosis, and suspected *P. carinii* pneumonia.
- nosocomial pneumonia was acquired at least 48 hours after a hospitalization for reasons other than respiratory infection.
- Nonambulatory, institutionalized (nursing home) subjects being admitted to a hospital for suspected gram negative pneumonia may also have been enrolled.

Medical Officer's Comment: The MO agreed with this definition and points out the concurrence between this definition and that found in the FDA Guidance document. The characterization of purulent sputum as sputum which on Gram stain shows > 25 PMNs and < 10 squamous epithelial cells per low power field, is well established.

Systemic Antibiotic Usage (copied from page 12 of section H.3.A):

Prior systemic antibiotic usage for more than 24 hours within 72 hours of baseline was prohibited unless there was documented bacterial resistance, or the subject was a clinical failure or developed new infiltrate on the antibiotic.

Medical Officer's Comment: The MO agreed with this definition.

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Data Analysis:

Copied below from page 14, section H.3.A, are the sponsor's definitions of subject subsets:

- **All Randomized (Double-Blind Studies) or Enrolled (Non-Randomized Open Studies) Subjects**
The all randomized or enrolled subjects subsets included all subjects who were randomized or enrolled to a treatment group, regardless of whether or not a particular subject received any study medication.
- **All Treated Subjects**
The all treated subjects subset included all subjects who received one or more doses of study medication (active double-blind study medication for the double-blind studies).

- **Clinical Intent-to-Treat Subjects**

The clinical intent-to-treat subjects subset included those subjects in the all randomized or enrolled subjects subset who had a baseline diagnosis of the disease or condition under investigation determined by protocol specific inclusion and exclusion criteria (not applicable to protocol 154-101, which had a check box on the case report form for underlying disease rather than inclusion/exclusion criteria). Some subjects in this subset may never have received any study medication.

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- **Clinically Evaluable Subjects**

The clinically evaluable subjects subset included all subjects in the clinical intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied.

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- **Bacteriological Intent-to-Treat Subjects**

The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline. Some subjects in this subset may never have received any study medication.

- **Bacteriologically Evaluable Subjects**

The bacteriologically evaluable subjects subset included all subjects in the clinically evaluable subjects subset, unless one or more of the criteria for non-evaluability applied.

Medical Officer's Comment: *The MO's evaluable population was compromised of a subset of the sponsor's clinically evaluable subset. That is all patients who did not have an EOS visit were excluded from the analysis.*

Evaluability Criteria (copied from pages 15- 16 of section H.3.A):

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Clinical:

If any of the following were present, the subject was considered non-evaluable for clinical efficacy:

- insufficient therapy (subject discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement);

Medical Officer's comment: *The sponsor's representative, Dr. Debra Williams verified that all failures were carried forward. However, the above statement infers that if a patient was discontinued on day 4 because of an AE, this patient would not be labeled as a failure. The MO elected to evaluate these patients separately in order to determine outcome.*

- prior antibiotic usage (for >24 hours within 3 days before Day 1 of the study); unless, the subject had a culture positive baseline pathogen in the evaluable baseline window (as determined by exclusion criteria);
- use of a concomitant antibiotic, given for intercurrent illness or adverse event, that was potentially effective against the condition under study (unless given for insufficient response);
- or intercurrent illness that could confound clinical evaluation of the condition under study.

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Subjects in Phase III studies were also non-evaluable for clinical efficacy if the following applied:

- no post-baseline assessment in the evaluable analysis window, unless the investigator's clinical response was failure before the beginning of the end of treatment window,
- or the subject was given an antibiotic for insufficient response at any time during the study.

A subject was included in the analysis at the end of study assessment if the subject:

- was clinically evaluable at the end of treatment visit, and
- was not given any antibiotics for intercurrent illness before the assessment at the end of study visit (unless given for insufficient response), and
- had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study,

or the subject was:

- clinically evaluable at the end of treatment visit, and
- the sponsor-defined clinical response was failure or relapse at end of treatment.

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Medical Officer's Comment: The MO agreed with the sponsor's evaluability criteria. All failures were carried forward and the EOS visit was necessary to apply the TOC. The MO did not consider the EOT visit necessary.

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Bacteriological:

For subjects with no baseline atypical pathogen, if any of the following were present the subject was considered non-evaluable for bacteriological efficacy:

- no baseline pathogen or baseline culture outside baseline visit window (>2 days before the first dose of study medication).
- no post-baseline culture, except in the instance of no suitable culture material due to clinical cure or improvement based on the investigator-defined clinical response,
- or the subject was given an antibiotic for insufficient response or the investigator's clinical response was failure (at any time up to and including the last day of the evaluable end of study analysis window.
- Subjects with a serologically defined baseline atypical pathogen were bacteriologically evaluable if they were clinically evaluable.

For all protocols and for subjects with no baseline atypical pathogens, bacteriologically evaluable subjects were excluded from the analysis at the end of study visit if:

- they were excluded from the clinical analysis at the end of study visit, or
- they did not have a culture result in the end of study window, unless given an antibiotic for inadequate response or the investigator's clinical response was failure any time during the study, up to and including the last day of the end of study analysis window.

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Subjects in protocols with a serologically defined baseline atypical pathogen were included in the bacteriological analysis at end of study if they were included in the clinical analysis at end of study.

Medical Officer's Comment: The MO agreed with these criteria. The MO's bacteriologically evaluable population was a subset of the clinically evaluable. As the MO TOC was applied to the EOS visit, the presence of a culture result in the EOS window was necessary within the context of making a presumptive

versus a definite determination of outcome. However, as stated above, as the main determinant of efficacy was clinical, the MO accepted a presumptive determination in correlation with the clinical.

Primary and Secondary Endpoints for Efficacy (copied from page 16 of section H.3.A):

The primary efficacy endpoints were:

- Sponsor-defined subject clinical response at the end of treatment visit;
- Pathogen eradication rates at the end of treatment visit.

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Secondary efficacy endpoints were:

- Pathogen eradication rates at the end of study visit;
- Investigator-defined subject clinical response at the end of treatment visit, and sponsor-defined and investigator-defined subject clinical response at the end of study visit. - -

Medical Officer's Comment: *In accordance with regulatory precedence as well as the DAIDP's guidance document and the AC recommendations, the MO elected to assess outcome, clinical and bacteriological, at the EOS as opposed to the EOT visit. Any patient without an EOS visit was not considered evaluable and any patient excluded by the sponsor because they did not have an EOT visit but did have an EOS visit was considered evaluable. Information submitted by the sponsor on September 23, 1997 revealed that 16 trovafloxacin patients and 24 ciprofloxacin patients would be excluded from the MO's evaluable population in study 113. 2 ciprofloxacin patients who had an EOS visit but no EOT visit were considered evaluable by the MO. Thus, the MO's population consisted of 72 trovafloxacin and 70 ciprofloxacin patients as compared to 88 and 101 per arm respectively, as per the sponsor's analysis.*

The respective numbers in study 137 were 18 trovafloxacin patients without an EOS visit and 3 without an EOT visit, thus leaving 85 MO evaluable patients as compared to 100 as per the sponsor. On the ceftazidime arm, there were 20 patients without an EOS visit and 2 without an EOT visit; thus 89 patients were initially evaluable as per the MO as compared to 107 as per the sponsor.

Additionally, if there was no bacteriologic response documented at the EOS, the EOT response was carried forward from the EOT to the EOS by the MO as a presumptive response.

Definitions of Response (copied from pages 17,18, and 19 of section H.3.A.A):

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Sponsor-Defined Subject Clinical Response:

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the global evaluations made by the investigator at the end of treatment and end of study visits.

The investigator classified the clinical response of the subject as cure (resolution of all signs and symptoms of the disease under study to the level that existed before baseline), improvement (incomplete resolution of signs and symptoms), or failure (lack of resolution of any of the signs and symptoms of infection).

The occurrence of the following conditions superseded the investigator's assessment:

- **Failure.** If the investigator defined subject clinical response was failure at any visit, then the sponsor-defined subject clinical response was failure at all subsequent visits.

- **Failure.** If a subject was given a concomitant antibiotic for insufficient clinical response or failure then the sponsor-defined subject clinical response was failure at that visit and at all subsequent visits.
- **Failure:** If a subject had no post-baseline assessment, that subject was classified as a clinical failure at both the end of treatment and end of study visits (ITT only).
- **Relapse:**
- If a subject was a clinical cure or improvement at the end of treatment visit, and was assessed by the investigator to be a failure at a subsequent visit, then that subject was classified as a clinical relapse at the end of study visit.
- If a subject was a clinical cure or improvement at the end of treatment visit, but required additional antibiotic therapy for the primary disease before the end of study visit, then the subject was classified as a clinical relapse at the end of study visit.

For the analysis of the Clinically Intent-to-Treat Subject subset, a 'last observation carried forward' strategy will be used for subjects who are lost to follow-up before the End of Study visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment will be treated as missing data.

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Sponsor-Defined Pathogen Outcome

For both evaluable and intent-to-treat subjects, the sponsor classified each baseline organism as a pathogen or as a non-pathogen. Each baseline organism classified as a pathogen was assigned a sponsor-defined pathogen outcome. Multiple baseline pathogens identified in culture samples from the same subject were assigned separate outcomes. Baseline pathogens were assigned a separate outcome for the end of treatment and end of study visits. If multiple visits occurred in the end of treatment analysis window, the last outcome assigned to each baseline pathogen was used. If multiple visits occurred in the end of study window, the worst case outcome was used. Selection of the worst case outcome followed the order persistence or relapse, presumed persistence, presumptive eradication, eradication.

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The sponsor-defined pathogen outcomes were defined as follows:

1. **Eradication:** Baseline pathogen absent from a culture from the same site. If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this negative culture, the eradication was carried forward to all subsequent visits, regardless of subsequent culture results.
2. **Presumptive eradication:** Absence of adequate culture material for evaluation and the sponsor-defined subject clinical response was cure or improvement.
3. **Persistence:** Baseline pathogen present in a culture sample from the same site (or any relevant site, including blood). If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this positive culture, the persistence was carried forward to all subsequent visits, regardless of subsequent culture results.
4. **Presumed Persistence:**
 - Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day, or within 3 days after, a positive or negative culture, in the absence of prior microbiological data in the same evaluable analysis window resulted in a

sponsor-defined pathogen outcome of presumed persistence at that visit and all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up, the presumed persistence was carried forward to subsequent implied visits. Absence of microbiological data was either no visit in the window or culture not done at all visits in the window.

- No culture was obtained (either not done or absence of adequate culturable material) and the sponsor-defined subject clinical response was failure.
 - The baseline pathogens of subjects who were lost to follow-up (i.e., no visit) at either the end of treatment or end of study visits were assigned the outcome of presumed persistence if the pathogen was persistent at any previous visit.
5. Relapse: The original baseline pathogen was present at the end of study visit in a culture from the same site after the end of treatment culture was negative.

Organisms not present at baseline were classified as superinfection or colonization, defined as follows:

6. Superinfection: A pathogen, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and associated with emergence or worsening of clinical and laboratory evidence of infection.
7. Colonization: Any organism, other than one identified at baseline, that is identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study, and not associated with signs or symptoms of active infections.

Each atypical pathogen, identified by serology test, was assigned a sponsor-defined pathogen outcome as follows:

1. Presumed persistence: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and sponsor-defined subject clinical response was failure.
2. Presumed eradication: A positive antigen or antibody titer rise for atypical pathogens but no positive culture at baseline, and the sponsor-defined subject clinical response was cure or improvement.

Medical Officer's Comment: *The MO agreed with the sponsor's definitions of bacteriologic outcome for those cases where the change in the TOC did not affect the response.*

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Evaluability Windows:

As per the original protocols, the sponsor-designated evaluable for analysis windows were study days 12 – 16 for the EOT and study days 28 – 35 for the EOS. As per the electronic submission as well as verbal communication with Dr. Debra Williams, these windows were changed during the data analysis to EOT: days 7 – 20 and EOS: days 21 - 40. The rationale for these changes was, as in previously reviewed indications, to capture as many patients as possible. As stated above, as the MO applied the TOC to the EOS visit, there was no disagreement in the analysis window set by the sponsor for that visit as it routinely represented at least 1 week post-therapy.

It is once again noted that a "failure" could be designated as such from day 1 and as per the sponsor's analysis, a "cure" could be designated as such as of day 7. The MO however, required a minimum of 80% of therapy, or 8 days of therapy before a patient could be designated as a "cure."

Study 154-113

TITLE:

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN (CP-116, 517) FOLLOWED BY ORAL TROVAFLOXACIN (CP-99, 219) WITH INTRAVENOUS CIPROFLOXACIN FOLLOWED BY ORAL CIPROFLOXACIN FOR THE TREATMENT OF NOSOCOMIAL PNEUMONIA.

Study Dates: February 3, 1995 - June 13, 1996

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Objective: the objective of this Phase III study was to compare the safety and efficacy of intravenous alatrofloxacin, followed by oral trovafloxacin (with optional aztreonam and/or vancomycin), compared to intravenous ciprofloxacin followed by oral ciprofloxacin (with optional aztreonam, vancomycin, clindamycin and/or metronidazole), for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

List of Principal Investigators:

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5017	John Gezon, MD
	5050	Charles VanHook, MD
	5079	W. Travis Ellison, MD
	5106	Charles Ballow, PharmD
	5108	Edward Britt, MD
	5111	Daniel Herr, MS, MD
	5112	Timothy Kotschwar, PharmD
	5115	Michael Niederman, MD
	5117	Curtis Sessler, MD
	5118	Claude Tellis, MD
	5119	Scott Traub, PharmD
	5121	Marcus Zervos, MD
	5123	Dennis Mikolich, MD
	5126	Dennis Mikolich, MD
	5173	Selwyn Spangenthal, MD
	5174	Faroque Khan, MD
	5175	Timothy Klein, MD
	5181	James Taylor, MD
	5184	Paul Alessi, DO
	5185	Matthew Brenner, MD
	5188	Donald Fry, MD
	5190	Stephen Green, MD
	5191	Paul Marik, MD
5193	Charles Schlepner, MD	
5211	Andrew Quartin, MD	
5249	David Smith, MD	
5368	Jeffrey Timby, MD	
5384	Martin Tauber, MD	
5385	Maria Rodriguez-Barradas, MD	
5386	Donald Graham, MD	
5467	Michael Gelfand, MD	

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States (continued)	5483	Ronald Wainz, MD
	5541	Roy Brower, MD
		Pamela Lipsett, MD
	5546	Howard Koffler, MD
	5628	Arthur Clinton White, MD
	5760	Jeffery Silber, MD
	5778	John Black, MD
	5837	Burt Meyers, MD
	5850	Martin Topiel, MD
	5970	Alan Sugar, MD
	5984	John Samies, MD
	5985	David McEniry, MD
	5987	Lance Kirkegaard, MD
	6127	John Flaherty, MD
	6367	Del Dehart, MD
6376	E. Joe Schelbar, MD	
6455	Byungse Suh, MD	
6538	Eileen Hilton, MD	
Germany	5514	Dr. Wilfried Bohning
	5515	Dr. Franz Daschner
	5516	Dr. Rudolf Huber
	5517	Dr. Christian Witt
	5780	Dr. Werner Bachmann
	5903	Dr. Walther Grau
	6111	Dr. H. Landgraf
	6112	Dr. Peter-Henning Althoff
	6113	Dr. Gerhard Cieslinski
	6404	Dr. Hans Schulz
6477	Dr. Franz Hartmann	
6543	Dr. Thomas Muller	
United Kingdom	5395	Dr. Ian Gould
		Dr. David Noble
	5396	Dr. Ian Grant
		Dr. Robert Masterton
	5407	Dr. Peter Duncan
	5408	Dr. Robin Macmillan
	5409	Dr. Martin Street
	5410	Dr. Graham Sunderland
6115	Dr. Shane O'Neill	
6339	Dr. John Colvin	
France	5441	Dr. Rene Pariente
	5508	Dr. Yann Curran
	5511	Dr. Fabrice Pierre Brunet

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
France (continued)	5513 6497	Dr. Francois Hilpert Jacques Ameille
Canada	5030 5423 5986	Coleman Rotstein, MD Michael Alexander, MD Mark Miller, MD
Spain	5623 5627 5835	Dr. Antoni Marti Dr. Jose Martin Dr. Joaquin Duran
Belgium	5510 5834	Dr. Vincent D'Orio Dr. Jean Petermans
Portugal	5543 5600	Dr. Raul Marques Dr. Jorge Pimentel
Costa Rica	5034	Guillermo Rodriguez, MD

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Study Design: Study 154-113 was a randomized, double-blind, double-dummy, multicenter trial of alatrofloxacin administered intravenously daily for 2 to 7 days, followed by oral trovafloxacin to complete 10 to 14 days of total treatment, compared to intravenous ciprofloxacin for 2 to 7 days followed by oral ciprofloxacin to complete 10 to 14 days of treatment of patients with nosocomial pneumonia requiring initial intravenous therapy. In subjects with documented *Pseudomonas aeruginosa* infection or MRSA, aztreonam or vancomycin respectively, may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added in a blinded manner to the ciprofloxacin arm only.

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Protocol Overview:

Copied below from the electronic submission, appendix A of the original protocol is the sponsor's schedule of visits and procedures:

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number	1	2	3	4
Study day:	Day 1	Day 4	Day 14	Day 30
Allowable Window	(-24 hours)	(Day 3-7)	(Day 12-16)	(Day 28-35)
Treatment Period	Day 1	to Day 10	to Day 14	Day 15
Follow-up period				to Day 35
Informed consent	X			
Demographic Information	X			
Targeted Physical Exam	X			
Apache II Score	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record		X	X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X		X	abn
Microbiology				
sputum Gram stain	X	X	X	X2
culture & sensitivity	X	X	X	X2
blood culture	X	X3	X4	
Serology	X			X
Safety laboratory tests				
haematology	X	X	X	abn
biochemistry	X	X	X	abn
urinalysis	X		X	abn
Pregnancy test1	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's assessment of clinical response5			X	X

abn = abnormal at previous visit or clinically significant adverse event

1 to be done by local site for women of child bearing potential

2 to be done if clinically indicated

3 to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure

4 to be done if a positive culture was obtained at visit 2

5 to be done at the time of discontinuation, if applicable

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As can be appreciated from the above schedule, at the baseline assessment (Visit 1, Day 1), all subjects were to have had a medical history and clinical and radiological findings consistent with nosocomial pneumonia. The NP must have been acquired at least 48 hours after hospitalization for reasons other than respiratory infection, and the patients must have required initial intravenous therapy. Nonambulatory nursing home patients who were admitted to a hospital for suspected gram-negative pneumonia were also eligible for enrollment.

The following characteristics were to have been present:

- New infiltrate on chest x-ray;

and

- At least one of the following:

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- Cough or increasing severity of coughing.
- Acute changes in the quality of sputum.
- Body temperature $>38^{\circ}\text{C}$ (100.4°F) or $<36.1^{\circ}\text{C}$ (97°F) or documented fever or hypothermia within the last 24 hours.
- Auscultatory findings such as rales or evidence of pulmonary consolidation.
- Leukocytosis (blood leukocyte count $>10,000/\text{mm}^3$ or $>15\%$ bands).

All subjects who met the criteria for the clinical diagnosis of NP at V1, and who gave informed consent and met all additional inclusion criteria and none of the exclusion criteria were eligible for randomization.

V1 assessments included collection of demographic information, medical history and physical examination (including APACHE II score), concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature). Clinical assessment of signs and symptoms of pneumonia included sputum characteristics, cough, dyspnea, chills/rigors, pleuritic chest pain, lung sounds, and CxR (PA and lateral views). In addition, a standard panel of blood (including culture), and urine (including culture), tests were performed. Initial serology testing for evidence of infection with *Legionella* spp. was performed. Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per low power field [LPF], squamous epithelial cells per LPF) of sputum were performed. If a satisfactory specimen could not be obtained the investigator could have induced sputum with nebulised saline solution or physiotherapy. If this technique was unsuccessful the investigator could have used such techniques as transtracheal aspiration, bronchial brushings or biopsy material obtained by bronchoscopy.

Susceptibility to the study drugs, trovafloxacin and ciprofloxacin, was determined for all potentially significant organisms isolated from sputum specimens, that were considered adequate. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. If no pathogen was detected on baseline culture or if a pathogen was resistant to study medication, study therapy could continue, at the discretion of the investigator.

At Visit 2 (V2: Day 4), a patient's need for continued intravenous therapy was assessed (daily from study days 3 to 7). Subjects were switched to oral therapy if the following conditions applied:

- resolution of fever (based on daily maximum temperature);
- improvement of symptoms;
- no progression of x-ray changes.

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Efficacy observations were performed at this visit, including clinical assessment of signs and symptoms of pneumonia to assess response to study therapy. Bacteriologic response was assessed through sputum samples. Blood cultures were repeated only if they had been positive at the previous visit. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory (hematology and biochemistry) evaluations.

At Visit 3 (V3: Day 14: EOT) efficacy observations were performed including clinical assessment of signs and symptoms of pneumonia to assess response to study therapy. Bacteriologic response was assessed through sputum samples. Blood cultures were repeated only if they had been positive at the previous visit; a chest x-ray was also performed. In addition to efficacy observations, safety was assessed through the recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory

(hematology, biochemistry, and urinalysis) evaluations. The investigators provided an evaluation of clinical response.

At Visit 4 (V4: Day 30: EOS), efficacy observations were performed including clinical assessment of signs and symptoms of pneumonia to assess response to study therapy. Bacteriologic response was assessed through sputum samples. If the V3 CxR had not resolved to the patient's baseline, a final x-ray was obtained. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, and adverse events. Laboratory evaluations (hematology, biochemistry, and urinalysis) were only performed if a clinically significant abnormality was present as V3 (Day 14) or if the subject was experiencing a clinically significant adverse event. A final serology was performed and the investigator provided a final evaluation of clinical response.

Medical Officer's Comment: The MO determined that the study was well designed and in accordance with current guidelines. Efficacy evaluations were performed at V3 and V4. However, per the sponsor, only V3 was obligatory for evaluability.

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Compliance:

This study was conducted in compliance with a local or central Institutional Review Board (IRB) and informed consent regulations.

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Concomitant Illnesses and Medications:

At each visit, the investigator obtained information about concomitant illnesses and any therapeutic interventions (e.g., drug therapy, surgery, etc.) that had occurred. Included, was the diagnosis and dates of onset and remission of all illnesses, as well as the name and start date of medications (including self-prescribed medication), date(s), and description of surgery, etc.

If any antibiotic was taken during the study period, the reason for its use was documented. If the antibiotic was taken for a different infection, then, in order to ensure that such subjects remained evaluable, final efficacy assessments were performed prior to starting new antibiotic treatment.

Medical Officer's Comment: As stated in the introduction, the MO agreed to accept as evaluable patients, those patients who received another anti-microbial for a clearly documented different infection and only where the concomitant anti-microbial could have had no activity against the primary pathogen. If there was no primary pathogen however, the MO determined that these patients should be excluded from the analysis.

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Discontinuation of Study Therapy:

The investigator discontinued study therapy in the event of limiting side effects or significant laboratory abnormalities (including marked liver function abnormalities), independent of their suspected causal relationship to study drug. Discontinuations due to serious adverse events were reported to the Pfizer monitor immediately. The reasons for discontinuation of any subject were recorded on the case report form.

In the event of discontinuation of study therapy, appropriate non-study therapy was initiated and the subject was followed for safety observations throughout the remainder of the study (V 4). Untoward events leading to discontinuation of study therapy were followed until they returned to normal or had stabilized; the frequency of follow-up was at the discretion of the investigator. For subjects discontinued from study therapy because of clinical failure, the final clinical and microbiological efficacy evaluation required by the protocol was performed at the time of study drug discontinuation

Protocol Amendments:

The protocol was amended three times (October 20, 1994, November 16, 1994, and October 5, 1995).

The October 20, 1994 and November 16, 1994 amendments were prior to the study start and concerned the addition of optional vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, and simplified placebo dosing.

The October 5, 1995 amendment was primarily to allow the addition of clindamycin or metronidazole to the ciprofloxacin arm of the study and to allow a total of 14 days of intravenous study drug dosing for subjects unable to take oral study drugs.

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Precautions:

Subjects were instructed not to donate blood during and for 30 days after the end of study.

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Study Population:

It was expected that up to 320 subjects were to be randomized to one of two treatment groups, with each center enrolling approximately 8 patients.

Inclusion and Exclusion Criteria:
(Copied from page 9 of the original protocol)

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Inclusion criteria

1. Aged 18 years or more.

Women of childbearing potential (i.e., not surgically sterile or less than one year post-menopausal) must have a negative gonadotrophin pregnancy test (urine or serum) immediately prior to entry in the study and must use adequate contraception (for women on oral contraceptives, additional barrier contraception must be used) both during and for one month after the end of treatment.

2. Subjects with a medical history, and clinical and radiological findings consistent with a nosocomial pneumonia acquired at least 48 hours after a hospitalisation for reasons other than respiratory infection. Nonambulatory, institutionalised (nursing home) subjects being admitted to a hospital for suspected gram negative pneumonia may also be enrolled.

The following criteria must be met:

- a. New infiltrate(s) on chest X-ray

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AND

- b. At least one of the following signs or symptoms:

- 1) Cough or increasing severity of coughing
- 2) Acute changes in the quality of sputum
- 3) Body temperature > 38°C (100.4°F) or < 36.1°C (97°F)
- 4) Auscultatory findings such as rales or evidence of pulmonary consolidation.
- 5) Leukocytosis (blood leukocyte count > 10,000/mm³ or > 15% bands)

3. Written informed consent from the subject or the appropriate third party (parent, guardian, legal representative, or next of kin) if the subject is not competent to give consent.

Exclusion criteria

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1. Pregnant women, nursing mothers or women of childbearing potential not practising adequate means of contraception.

2. Known or suspected hypersensitivity or intolerance to any quinolone

<October 20, 1994 Amendment>

antibiotic, or aztreonam, or vancomycin.

3. Treatment with any potentially effective systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline assessment unless patient is a clinical failure for a nosocomial pneumonia or has a new infiltrate which developed on the antibiotic.
4. Concurrent treatment with any potentially effective systemic antibiotic.
5. Subjects with any of the following conditions:
 - a. Known Acquired Immunodeficiency Syndrome (AIDS) or suspected *Pneumocystis carinii* pneumonia.
 - b. Neutropenia, defined as a total white blood cell count less than 2500 leukocytes/mm³ or absolute neutrophil count less than 1000/mm³.
 - c. Immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including chronic treatment with greater than 10 mg/day of systemic prednisone or equivalent). Subjects may be treated during the study with medically necessary steroid therapy.
 - d. Cavitory lung disease by chest X-ray; or known lung cancer.
 - e. Cystic fibrosis.
 - f. A history of all forms of epilepsy or seizure.
6. Treatment with another investigational drug within four weeks prior to the baseline visit.
7. Prior enrolment in this protocol.
8. Evidence of recent drug or alcohol abuse or dependence.

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Medical Officer's Comment: As stated in the introduction, the MO agreed with the inclusion and exclusion criteria.

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Randomization and Blinding:

The investigator sequentially assigned study numbers to the patients as they were determined to be eligible for treatment. This number was entered onto the CRF and the subject received the study medication assigned to the corresponding number.

The primary study drugs (trovafloxacin and ciprofloxacin) were blinded by a double-dummy technique.

Dosage Form and Administration:

(Copied from pages 21 and 22 of the study report)

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Study drug for intravenous administration was prepared using a double-dummy technique to maintain blinding. Intravenous alatrofloxacin (equivalent to 300 mg trovafloxacin) or matching placebo (sterile water) for intravenous administration was provided in vials of 5 mg/mL (100 mg/20 mL) to be diluted to 1.5 mg/mL with 5% dextrose in water (D5W). Intravenous ciprofloxacin or matching placebo (sterile water) was provided in vials of 10 mg/mL (200 mg/20 mL) to be diluted to 2 mg/mL with D5W.

Subjects received one of the following intravenous treatment regimens:

Alatrofloxacin 300 mg (3 x 100 mg vials) in 200 mL of D5W administered once daily as a 60-minute infusion in the morning; 200 mL D5W (ciprofloxacin placebo; 2 vials) administered as a 60-minute infusion once daily in the evening.

Ciprofloxacin 400 mg (2 x 100 mg vials) plus alatrofloxacin placebo (1 vial) in 200 mL of D5W administered in the morning and ciprofloxacin 400 mg (2 x 100 mg vials) in 200 mL of D5W in the evening, each as a 60-minute infusion.

When the investigator had determined a subject's resolution of fever with an improvement of symptoms and no new x-ray findings, the subject was switched from intravenous to oral therapy. Intravenous dosing could have been extended to 14 days in subjects unable to take oral medication. Doses of study medication for subjects that needed to continue intravenous dosing beyond 10 days were to be pharmacy blinded using unblinded vials of alatrofloxacin or ciprofloxacin to prepare the blinded supplies.

Study drug for oral administration was in the form of trovafloxacin tablets and ciprofloxacin capsules and was packaged in blister packs, using a double-dummy technique to maintain blinding. After 2 to 7 days of intravenous treatment with randomized study medication subjects received one of the following treatments orally:

Trovafloxacin 200 mg/day as a single active dose (2 x 100 mg tablets) administered in the morning and three capsules (ciprofloxacin placebo) administered twice daily, once in the morning and once in the evening.

Ciprofloxacin 1500 mg/day in two equally divided doses (3 x 250 mg capsules) administered once daily in the morning and once in the evening and two tablets (trovafloxacin placebo) administered once daily in the morning.

Subjects were to receive the appropriate oral therapy to complete a total maximum treatment duration of 10 to 14 days.

Subjects with *Pseudomonas* infection, methicillin-resistant *Staphylococcus aureus*, and/or anaerobic infection may have received optional antibiotic therapy, as follows:

Optional Aztreonam

For subjects with documented *Pseudomonas* infection at baseline, treatment with open-label aztreonam, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in either treatment regimen. Treatment with aztreonam was to continue for a maximum of 14 days.

Optional Vancomycin

For subjects with documented methicillin-resistant *Staphylococcus aureus* at baseline, treatment with open-label vancomycin, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in either treatment regimen. Treatment with vancomycin was to continue for a maximum of 14 days.

Optional Clindamycin / Metronidazole

For subjects randomized to ciprofloxacin who had suspected anaerobic pneumonia at baseline, treatment with clindamycin or metronidazole, at medically appropriate and approved doses was to be initiated. The study pharmacist was to break the blind on a particular subject when such a request was made. For subjects randomized to ciprofloxacin, the prescribed dose of clindamycin or metronidazole was to be prepared in a blinded fashion. For subjects randomized to alatrofloxacin/trovafloxacin, an identical placebo dose was to be prepared to the same final volume in the same diluent. Clindamycin or metronidazole or matching placebo were to be administered at a frequency prescribed by the physician. Only the pharmacist was to have knowledge of or access to the randomization assignment.

At intervals during treatment or at the time of premature discontinuation of study therapy, appropriate entries for tablets/capsules taken and returned were completed on the case report form (CRF) and the Pfizer Drug Inventory Record (PDIR). If doses were missed, the reason was to be recorded on the CRF.

Medical Officer's Comment: *The study pharmacist was unblinded in the case of prolonged intravenous therapy or when clindamycin or metronidazole were utilized for additional anaerobic coverage. Per the original protocol and the study report, the investigator remained blinded.*

The MO points out the necessity of a documented culture result for Pseudomonas aeruginosa or Staphylococcus aureus prior to the initiation of aztreonam or vancomycin on either arm. The MO determined that this prerequisite, maintained not only the blind but also the equal treatment of patients on both arms, thereby avoiding not only bias but the use of alternative effective agents during active therapy as much as possible.

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Compliance:

The patients were informed that compliance with taking all tablets and capsules was imperative.

Inpatients received all medications under supervision. Outpatients were instructed to bring used blister packs to V2 and V3. All missed doses and the reasons they were missed were recorded on each patient's medication log.

Microbiologic Methods:

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Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 24 of the study report)

Criteria	Trovafoxacin		Ciprofloxacin		Aztreonam	
	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (30 µg Disk)
Susceptible	≤2	≥15	≤2	≥15	≤2	≥21
Intermediate	4		4		4	
Resistant	≥8	≤10	≥8	≤10	≥8	≤13

Note: Trovafoxacin 5 µg disks were never approved for clinical trial use and were subsequently replaced with 10 µg disks. Results using the 10 µg disks were not available during the study report period.

Susceptibility breakpoints for trovafoxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and zone diameter (mm) for ciprofloxacin and aztreonam are based on NCCLS criteria.

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Clinical Response:

(Copied from page 23 of the study report)

Clinical response was determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from the study.

Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical

condition. Subjects were to be assessed for signs and symptoms, as detailed below, and these assessments were recorded on the case report form.

1. Cough, dyspnea, chills/rigors, pleuritic chest pain, and increased sputum volume were each to be assessed at baseline (Day 1) and at every clinic visit thereafter by the investigator and rated on a scale of 0 to 3 as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. In addition, fever and abnormal focal or diffuse lung sounds were to be recorded by the investigator as present or absent at these timepoints.
2. Chest x-ray was to be obtained at baseline (Day 1) and Visit 3 (Day 14) and at any other timepoint deemed necessary by the investigator (e.g., previous x-ray had not cleared). Consecutive chest x-rays were to be evaluated and graded as resolution (disappearance of all radiological signs of infection), marked improvement (significant improvement in the radiological signs of infection compared to baseline), or radiological failure (no significant change in radiological signs of infection compared to baseline or worsening as compared to baseline).

Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia and a need for additional antibiotic).

Medical Officer's Comment: As previously stated, the final determination of clinical response was made by the sponsor. As per the sponsor's representative, Dr. D. Williams, the sponsor never overrode an assessment of failure made by the investigator. In other words, once a failure, always a failure.

Although a severity scoring system was utilized, this system was not additive but rather, each parameter was evaluated separately and the scoring system served as merely as a guide to outcome assessment.

The sponsor applied the TOC to the EOT (V3) visit, but also to the EOS. However, sponsor evaluability was not contingent upon the evaluation of a patient at the final timepoint.

Bacteriologic Response:

(Copied from page 24 of the study report)

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Bacteriological response was determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study.

Bacteriologic response was classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Only "adequate" specimens, as defined in the Protocol and determined by Gram stain, were to be cultured. The absence of "adequate" sputum specimens was to be considered equivalent to a negative culture if the subject was cured or improved.

Sputum samples were first sent to the local laboratory for culture. Isolates were sent to the central laboratory (SciCor) where disk susceptibility and minimum inhibitory concentrations (MIC) for all drugs were determined using standard techniques. Each time an organism was isolated, susceptibility to the study drugs was re-established. Susceptibility to both study drugs was recorded on the subject's case report form for all isolates. Local susceptibility data obtained at some sites were used in the analyses only when a SciCor value was missing for a particular pathogen.

Legionella spp. serology was performed at baseline (Day 1) and at Visit 4 (Day 30).

Medical Officer's Comment: Only the sponsor determined bacteriologic efficacy. This determination was based on culture data as described above. The MO determined that the bacteriologic assessment of the patients was appropriately performed and consistent with the methods utilized in past submissions that have received approval.

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Safety Assessments:

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page of the case report form. Following resolution of the adverse event or at the end of study, the investigator's judgment of causality of the adverse event was recorded.

Serious Adverse Events:

Adverse events were classified as serious if they were fatal; life threatening; resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer, or drug overdose. Any other adverse experience considered by the investigator to be serious was also reported to the Pfizer-appointed project clinician immediately by telephone. All deaths were immediately reported, regardless of elapsed time between the last dose in a clinical trial and death, and thus extended beyond the 30-day post-study timepoint. In the case of death, a summary of available autopsy findings was submitted as soon as possible to the sponsor.

Clinical Laboratory Tests:

Hematology, serum chemistry, and urinalysis determinations were performed at baseline (V1), and at V2 (excluding urinalysis) and V3 (Days 4 and 14, respectively). In addition, blood cultures were obtained at baseline; if positive, or if the subject was discontinued due to clinical failure, they were obtained again at V2 (Day 4) and/or at V3 (Day 14). At V4 (Day 30), hematology, serum chemistry, and urinalysis were only performed if a clinically significant abnormality was present at V3.

Other Safety Parameters

Physical examination was performed at baseline (V1). Concomitant medication use and vital signs (pulse, respiration, blood pressure, and body temperature) were evaluated at V1 and at V2, V3 (EOT), and V4 (EOS).

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Data Analysis:

See the introduction to the MOR (page 382) for an overview of the sponsor's subject subsets.

Clinical Evaluability Criteria:

See the introduction to the MOR (page 383) for a review of the sponsor's criteria.

Criteria for Bacteriological Evaluability:

See the introduction to the MOR (page 384), for a review of the sponsor's criteria.

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Primary and Secondary Endpoints for Efficacy:

See the introduction to the MOR (page 384) for a review of the sponsor's endpoints and the Reviewer's comments.

Medical Officer's Comment: As noted in the introduction, the primary efficacy variable was clinical response at the EOT, as determined by the sponsor, unless the patient was determined to be a failure by the investigator. The MO agreed with the use of clinical response as the primary efficacy variable and points out that this is in accordance with both the FDA guidance document as well as with IDSA guidelines.

The primary difference between the sponsor's and the MO's assessments was that of timing. The sponsor applied the TOC to the EOT visit whereas the MO applied the TOC to the EOS.

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Definitions of Response:

Please see the introduction to the MOR (pages 384 – 386) for the sponsor's definitions and the Reviewer's comments.

Interim Analyses:

No interim analyses were performed.

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Demographics:

As per the sponsor, 274 patients signed consent, 7 of these however, were withdrawn prior to randomization because they did not meet the study entry criteria. Thus 269 subjects were randomized, 129/269 (47.9%) to receive alatrofloxacin/trovafloxacin and 138/269 (51.3%) to receive ciprofloxacin. 2 randomized subjects on the trovafloxacin arm (#51150121 and #59850262) and 1 subject (#54670139), on the ciprofloxacin arm did not receive treatment. Thus 127 of the randomized trovafloxacin and 137 of the randomized ciprofloxacin subjects were treated (Total treated = 264).

The MO has recreated sponsor's Table 1.1, the Disposition of Enrolled subjects.

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Table 113.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)

	274	Alatro/Trovafloxacin 300 mg → 200 mg	Ciprofloxacin 400 mg bid → 750 mg bid
Subjects with Signed Consent	274		
Withdrawn Prior to Randomization	7		
Randomized		129	138
Randomized, But Not Treated		2	1
All Treated Subjects		127 (100%)	137 (100%)
Withdrawn During Treatment		53 (42%)	43 (31%)
Completed Treatment		74 (58%)	94 (69%)
Withdrawn During Follow-up		9 (7%)	24 (18%)
Completed Study		86 (68%)	90 (66%)
Completed Treatment and Study		65 (51%)	70 (51%)
Withdrawn During Treatment and Study		32 (25%)	23 (17%)

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Medical Officer's Comment:

There were a larger number of patients withdrawn during treatment on the trovafloxacin arm as compared to the ciprofloxacin arm. 17/53 (32%) of the discontinuations on the trovafloxacin arm were considered related to the study drug and included 5 withdrawals (4%) for an AE, 11 for an insufficient response, and 1 because of a laboratory abnormality. 36/53 discontinuations on this arm were considered unrelated to the study drug and included 6 withdrawals because of an AE, 12 deaths, 15 "other", 1 protocol violation and 2 withdrawn consents.

On the ciprofloxacin arm, 9/43 discontinuations from treatment (21%) were considered related to the study drug. 8 of these were due to insufficient response and 1 to a laboratory abnormality. Of the 34/43 discontinuations unrelated to ciprofloxacin therapy, 8 were due to an AE, 1 patient was lost to follow-up, 12 "other," 10 deaths, 2 protocol violations, and 1 withdrawn consent.

Of the 53 trovafloxacin patients withdrawn from treatment, 21 completed the study as compared to 20/43 of the ciprofloxacin patients.

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Discontinuation from treatment or the study had no predetermined effect on evaluability. Evaluability was determined solely by the previously described criteria.

Copied below is the sponsor's table of all randomized patients and the study evaluation groups:

Table 113.2
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

	Alatro/Trovaflaxacin	Cipro/Ciprofloxacin
All Randomized Subjects	129 (100%)	138 (100%)
All Treated Subjects	127 (98%)	137 (>99%)
Subjects with Inappropriate Baseline Diagnosis	2 (2%)	3 (2%)
Clinically Intent- to- Treat Subjects	127 (98%)	135 (98%)
Subjects with Negative Baseline Culture	56 (43%)	67 (49%)
Bacteriologically ITT Subjects	71 (55%)	68 (49%)
Clinically Evaluable Subjects	88 (68%)	103 (75%)
Clinically evaluable with baseline pathogen	47 (36%)	52 (38%)
Clinically Not Evaluable Subjects	39 (30%)	32 (23%)
Insufficient Therapy	27 (21%)	23 (17%)
No post-baseline clinical assessment	20 (16%)	16 (12%)
Prior Antibiotic therapy	0	1 (<1%)
Concomitant Antibiotic therapy	14 (11%)	9 (7%)
No post-baseline clinical assessment in evaluable analysis window	20 (16%)	16 (12%)
Other	1 (< 1%)	4 (3%)
Clinically evaluable at EOS	72 (56%)	79 (57%)
Clinically evaluable at EOS with baseline pathogen	39 (30%)	38 (28%)
Bacteriologically Evaluable Subjects	47 (36%)	52 (38%)
Bacteriologically Not Evaluable Subjects	41 (32%)	51 (37%)
No Baseline Pathogen	41 (32%)	51 (37%)
No post-baseline cultures	1 (<1%)	1 (<1%)
Bacteriologically Evaluable at EOS	39 (30%)	38 (28%)
Baseline Blood Cultures Performed	124 (96%)	125 (91%)
Analyzed for Safety		
Adverse Events	127 (100%)	137 (100%)
Laboratory Data	115 (91%)	126 (92%)

* Subjects may have had more than one reason to have been unevaluable

Medical Officer's Comment: It can be appreciated from table 113.2 that on the trovaflaxacin arm there were 39/127 (30.7%) randomized and treated subjects with an appropriate baseline diagnosis who were clinically unevaluable at the EOT and an additional 16/127 (12.5%) clinically unevaluable at the EOS, thus there were a total of 55/127 (43.3%) that were clinically unevaluable.

On the ciprofloxacin arm, there were 32/135(23.7%) randomized and treated subjects with an appropriate baseline diagnosis, who were clinically unevaluable at the EOT and an additional 24/135 (17.7%) subjects clinically unevaluable at the EOS. Thus, on the ciprofloxacin arm there were 56/135 (41.4%) subjects who were clinically unevaluable.

Additionally, the bacteriologically evaluable population was a subset of the clinically evaluable and the bacteriological ITT population, which were both subsets of the clinical ITT population.

Copied and modified below is sponsor's Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

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Table 113.3
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)

Center	Total Randomized N = 267 (100%)		Alatrofloxacin/Trovafloxacin				Ciprofloxacin/Ciprofloxacin			
			Randomized and Treated				Randomized and Treated			
			N = 129 (100%)		N = 127 (100%)		N = 138 (100%)		N = 137 (100%)	
5423	1	0.4	1	0.7	1	0.7	0	-	0	-
5467*	3	1.1	1	0.7	1	0.7	2	1.4	1	0.7
5483*	15	5.6	7	5.4	7	5.5	8	5.8	8	5.8
5508	1	0.4	1	0.7	1	0.7	0	-	0	-
5510	3	1.1	2	1.4	2	1.5	1	0.7	1	0.7
5511	3	1.1	2	1.4	2	1.5	1	0.7	1	0.7
5513	2	0.7	0	-	0	-	2	1.4	2	1.4
5515	1	0.4	0	-	0	-	1	0.7	1	0.7
5516	1	0.4	0	-	0	-	1	0.7	1	0.7
5541*	2	0.7	0	-	0	-	2	1.4	2	1.4
5546*	4	1.4	2	1.4	2	1.5	2	1.4	2	1.4
5623	18	6.7	9	6.9	9	7.1	9	6.5	9	6.6
5627	4	1.5	1	0.7	1	0.7	3	2.2	3	2.9
5628*	1	0.4	0	-	0	-	1	0.7	1	0.7
5834	3	1.1	2	1.7	2	1.5	1	0.7	1	0.7
5835	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
5837*	1	0.4	0	-	0	-	1	0.7	1	0.7
5903	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5970*	1	0.4	1	0.7	1	0.7	0	-	0	-
5984*	1	0.4	1	0.7	1	0.7	0	-	0	-
5985*	3	1.1	2	1.4	1	0.7	1	0.7	1	0.7
5987*	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
6111	1	0.4	1	0.7	1	0.7	0	-	0	-
6112	1	0.4	1	0.7	1	0.7	0	-	0	-
6127*	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
6367*	3	1.1	0	-	0	-	3	2.2	3	2.9
6376*	1	0.4	0	-	0	-	1	0.7	1	0.7
5030	2	0.7	2	1.4	2	1.5	0	-	0	-
5034	3	1.1	1	0.7	1	0.7	2	1.4	2	1.4
5079*	5	1.8	3	2.3	3	2.3	2	1.4	2	1.4
5106*	4	1.5	2	1.4	2	1.5	2	1.4	2	1.4
5111*	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0
5112*	14	5.2	7	5.4	7	5.5	7	5.0	7	5.1
5115*	2	0.7	1	0.7	0	-	1	0.7	1	0.7
5117*	1	0.4	1	0.7	1	0.7	0	-	0	-
5118*	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5119*	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0
5121*	5	1.8	3	2.3	3	2.3	2	1.4	2	1.4
5173*	5	1.8	2	1.4	2	1.5	3	2.2	3	2.9
5174*	6	2.2	3	2.3	3	2.3	3	2.2	3	2.9
5175*	19	7.1	10	7.7	10	7.9	9	6.5	9	6.6
5181*	1	0.4	0	-	0	-	1	0.7	1	0.7
5188*	11	4.1	6	4.6	6	4.7	5	3.6	5	3.6
5191*	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0

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5193*	1	0.4	0	-	0	-	1	0.7	1	0.7
5211*	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
5249*	3	1.1	2	1.4	2	1.5	1	0.7	1	0.7
5384*	1	0.4	1	0.7	1	0.7	0	-	0	-
5386*	20	7.5	9	6.9	9	7.1	11	8.0	11	8.0
5395	1	0.4	0	-	0	-	1	0.7	1	0.7
5396	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5407	2	0.7	1	0.7	1	0.7	1	0.7	1	0.7
5409	8	3.0	4	3.1	4	3.1	4	2.8	4	3.0
5410	7	2.6	3	2.3	3	2.3	4	2.8	4	3.0
6404	11	4.1	5	3.9	5	3.9	6	4.3	6	4.4
6455*	1	0.4	0	-	0	-	1	0.7	1	0.7
6543	7	2.6	4	3.1	4	3.1	3	2.2	3	2.9

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* Designates US centers

Medical Officer's Comment: No center had > 8% of the patients and that the patients were well distributed over the 57 centers listed: 34 of these centers were located in the US. The 34 US centers randomized 180/267 of all of the patients or 67.4% of the total.

The MO found that the number of centers decreased from 84, as found in the initial study report to 57. The total number of US centers decreased from 48 to 34. The sponsor was queried as to this change on September 25, 1997. The sponsor responded that there was difficulty in enrollment at many of the centers with a resultant high attrition rate. These difficulties were mostly associated with "consent" issues.

At this point and because of the overall concurrence between the MO and the sponsor as to the design and implementation of this trial, the MO elected to review a selected sample of patients. This random sample was generated by the FDA statistician, Dr. Nancy Silliman, and is representative in terms of demographic content with the randomized population. This list was generated and reviewed in a blind manner.

Alatrofloxacin/Trovafloxacin (N = 15):

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- #51110083: 84 YO male, never smoked, who received study drug for 4 days. The patient had findings consistent with a new right upper lobe pneumonia and had *Morganella morganii* isolated from the sputum. The patient was withdrawn from therapy because of a variety of AEs including an infection of a right groin surgical site and tremor. In addition to the study drug, the patient received vancomycin for a coagulase negative staphylococcus isolated in the blood. This patient was neither clinically nor microbiologically evaluable. The investigator and the sponsor rated this patient as an "improvement at the EOT. The patient did not receive any other antimicrobial specifically directed against the initial sputum isolate. The Reviewer agreed with the unevaluability in this case, as the patient did not receive the appropriate duration of therapy.
- #51110108: 69 YO male, smoker, both clinically and bacteriologically evaluable. The patient received a 10 day course of therapy for a new left and right lower lobe pneumonia. The initial sputum sample had growth of *Acinetobacter anitratus* which was persistent at the EOT but presumed eradicated at the EOS where the patient was unable to produce a sample. The patient was rated as an improvement at the EOT and a cure at the EOS. The Reviewer agreed.
- #51120277: 78 YO male, ex-smoker, who was neither clinically nor bacteriologically evaluable despite a 10 day course of therapy. The initial CxR revealed patchy fibronodular infiltrates throughout the left lung and at the right base, however the patient was unable to produce a sputum sample. The patient was characterized as an "improvement" at the EOS as opposed to a "cure" at the EOT. A UTI developed on study day 13 for which the patient received intravenous cefotaxime, followed by oral ciprofloxacin. The Reviewer agreed with the unevaluability of this patient in the face of concomitant antimicrobial therapy.

- #51210230: 80 YO male, never smoked, clinically and bacteriologically evaluable. This patient received 15 days of therapy. Initial sputum was unobtainable, however later specimens were positive for *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Additionally, *Escherichia coli* and *Enterococcus faecalis* were isolated from the blood and subsequently eradicated at day 4. The *Pseudomonas aeruginosa* was eradicated on day 8 but the *Staphylococcus aureus* was never eradicated. Initial CxR revealed a left lower lobe density which worsened over the course of therapy, at both the EOT and EOS. The patient received vancomycin, aztreonam, and metronidazole after the 12th day of study drug. This patient was rated as a "failure" at both the EOT and EOS. Reviewer agreed.
- #51880004: 41 YO male, smoker, neither clinically nor bacteriologically evaluable. This patient was withdrawn from the study within the first 24 hours because of his poor prognosis. Patient had sustained a fatal brain injury. Bilateral airspace disease was noted on CxR and a bronchoscopy specimen was notable for growth of *Proteus mirabilis*. In the ITT analysis this patient was rated as a failure, however, the Reviewer agreed with the unevaluability of this patient who did not receive enough study drug to determine any outcome.
- #54090358: 65 YO female, never smoked, both clinically and bacteriologically evaluable after 10 days of study drug. *Pseudomonas aeruginosa* was isolated at baseline and presumed eradicated at the EOS when the patient was unable to produce a specimen. Initial CxR revealed bilateral patchy alveolar infiltrates which improved. No other antimicrobial was utilized. The Reviewer agreed with the evaluability of this patient as well as with the outcome of cure at the EOS.
- #54100363: 49 YO female, smoker, clinically evaluable only after 8 days of therapy. This patient had a history of metastatic esophageal cancer and had a new right lower lobe pneumonia on CxR. No concurrent antimicrobials were given and the sponsor rated the patient as a cure at the EOT. This patient was unevaluable for the Reviewer, in accordance with the previously specified MO TOC at the EOS. The patient did not have an EOS visit as all therapy was withdrawn and she died before the EOS. The infiltrate did completely resolve.*
- #54830113: 84 YO male, ex-smoker, neither clinically nor bacteriologically evaluable. The patient received 5 days of therapy but initial CxR was negative for a new infiltrate. *Staphylococcus aureus* was isolated from an initial sputum sample despite previous antimicrobials for 96 hours prior to enrollment. This patient died of respiratory failure on day 5. The Reviewer agreed that this patient was unevaluable in view of the negative CxR and the previous antimicrobial therapy.
- #54830115: 54 YO male, ex-smoker, clinically evaluable only as per the sponsor after 11 days of therapy as a cure. This patient was unevaluable as per the Reviewer because he had no EOS visit. The patient did have a new middle lobe (L) pneumonia on CxR, which resolved at the EOT.*
- #55080613: 70 YO female, never smoked, clinically evaluable only, after 3 days of therapy as a failure. The patient was withdrawn for insufficient response and treated with amikacin and cefotaxime for a patchy left lower lobe infiltrate. The CxR cleared on the rescue regimen and the patient was carried forward as a failure. Reviewer agreed.
- #55460090: 98 YO male, never smoked, neither clinically nor bacteriologically evaluable after 4 days of therapy. The patient's family withdrew him from the study and he subsequently died of his underlying CHF. No isolates were grown from the sputum or the blood and the initial CxR revealed bilateral alveolar densities, the etiology of which appeared unclear. This patient was characterized as a "failure" in the ITT analysis. The reviewer agreed with the unevaluability of this patient because there does not appear to be a confirmed diagnosis of pneumonia as opposed to CHF.
- #55460091: 77 YO female, never smoked, clinically evaluable only as a cure at the EOT and EOS. The patient received 10 days of study drug for a new left lower lobe infiltrate, without bacteriologic

confirmation, which completely resolved by the EOT without any other antimicrobial coverage. Reviewer agreed.

- #65430538: 72 YO female, never smoked, clinically evaluable only after 11 days of study drug as a cure at the EOS. The patient was treated for a new right middle lobe infiltrate of uncertain bacterial etiology, which resolved completely by the EOS. Reviewer agreed.
- #65430540: 69 YO male, never smoked, clinically evaluable only after 7 days of therapy as a cure at the EOS. This patient had a right middle lobe pneumonia which resolved by the EOS. This patient was unevaluable as per the Reviewer because he did not receive the minimum required 80% of therapy.*
- #65430809: 85 YO female, never smoked, clinically evaluable only after 10 days of study drug for a new left lower lobe pneumonia which resolved by the EOS. Reviewer agreed.

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Ciprofloxacin/Ciprofloxacin (N = 12):

- #51110106: 70 YO male, smoker, clinically evaluable only after 7 days of therapy as a cure for new bibasilar infiltrates without a bacterial isolate. The patient was withdrawn after 7 days for unknown reasons but he did not receive alternative antimicrobials and had improvement on the repeat CxR. This patient would be unevaluable as per the Reviewer because he did not receive the minimum duration of therapy (80%) to be considered evaluable as a cure. *
- #51150122: 75 YO female, smoker, clinically and bacteriologically evaluable after 10 days of therapy as a cure at the EOS. The patient presented with bilateral infiltrates on initial CxR, which improved and had growth of *Haemophilus influenzae* in the initial sputum. The isolate was presumed eradicated in the face of clinical improvement and the inability to produce additional sputum. Reviewer agreed.
- #51180069: 61 YO female, never smoked, clinically evaluable only after 24 days of therapy for a new left lower lobe infiltrate that resolved. The patient was assessed as a cure at both the EOT and EOS. Reviewer agreed.
- #52110782: 71 YO male, never smoked, clinically and bacteriologically unevaluable after 1 day of therapy for a questionable new infiltrate. The patient died. Initial sputum revealed mixed flora, and a severe pneumothorax developed on the first day which appeared related to the cause of death. Reviewer agreed.
- #53860247: 80 YO female, never smoked, clinically evaluable only as a cure at the EOT and EOS. The patient received 14 days of study drug for a right lower lobe pneumonia which resolved completely. Reviewer agreed.
- #54090345: 72 YO male smoker, clinically evaluable only after 8 days of therapy as an improvement. Initial CxR revealed ARDS with bilateral infiltrates and no bacterial etiology. The patient was withdrawn from the study because of respiratory failure and despite improvement on the CxR. No further antimicrobial therapy was given. Reviewer considered this patient unevaluable because there was no EOS evaluation.*
- #54830116: 28 YO female, never smoked, clinically evaluable only after 10 days of therapy as an EOT improvement. The patient was treated for a new right basilar infiltrate without a bacterial pathogen. This patient was unevaluable per the Reviewer because there was no EOS visit.*
- #54830254: 72 YO male, never smoked, clinically and bacteriologically evaluable after 8 days of therapy as an EOS cure with presumed eradication of the baseline sputum isolate, *Aerococcus* spp. Had new bilateral infiltrates at onset which completely resolved and no further therapy was provided. Reviewer agreed.

- #55100609: 80 YO male, smoker, clinically evaluable only after 7 days of therapy for a right upper lobe pneumonia. This patient was classified as a failure and therapy was changed to piperacillin on day 8. Reviewer agreed that this patient should be carried forward as a failure.
- #55110619: 59 YO male, never smoked, neither clinically nor bacteriologically evaluable after 11 days of therapy. This patient was withdrawn from the study during the post-therapy period because he developed septic shock associated with a central line and died. No baseline pathogen was isolated and the patient was treated in violation of the protocol from day 1 with vancomycin, aztreonam, and clindamycin. Reviewer agreed with the unevaluability of this patient in view of the treatment with multiple antimicrobials in violation of the protocol.
- #55130622: 41 YO male, smoker, clinically and bacteriologically evaluable after 14 days of therapy for a bilateral pneumonia which completely resolved. The patient was classified as an EOT and EOS "cure" with presumed eradication of the baseline pathogens, *Haemophilus parainfluenzae* and *Morganella morganii*. Reviewer agreed.
- #56280117: 35 YO male, smoker, clinically and bacteriologically evaluable after 14 days of therapy for a bilateral pneumonia apparently due to *Haemophilus influenzae*, which completely resolved. This patient was lost to follow-up and therefore unevaluable as per the reviewer's criteria.*

Medical Officer's Comment: As can be appreciated by the synopsis of the above 27 patients, there was concordance between the MO and the sponsor both in terms of evaluability and outcome assessments. The only exceptions were in 3 trovafloxacin-treated and 4 ciprofloxacin-treated patients who were excluded from the MO's evaluable population because they either had no EOS visit or they did not receive the minimum duration of therapy necessary to be assessed as "cures".

The MO was satisfied however, that all cases evaluated were seen in patients already hospitalized, that all failures were carried forward and that the sponsor generally adhered to the protocol. Because of the above, the MO elected to accept the sponsor's determinations of evaluability and outcome in all cases. The only exceptions to the above were the exclusion from the MO's evaluable population of those 16 trovafloxacin and 24 ciprofloxacin patients who did not have an EOS visit and therefore did not meet the MO's evaluability criteria. An additional 4 patients were excluded from the MO's population because they were classified as cures after 7 days of therapy only and therefore did not meet the pre-specified minimum duration of therapy necessary to be evaluable as per the MO.

The patients who did not have an EOS visit are listed by study arm below:

Trovafloxacin (N = 16):

- #51110129: cure
- #51120280: improvement
- #51190227: cure
- #51740016: improvement
- #51910196: improvement
- #53860207: cure
- #54070351: cure
- #54090346: cure
- #54090348: cure
- #54100363: cure
- #54830115: improvement
- #56230311: improvement
- #58350329: improvement
- #59850145: cure
- #64040533: cure

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- #64040802: *improvement*

Ciprofloxacin (N = 24)

- #51110107: *cure*
- #51120221: *cure*
- #51120279: *improvement*
- #51740014: *cure*
- #51880002: *cure*
- #51910040: *improvement*
- #51930029: *cure*
- #53860033: *improvement*
- #53860252: *improvement*
- #54090345: *improvement*
- #54100362: *improvement*
- #54830116: *improvement*
- #54830125: *improvement*
- #54830256: *cure*
- #55130621: *improvement*
- #55410735: *cure*
- #56230306: *cure*
- #56270302: *cure*
- #56280117: *cure*
- #58340605: *improvement*
- #59870258: *improvement*
- #61270211: *improvement*
- #64040535: *cure*
- #65430539: *cure*

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The 4 additional patients excluded from the MO evaluable population are listed below:

Trovafloxacin (N=2)

- #53860200: *cure*
- #65430540: *cure*

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Ciprofloxacin (N = 2)

- #51110106: *cure*
- #54830769: *cure*

Sponsor's Evaluable Populations: As per the sponsor, of the 129 trovafloxacin and 138 ciprofloxacin subjects who were randomized, 2 trovafloxacin and 3 ciprofloxacin subjects had an inappropriate baseline diagnosis and were excluded from the ITT and evaluable analyses.

Of the 127 trovafloxacin and 135 ciprofloxacin clinical ITT patients, 39 trovafloxacin and 32 ciprofloxacin patients were not clinically evaluable at the EOT therefore, 88 trovafloxacin-treated subjects and 103 ciprofloxacin-treated subjects were clinically evaluable at the EOT.

The most common reasons for exclusion from the clinical efficacy analyses can be seen in table 113.2.

71/127 trovafloxacin ITT subjects and 68/103 ciprofloxacin ITT subjects were included in the bacteriological ITT analysis. The remaining patients (56 and 67 per arm respectively, had negative baseline cultures.

Of the 88 clinically evaluable as per the sponsor, trovafloxacin patients, and the 103 ciprofloxacin patients, 41 and 51 per arm respectively, were not included in the bacteriologically evaluable analysis. Therefore, 47 trovafloxacin-treated subjects and 52 ciprofloxacin-treated subjects, were bacteriologically evaluable.

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Baseline Characteristics:

78/127 alatrofloxacin/trovafloxacin-treated subjects (61%) were male and 49 (39%) were female. 76/137 ciprofloxacin-treated subjects (55%) were male and 61 (45%) were female. Treated subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups were generally comparable with respect to age, race, weight, and smoking classification.

The distribution of treated subjects according to smoking classification was similar between the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups (38% and 39% ex-smoker, 42% and 40% never smoked, and 20% and 21% smoker, respectively).

The primary diagnosis for the clinically intent-to-treat subjects was nosocomial-acquired pneumonia. The median duration (range) since onset of pneumonia was 2 days (1-13 days), for subjects in the alatrofloxacin/trovafloxacin group and 2 days (1-12 days), for subjects in the ciprofloxacin group.

There were no marked differences between subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups with respect to medical history at baseline.

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Copied below, from page 34 of the study report, is Sponsor's Table A:

Table A. Summary of Baseline Characteristics and Selected Underlying Diseases and Syndromes at Baseline All Treated Subjects				
Baseline Characteristic	Alatrofloxacin ↓ Trovafloxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=137)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	68.2		70.7	
Minimum				
Maximum				
16-44	16	(13%)	15	(11%)
45-64	28	(22%)	19	(14%)
≥65	83	(65%)	103	(75%)
Smokers	25	(20%)	29	(21%)
Chronic Obstructive Lung Disease	33	(26%)	43	(31%)
Congestive Heart Failure	38	(30%)	45	(33%)
Diabetes Mellitus	28	(22%)	34	(25%)
Asthma	9	(7%)	12	(9%)

Ref.: Table 2.1.1 and Appendix I, Table 1

Evidenced by this table is that the 2 treatment groups were comparable in terms of age and underlying disease.

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Of the clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups, 24/88 (27%) and 29/103 (28%) subjects, respectively, had post-surgical nosocomial pneumonia, 18/88 (20%) and 28/103 (27%) subjects, respectively, had nosocomial pneumonia resulting from suspected aspiration, 11/88 (13%) and 9/103 (9%) subjects, respectively, had nosocomial pneumonia resulting from mechanical ventilation, and 35/88 (40%) and 38/103 (37%) subjects, respectively, had nosocomial

pneumonia resulting from "other" reasons. (Subjects may have had more than one reason for nosocomial pneumonia.)

Severity Factors and APACHE II Scores at Baseline:

Of the clinically evaluable subjects, 29/88 (33%) of the alatrofloxacin/trovafoxacin subjects and 35/103 (34%) of the ciprofloxacin subjects required respiratory supportive therapy as baseline. This support was in the form of supplemental oxygen therapy or mechanical ventilation. 24/88 (27%) of the alatrofloxacin/trovafoxacin subjects and 22/103 (21%) of the ciprofloxacin subjects required mechanical ventilation.

The mean APACHE score at baseline for both treatment groups was 13.09.

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In addition, among clinically evaluable subjects, 33/88 (38%) on the alatrofloxacin/trovafoxacin arm and 49/103 (48%) on the ciprofloxacin arm had bilateral pneumonia at baseline. 15/88 (17%) on the alatrofloxacin/trovafoxacin arm and 20/103 (19%) on the ciprofloxacin arm had abnormalities in ≥ 3 lobes at baseline.

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Duration of Treatment:

On the alatrofloxacin/trovafoxacin arm, the subjects were treated for a median number of 5 days with alatrofloxacin and 7 days with trovafoxacin. The total median number of days of treatment was 10 (range 1 - 16). On the ciprofloxacin arm, the subjects were treated with a median number of 6 days intravenously and 7 days orally. The total median number of days of therapy was 10 on this arm also (range 1 - 17).

Concomitant Medications:

Protocol-specified Antimicrobials:
(Copied from page 38 of the study report):

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Among treated subjects, 27 alatrofloxacin/trovafoxacin and 29 ciprofloxacin/ ciprofloxacin subjects received additional protocol-specified therapy with aztreonam (for documented baseline *Pseudomonas* infection), vancomycin (for documented baseline methicillin-resistant *Staphylococcus aureus*), clindamycin/placebo (for suspected anaerobic infections), and/or metronidazole/placebo (for suspected anaerobic infections). (Subjects in the alatrofloxacin/trovafoxacin group may have received aztreonam, vancomycin, and/or placebo; subjects in the ciprofloxacin group may have received aztreonam, vancomycin, clindamycin, and/or metronidazole.)

- Additional Therapy with Aztreonam and/or Vancomycin

Nine (9) subjects in the alatrofloxacin/trovafoxacin group and 11 subjects in the ciprofloxacin group received additional therapy with aztreonam and nine subjects in the alatrofloxacin/trovafoxacin group and seven subjects in the ciprofloxacin group received additional therapy with vancomycin.

The median number of days that subjects in the alatrofloxacin/trovafoxacin and ciprofloxacin groups were treated with aztreonam was 6 and 8 days, respectively, and that for vancomycin was 8 days for subjects in both treatment groups.

- Additional Therapy with Clindamycin/Placebo and/or Metronidazole/Placebo

Eleven (11) subjects in the alatrofloxacin/trovafoxacin group received clindamycin placebo and 14 subjects in the ciprofloxacin group received additional therapy with clindamycin. The median number of days that subjects in the alatrofloxacin/trovafoxacin

were treated with placebo was 6 days and the median number of days that subjects in the ciprofloxacin group were treated with clindamycin was 7 days.

No subjects in the alatrofloxacin/trovafloxacin group received metronidazole placebo and two subjects in the ciprofloxacin group received additional therapy with metronidazole. The median number of days that subjects in the ciprofloxacin group were treated with metronidazole was 4 days.

Medical Officer's Comment: From the sponsor's submission, it was apparent that approximately the same numbers of patients (10%) in each treatment group received protocol-specified concomitant antimicrobials. The investigators adhered to the use of additional anaerobic coverage only in the ciprofloxacin-treated patients, thus creating a "worst case" scenario in favor of that arm.

Other Medications:

One hundred twenty-seven (127/127, 100%) subjects in the alatrofloxacin/trovafloxacin group and 137 (137/137, 100%) subjects in the ciprofloxacin group received concomitant medications during study therapy. The most commonly used medications during therapy were analgesics, antibacterial drugs, anticoagulants, diuretics, electrolyte and water replacement, hypnotics, oxygen treatment, and ulcer-healing drugs.

Concomitant Antimicrobials:

During the study, 84 subjects in the alatrofloxacin/trovafloxacin group and 86 subjects in the ciprofloxacin group received antibiotics or other anti-microbials other than study drug for the following reasons:

- inadequate response (19, alatrofloxacin/ trovafloxacin; 14, ciprofloxacin),
- early discontinuation of study drug due to an adverse event (8, alatrofloxacin/trovafloxacin; 4, ciprofloxacin)
- other reasons (57, alatrofloxacin/trovafloxacin; 68, ciprofloxacin).

These numbers included subjects whose last dose of prior antibiotic therapy was taken on Day 1 of the study.

Medical Officer's Comment: The MO performed a separate audit on the CRFs of those patients on concomitant, non-protocol-specified antimicrobials and found that 59/84 trovafloxacin patients were clinically evaluable. Of the trovafloxacin patients who received alternative antimicrobials for other reasons, the most common reason was the development of a new and different infectious process. This is an expected phenomenon in this group of patients. On the ciprofloxacin arm, 59/86 subjects were clinically evaluable. Once again, the use of the category "other" predominantly referred to other infectious processes.

All cases where antimicrobials were utilized for "inadequate response" were carried forward as failures. Additionally, all of the "other" category of patients who received antimicrobials for a pulmonic process were carried forward as failures.

Protocol Deviations:

(Copied from page 38 of the study report and modified in Times New Roman font by the MO)

Deviations from protocol were noted for 51 subjects, of whom four subjects had more than one protocol deviation, during the study. These deviations were categorized as follows.

Subjects with nursing home acquired pneumonia, meeting inclusion criteria #2, were in some cases allowed to be treated in the nursing home rather than being transferred to a hospital. This was approved by Pfizer in cases where the nursing home was in the immediate vicinity of the hospital, study drug was prepared in the hospital pharmacy, and it was already customary to treat patients in the nursing home with intravenous antibiotics.

Subjects given optional study antibiotics (aztreonam or vancomycin) without meeting study defined requirements for use are included below. These patients were made not evaluable if they had a baseline pathogen potentially treatable by the optional antibiotic or if they had no identified baseline pathogen. Subjects with a baseline pathogen for which the optional antibiotic would have no activity were kept evaluable (e.g. vancomycin use in a subject with a gram negative infection).

- Inclusion criteria deviations included five subjects who were nursing home patients not admitted to the hospital, but approved for treatment in the nursing home; one subject who acquired nosocomial pneumonia when hospitalized for less than 48 hours; one subject who was admitted to the hospital with pneumonia acquired on prior admission; two subjects who had no baseline chest x-ray findings recorded; and three subjects who had no pneumonia on chest x-rays (1 trovafloxacin and 4 ciprofloxacin).
- Exclusion criteria deviations included two subjects who had recent alcohol abuse or dependence (1 trovafloxacin and 1 ciprofloxacin); two subjects who had past history of seizures (1 trovafloxacin and 1 ciprofloxacin); three subjects who had prior antibiotic use for >72 hours (2 trovafloxacin and 1 ciprofloxacin); two subjects who received prior and/or concurrent systemic antibiotics (both ciprofloxacin, one with a baseline pathogen and evaluable); and two subjects who were on immunosuppressive therapy (2 ciprofloxacin).
- Study drug administration deviations included 11 subjects who received vancomycin without documented MRSA (6 trovafloxacin and 5 ciprofloxacin); eight subjects who received aztreonam without documented *Pseudomonas* (3 trovafloxacin and 5 ciprofloxacin); one subject who received both vancomycin and aztreonam with no positive cultures (ciprofloxacin); and one subject who was given 600 mg ciprofloxacin for the evening dose for 4 days in error (no known adverse consequences).
- Other deviations (study procedure) included two subjects who were unblinded; four subjects who were randomized out of sequence; one subject who was randomized but not treated; and five subjects who were withdrawn prior to consent due to missed randomization numbers.

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Subjects with protocol deviations are listed in the following table.

Table B. Summary of Protocol Deviations All Randomized Subjects	
Inclusion Criteria	5112-0055; 5112-0056; 5112-0223; 5112-0222; 5112-0278; 5119-0227; 5188-0189; 5249-0158; 5396-0333; 5467-0139 ^a ; 5483-0771; 6404-0534
Exclusion Criteria	5115-0122; 5175-0047 ^b ; 5175-0155 ^c ; 5395-0338; 5409-0348; 5467-0137; 5628-0117; 6127-0212; 6376-0709 ^d
Study Drug Administration	5111-0107; 5174-0015; 5174-0241; 5191-0040; 5175-0718; 5386-0202; 5386-0246; 5386-0250; 5467-0138; 5511-0617; 5511-0619; 5546-0091; 5546-0092; 5623-0307; 5623-0310; 5623-0311; 5623-0320; 5623-0324; 5623-0684; 5627-0301; 6376-0709 ^d
Other: Study Procedure Randomization	5119-0226; 5191-0038 5173-0149; 5173-0150; 5175-0155 ^c ; 5175-0156; 5396-0334; 5407-0350; 5410-0343; 5467-0139 ^a ; 5834-0607; 6404-0815
a Subject 5467-0139 had one inclusion criteria deviation and one "other" deviation. b Subject 5175-0047 had two exclusion criteria deviations. c Subject 5175-0155 had one exclusion criteria deviation and one "other" deviation. d Subject 6376-0709 had one exclusion criteria deviation and one study drug administration deviation Ref.: Appendix II. E	

Sponsor's Efficacy Analysis:

Sponsor-Defined Clinical Response:

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Table 113.4

Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)

Timepoint	Trovafloxacin N= 88	Ciprofloxacin N = 103
Number of patients evaluated at EOT	88 (100%)	101 (100%)
Cure	42 (48%)	51 (50%)
Improvement	26 (30%)	28 (28%)
Failure	20 (23%)	22 (22%)
Success (Cure + Improvement)	68 (78%)	79 (78%)
Number of patients evaluated at EOS	72 (100%)	79 (100%)
Cure	42 (58%)	53 (67%)
Improvement	8 (11%)	1 (1%)
Failure	20 (28%)	22 (28%)
Relapse	2 (3%)	3 (4%)
Success (Cure + Improvement)	50 (69%)	54 (68%)

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The sponsor provided the following CIs without continuity correction factor:

EOT: Trovafloxacin versus Ciprofloxacin: -12.8%, 10.9% ($\Delta = 20$)
 EOS: Trovafloxacin versus Ciprofloxacin: -13.7%, 15.9% ($\Delta = 20$)

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The sponsor stated that (copied from page 41 of the study report):

Sponsor-defined clinical success rates (cure + improvement) were comparable between the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups at the end of treatment (77% and 78%, respectively) and at the end of study (69% and 68%, respectively).

Medical Officer's Comment: *The MO agreed with the sponsor's determination that the 2 agents were equivalent at both timepoints. CIs with continuity correction factor, were provided by the FDA statistician, Dr. Nancy Silliman:*

EOT: Trovafloxacin versus Ciprofloxacin: -13.9%, 12.0% ($\Delta = 20$)
 EOS: Trovafloxacin versus Ciprofloxacin: -15.0%, 17.2% ($\Delta = 20$)

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The results seen in the ITT population were similar, with an overall success rate at the EOT of 80/127 (63%) for the trovafloxacin-treated patients as compared to 94/135 (70%) for the ciprofloxacin-treated patients (CI: -18.8%, 5.6% with continuity correction factor ($\Delta = 20$). Thus indicating equivalence of ciprofloxacin at this early timepoint.

At the EOS, the overall success rate was 77/127 (61%) trovafloxacin versus 91/135 (67%) ciprofloxacin, (CI: -19.1%, 5.6% with continuity correction factor ($\Delta = 20$). Once again it appeared as if trovafloxacin was equivalent to ciprofloxacin in this broader population at the MO TOC, the EOS.

Although clinical response by severity of illness can be found below, the MO found that patients on ciprofloxacin with mild disease had a higher response rate as compared to the trovafloxacin-treated patients, thus accounting for the numerical superiority of ciprofloxacin in the ITT population.

Clinical Response by Baseline Severity:

Table 113.5

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Sponsor-Defined Clinical Response/Clinically Evaluable Population with Mild/Moderate Disease at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Trovafloxacin N = 59	Ciprofloxacin N = 68
Number of patients evaluated at EOT	59 (100%)	66 (100%)
Cure	29 (49%)	39 (59%)
Improvement	20 (34%)	17 (26%)
Failure	10 (17%)	10 (15%)
Success (Cure + Improvement)	49 (83%)	56 (85%)
Number of patients evaluated at EOS	51 (100%)	53 (100%)
Cure	31 (61%)	39 (74%)
Improvement	8 (16%)	1 (2%)
Failure	10 (20%)	10 (19%)
Relapse	2 (4%)	3 (6%)
Success (Cure + Improvement)	39 (76%)	40 (75%)

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Medical Officer's Comment: The clinical success rates were comparable between the 2 arms for this subgroup of patients. Interestingly, and as stated above, ciprofloxacin was numerically superior to trovafloxacin in the ITT population for this subgroup only.

Below is the sponsor's table of clinical response for those patients with "severe" disease. Patients were defined as having severe disease if they required mechanical ventilation or on a fractional inspired oxygen concentration of ≥ 0.35 to maintain an arterial oxygen tension of 60 mmHg.

Table 113.6
Sponsor-Defined Clinical Response/Clinically Evaluable Population with Severe Disease at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Trovafloxacin N= 29	Ciprofloxacin N = 35
Number of patients evaluated at EOT	29 (100%)	35 (100%)
Cure	13 (49%)	12 (34%)
Improvement	6 (34%)	11 (31%)
Failure	10 (17%)	12 (34%)
Success (Cure + Improvement)	19 (66%)	23 (66%)
Number of patients evaluated at EOS	21 (100%)	26 (100%)
Cure	11 (52%)	14 (54%)
Improvement	-	-
Failure	10 (48%)	12 (46%)
Relapse	-	-
Success (Cure + Improvement)	11 (52%)	14 (54%)

Medical Officer's Comment: From this table, it can be appreciated that the 2 treatment arms were numerically equivalent for this subgroup of patients and that overall response was approximately 10 percentage points less at both the EOT and the EOS. Similarly equivalent results also occurred in the ITT population.

Sponsor-Defined Clinical Response for Clinically and Bacteriologically Evaluable subjects:

Table 113.7
Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.3)

Timepoint	Trovafloxacin N= 47	Ciprofloxacin N = 52
Number of patients evaluated at EOT	47 (100%)	52 (100%)
Cure	19 (40%)	21 (40%)
Improvement	14 (30%)	18 (35%)
Failure	14 (30%)	13 (25%)
Success (Cure + Improvement)	33 (70%)	39 (75%)
Number of patients evaluated at EOS	39 (100%)	38 (100%)
Cure	19 (49%)	24 (63%)
Improvement	3 (13%)	0
Failure	14 (36%)	13 (34%)
Relapse	1 (3%)	1 (3%)
Success (Cure + Improvement)	24 (62%)	24 (63%)

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Medical Officer's Comment: It appeared as if in this subpopulation, there was a slight numerical superiority of ciprofloxacin to trovafloxacin at the EOT, however, this difference was no longer apparent at the EOS. Overall, the results of this subpopulation mirror those for all clinically evaluable patients.

Clinical Response by Baseline Pathogen:

Table 113.8

Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population: Modified 5.3.1 by MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	8	7	88	9	8	89
	EOS	6	5	83	7	6	86
<i>Moraxella catarrhalis</i>	EOT	1	0	0	4	3	75
	EOS	1	0	0	2	1	50
<i>Streptococcus pneumoniae</i>	EOT	4	2	50	6	5	83
	EOS	4	2	50	4	3	75
<i>Stenotrophomonas maltophilia</i>	EOT	2	2	100	1	1	100
	EOS	2	2	100	1	1	100
<i>Haemophilus parainfluenzae</i>	EOT	5	5	100	3	2	67
	EOS	5	5	100	2	1	50
<i>Klebsiella pneumoniae</i>	EOT	4	3	75	7	3	43
	EOS	4	2	50	5	1	20
<i>Pseudomonas aeruginosa</i>	EOT	15	10	67	11	6	55
	EOS	13	8	62	8	2	25
<i>Klebsiella oxytoca</i>	EOT	3	2	67	2	2	100
	EOS	3	2	67	-	-	-
<i>Escherichia coli</i>	EOT	7	5	71	5	4	80
	EOS	6	3	50	5	4	80
<i>Proteus mirabilis</i>	EOT	3	2	67	1	1	100
	EOS	2	2	50	1	1	100
<i>Morganella morganii</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Acinetobacter spp.</i>	EOT	1	1	100	2	1	50
	EOS	1	1	100	2	1	50
<i>Staphylococcus aureus</i>	EOT	11	7	64	10	8	80
	EOS	8	4	50	6	4	67
<i>Serratia marcescens</i>	EOT	2	2	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Enterococcus faecalis</i>	EOT	2	1	50	1	0	0
	EOS	2	1	50	1	0	0
<i>Enterobacter cloacae</i>	EOT	1	1	100	4	3	75
	EOS	1	1	100	2	1	50
<i>Enterobacter aerogenes</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Neisseria meningitidis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Providencia spp.</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Aerococcus spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Citrobacter diversus</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Corynebacterium spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
<i>Haemophilus parahaemolyticus</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Legionella pneumophila</i>	EOT	2	2	100	-	-	-
	EOS	2	2	100	-	-	-
<i>Streptococcus anginosus</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
Total	EOT	74	55	74.3	74	52	70.3
	EOS	67	42	62.6	53	30	56.6

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Medical Officer's Comment: The results in table 113.8 closely mirror those in table 113.4, with a clinical response in the 70% range at the EOT which decreased by the EOS to 62.6% for the trovafloxacin-treated patients as compared to a much lower 56.6% for the ciprofloxacin-treated patients.

Notable to the MO was the lower clinical response rate of the patients treated with ciprofloxacin who had Enterobacteriaceae.

CIs were not applied to this variable as each patient could have had more than 1 bacterial isolate.

Table 113.9
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Requested Pathogens Only: Modified 5.3.1 by MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	8	7	88	9	8	89
	EOS	6	5	83	7	6	86
<i>Escherichia coli</i>	EOT	7	5	71	5	4	80
	EOS	6	3	50	5	4	80
<i>Klebsiella pneumoniae</i>	EOT	4	3	75	7	3	43
	EOS	4	2	50	5	1	20
<i>Staphylococcus aureus</i>	EOT	11	7	64	10	8	80
	EOS	8	4	50	6	4	67
<i>Pseudomonas aeruginosa</i>	EOT	15	10	67	11	6	55
	EOS	13	8	62	8	2	25
Total	EOT	45	32	71.1	42	29	69
	EOS	37	22	59.4	31	17	54.8

Medical Officer's Comment: When only clinical response by requested pathogen was assessed, the clinical response rates are essentially unchanged although slightly lower. It appeared as if trovafloxacin had better activity versus *Pseudomonas aeruginosa* and that ciprofloxacin had better activity versus *Staphylococcus aureus*.

CIs were not applied to this variable as each patient could have had more than 1 bacterial isolate.

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Clinical Response by Ventilator Status:

The MO requested that the sponsor provide an assessment of clinical response for this subpopulation.

Table 113.10
Sponsor-Defined Clinical Response/Clinically Evaluable Population requiring Mechanical Ventilation at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Trovafoxacin N= 24	Ciprofloxacin N = 22
Number of patients evaluated at EOT	24 (100%)	22 (100%)
Cure	10 (50%)	8 (36.4%)
Improvement	6 (31.2%)	6 (27.3%)
Failure	8 (18.8%)	8 (36.4%)
Success (Cure + Improvement)	16 (66.7%)	14 (63.6%)
Number of patients evaluated at EOS	18 (100%)	16 (100%)
Cure	10 (59.3%)	8 (50%)
Improvement	-	-
Failure	8 (22.2%)	8 (50%)
Relapse	-	-
Success (Cure + Improvement)	10 (55.6%)	8 (50%)

***Medical Officer's Comment:** As expected, clinical response was worse overall in this apparently more ill population by about 10 percentage points at both the EOT and the EOS. Trovafoxacin appeared numerically superior to ciprofloxacin at the MO TOC, the EOS.*

Signs and Symptoms:
 (Copied from page 50 of the study report)

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The percentage of clinically evaluable subjects in the alatrofloxacin/trovafoxacin and ciprofloxacin groups with moderate or severe signs and symptoms of pneumonia at baseline was as follows: dyspnea (54%, each group), cough (63% and 58%, respectively), pleuritic chest pain (16%, each group), chills/rigor (14%, each group), and increased sputum volume (58% and 56%, respectively).

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In both treatment groups, the percentage of subjects with these signs and symptoms of pneumonia decreased from baseline to the end of treatment and further decreases were observed at the end of study. In general, among subjects who continued to display these signs or symptoms, the severity was decreased. Similar trends were observed among clinically intent-to-treat subjects.

The percentage of clinically evaluable subjects in the alatrofloxacin/trovafoxacin and ciprofloxacin groups with additional signs and symptoms present at baseline, including fever, focal abnormal auscultatory findings (FAAF), and diffuse abnormal auscultatory findings (DAAF) was as follows: documented fever (54% and 50%, respectively), FAAF (73% and 84%, respectively), and DAAF (56% and 50%, respectively). The percentage of subjects with these signs and symptoms decreased from baseline to the end of treatment, with further decreases generally noted at the end of study. Similar trends were observed among clinically intent-to-treat subjects.

In addition, among the clinically evaluable subjects who were febrile within 24 hours of the baseline visit, the mean (± standard deviation) time to afebrile was 3.51 days (± 2.79) and 4.04 days (± 2.95) for subjects in the alatrofloxacin/trovafoxacin (n=47) and ciprofloxacin (n=51) groups, respectively. Among the clinically intent-to-treat subjects, the mean (± standard

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deviation) time to afebrile was 3.84 days (± 2.92) and 4.08 days (± 2.97) for subjects in the alatrofloxacin/trovafoxacin (n=61) and ciprofloxacin (n=63) groups, respectively.

A summary of the percentage of subjects with mild, moderate, or severe clinical signs and symptoms of pneumonia at baseline, end of treatment, and end of study is presented in the following table.

Table C. Summary of Clinical Signs and Symptoms						
	Alatrofloxacin ↓ Trovafoxacin			Ciprofloxacin ↓ Ciprofloxacin		
	Baseline	EOT	EOS	Baseline	EOT	EOS
Sign/Symptom^a	Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms					
Dyspnea	77%	37%	14%	71%	23%	25%
Cough	79%	37%	22%	87%	39%	24%
PCP	28%	1%	0%	25%	2%	0%
Chills/Rigors	32%	2%	0%	28%	2%	0%
ISV	80%	23%	13%	81%	27%	14%
Fever	54%	6%	4%	50%	6%	1%
FAAF	73%	14%	13%	84%	29%	16%
DAAF	56%	22%	10%	50%	22%	21%
	Baseline	EOT	EOS	Baseline	EOT	EOS
Sign/Symptom^a	Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms					
Dyspnea	74%	41%	16%	71%	28%	24%
Cough	79%	40%	24%	83%	40%	26%
PCP	25%	2%	0%	23%	3%	0%
Chills/Rigors	29%	5%	0%	24%	2%	0%
ISV	82%	32%	17%	81%	34%	15%
Fever	55%	14%	4%	50%	9%	3%
FAAF	75%	20%	16%	82%	31%	17%
DAAF	57%	30%	10%	53%	24%	20%
EOT=End of Treatment; EOS = End of Study; PCP=Pleuritic Chest Pain; ISV=Increased Sputum Volume; FAAF= Focal Abnormal Auscultatory Findings; DAAF=Diffuse Abnormal Auscultatory Findings						
a Not all subjects were evaluated for all signs/symptoms at all timepoints.						
Ref.: Tables 5.8.1a, 5.8.1b, 5.8.2a, and 5.8.2b						

Medical Officer's Comment: As can be appreciated from sponsor's Table C, the decrease in signs and symptoms was comparable between the 2 study arms. It appeared as if the ciprofloxacin patients had a more rapid initial decrease which however was matched by trovafoxacin by the EOS.

Radiographic Changes (Copied from pages 50 and 51 of the study report):

Three clinically evaluable subjects in the ciprofloxacin group had positive baseline chest X-rays findings that were not obtained within the assessable window (Day -1 to Day 1).

All other clinically evaluable subjects (alatrofloxacin/trovafoxacin, 88 and ciprofloxacin, 100) had x-rays obtained within the appropriate window at baseline. Of these, 55 (63%) alatrofloxacin/trovafoxacin subjects and 51 (50%) ciprofloxacin subjects had unilateral abnormalities and 33 (38%) alatrofloxacin/trovafoxacin subjects and 49 (48%) ciprofloxacin

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subjects had bilateral abnormalities. Fifteen (15) subjects (17%) in the alatrofloxacin/trovafloxacin group and 20 subjects (19%) in the ciprofloxacin group had abnormalities in ≥ 3 lobes at baseline. The mean number of lobes involved at baseline was 1.8 for subjects in the alatrofloxacin/trovafloxacin group and 1.9 for subjects in the ciprofloxacin group.

The majority of subjects in both treatment groups with positive baseline x-ray findings showed improvement (better or complete resolution) from baseline to the end of treatment (63%, each group) and to the end of study (68%, alatrofloxacin/trovafloxacin; 76%, ciprofloxacin). In addition, among clinically evaluable subjects in the alatrofloxacin/trovafloxacin group with abnormalities in ≥ 3 lobes at baseline, nine were clinically cured or improved and six were clinical failures at the end of treatment. Among clinically evaluable subjects in the ciprofloxacin group with abnormalities in ≥ 3 lobes at baseline, 11 were clinically cured or improved, eight were clinical failures, and one was not assessed at the end of treatment.

With the exception of two clinical intent-to-treat subjects in the alatrofloxacin/trovafloxacin group who had positive chest X-rays findings that were not recorded at baseline (both subjects were randomized but not treated), all clinical intent-to-treat subjects (alatrofloxacin/trovafloxacin, 125 and ciprofloxacin, 135) had positive x-rays findings recorded at baseline. Of these, 70 (55%) alatrofloxacin/trovafloxacin subjects and 65 (48%) ciprofloxacin subjects had unilateral abnormalities and 55 (43%) alatrofloxacin/trovafloxacin subjects and 70 (52%) ciprofloxacin subjects had bilateral abnormalities. In addition, 20 subjects (16%) in the alatrofloxacin/trovafloxacin group and 24 subjects (18%) in the ciprofloxacin group had abnormalities in ≥ 3 lobes at baseline. The mean number of lobes involved at baseline was 1.8 for subjects in the alatrofloxacin/trovafloxacin group and 1.9 for subjects in the ciprofloxacin group.

The majority of subjects in both treatment groups with positive baseline x-ray findings showed improvement (better or complete resolution) from baseline to the end of treatment (74%, alatrofloxacin/trovafloxacin; 76%, ciprofloxacin) and to the end of study (79%, alatrofloxacin/trovafloxacin; 89%, ciprofloxacin). Among clinically intent-to-treat subjects with abnormalities in ≥ 3 lobes at baseline, with the exception of five subjects in the alatrofloxacin/trovafloxacin group and four subjects in the ciprofloxacin group who were not clinically evaluable, nine in the alatrofloxacin/trovafloxacin group were clinically cured or improved and six were clinical failures at the end of treatment and 11 in the ciprofloxacin group were clinically cured or improved, eight were clinical failures, and one was not assessed at the end of treatment.

***Medical Officer's Comment:** As expected the radiographic findings followed the clinical. The MO concurred with the sponsor's analysis.*

Bacteriologic Response:

As per the sponsor, the pathogen eradication rates were comparable at both the EOT and the EOS. The pathogen eradication rates were derived by collapsing pathogen outcomes of eradication and presumed eradication for a response of eradication, and by collapsing the outcomes of persistence and presumed persistence for a response of persistence. That is, the results were not necessarily based on actual repeat positive culture results.

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Table 113.11
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically Evaluable Population: Modified 5.4.1 by MO)

Pathogen		Trovanoxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	8	7	88	9	9	100
	EOS	5	6	83	7	7	100
<i>Moraxella catarrhalis</i>	EOT	1	0	0	4	3	75
	EOS	1	0	0	2	1	50
<i>Streptococcus pneumoniae</i>	EOT	4	2	50	6	6	100
	EOS	4	2	50	4	4	100
<i>Stenotrophomonas maltophilia</i>	EOT	2	2	100	1	1	100
	EOS	2	2	100	1	1	100
<i>Haemophilus parainfluenzae</i>	EOT	5	5	100	3	2	67
	EOS	5	5	100	2	1	50
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	7	3	43
	EOS	4	2	50	4	1	25
<i>Pseudomonas aeruginosa</i>	EOT	15	9	60	11	3	27
	EOS	13	10	77	8	2	25
<i>Klebsiella oxytoca</i>	EOT	3	2	67	1	1	100
	EOS	3	2	67	-	-	-
<i>Escherichia coli</i>	EOT	6	4	67	5	5	100
	EOS	4	3	75	5	5	100
<i>Proteus mirabilis</i>	EOT	3	3	100	1	1	100
	EOS	2	2	100	1	1	100
<i>Morganella morganii</i>	EOT	1	1	100	1	1	100
	EOS	1	1	100	1	1	100
<i>Acinetobacter spp.</i>	EOT	1	0	0	0	0	0
	EOS	1	1	100	0	0	0
<i>Staphylococcus aureus</i>	EOT	11	6	55	9	6	67
	EOS	8	3	38	6	4	67
<i>Serratia marcescens</i>	EOT	2	1	50	1	1	100
	EOS	1	1	100	1	1	100
<i>Enterococcus faecalis</i>	EOT	1	0	0	1	0	0
	EOS	1	0	0	1	0	0
<i>Enterobacter cloacae</i>	EOT	1	1	100	4	3	75
	EOS	1	1	100	2	1	50
<i>Enterobacter aerogenes</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Neisseria meningitidis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Providencia spp.</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Aerococcus spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Citrobacter diversus</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Corynebacterium spp.</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	-	-	-
<i>Haemophilus parahaemolyticus</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Legionella pneumophila</i>	EOT	2	2	100	-	-	-
	EOS	2	2	100	-	-	-
<i>Streptococcus anginosus</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
Total	EOT	72	49	68	72	52	72.2
	EOS	61	44	72.1	52	34	55.3

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Medical Officer's Comment: MO table 113.11 mirrors MO table 113.8 with minor numeric differences. Interestingly however, the overall bacteriologic eradication rate of trovafloxacin at the EOS appeared superior to that of ciprofloxacin. Contributing to this may have been the low eradication rate of *Pseudomonas aeruginosa* on the ciprofloxacin arm as compared to the trovafloxacin arm.

Table 113.12
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically evaluable Population/Requested Pathogens Only: Modified 5.4.1 by MO)

Pathogen		Trovafloxacin			Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	8	7	88	9	9	100
	EOS	6	5	83	7	7	100
<i>Escherichia coli</i>	EOT	6	4	67	5	5	100
	EOS	4	3	75	5	5	100
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	7	3	43
	EOS	4	2	50	4	1	25
<i>Staphylococcus aureus</i>	EOT	11	6	55	9	6	67
	EOS	8	3	38	9	6	67
<i>Pseudomonas aeruginosa</i>	EOT	15	9	60	11	3	27
	EOS	13	10	77	8	2	25
Total	EOT	44	28	63.6	41	26	63.4
	EOS	35	23	65.7	33	21	63.6

Medical Officer's Comment: In table 113.12, the MO has shown only the eradication rates for the requested pathogens. Overall bacteriologic eradication rates were changed only slightly when the bacterial spectrum was narrowed to those organisms that appear to be clearly associated with NP. Additionally, both arms appear to be numerically equivalent. As noted in table 113.8, (clinical response by pathogen), trovafloxacin did not appear as active versus *Staphylococcus aureus* as compared to ciprofloxacin. Additionally, ciprofloxacin appeared numerically superior versus *Escherichia coli* and *Haemophilus influenzae*, but performed very poorly against *Pseudomonas aeruginosa*. The number of pathogens however was too small to be able to draw any valid conclusions.

Bacteriologic Response in Subjects with *Pseudomonas aeruginosa* at Baseline:
 (Copied from page 54 of the study report)

Of the 15 evaluable alatrofloxacin/trovafloxacin subjects and 11 ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, six alatrofloxacin/trovafloxacin (40%) and four ciprofloxacin (36%) received optional aztreonam therapy (dual therapy).

There appeared to be no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy in sponsor-defined clinical response at end of treatment or end of study. Subjects in both treatment groups who received dual therapy had a lower rate of persistence and presumed persistence for *Pseudomonas aeruginosa* at the end of treatment; however, due to the small number of subjects no definitive conclusions could be drawn.

Medical Officer's Comment: The MO independently audited the 15 trovafloxacin and 11 ciprofloxacin subjects who had *Pseudomonas aeruginosa* isolated at baseline. The MO concurred with the sponsor that 6 and 4 patients per arm respectively, received aztreonam as per protocol.

Of the 6 patients who received aztreonam on the trovafloxacin arm, 3 were clinical failures with eradication of the *Pseudomonas*, 2 were clinically improved at both the EOT and EOS visits with eradication and 1 patient was improved with persistence of the *Pseudomonas aeruginosa*. Resistance had not developed in this patient and no further therapy was utilized.

Of the remaining 9 patients on trovafloxacin who had *Pseudomonas aeruginosa* at baseline, 5 were clinical cures and the baseline pathogen was eradicated in 4 of these cases and persisted in one, once again without

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further antimicrobial therapy being prescribed. 2 patients were clinical failures with persistence and 2 were clinically improved with eradication in 1 and persistence in 1.

On the ciprofloxacin arm, of the 4 patients who received aztreonam, only 1 was a clinical failure with persistence. 2 were clinical cures with eradication and 1 was clinically improved with persistence.

*Of the remaining 7 patients on this arm, 6 were failures with persistence and 1 was a relapse at the EOS who had had persistence of the *Pseudomonas* in the sputum and who was subsequently treated with gentamicin.*

*Based on the above, the MO agreed with the sponsor that the number of patients evaluated was too small to make any firm statements. However, that the MO agreed to that the statement appended by the sponsor to the draft labeling ("As with other antibiotics, treatment of nosocomial infections due to *Pseudomonas aeruginosa* infections, may require combination therapy.") was accurate.*

Superinfecting Pathogens and Colonizing Organisms:

3 patients on the trovafloxacin arm and 1 subject on the ciprofloxacin arm had superinfecting pathogens at the EOS requiring further therapy. Specifically, of the trovafloxacin-treated patients, one patient had *Morganella morganii*, 1 had *Proteus mirabilis* and *Enterobacter aerogenes*, and 1 patient had *Staphylococcus aureus* and *Serratia marcescens*. The ciprofloxacin patient was found to have *Enterococcus faecalis* and a *Pseudomonas* spp.

23 trovafloxacin-treated subjects were found to have colonizing organisms not requiring treatment as compared to 22 ciprofloxacin subjects.

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Mortality:

The sponsor stated that amongst the 88 clinically evaluable trovafloxacin patents, there were 12 (14%) deaths within 5 days of the initiation of study therapy as compared to 17/103 (17%) on the ciprofloxacin arm.

Amongst the clinically ITT subjects, there were 30 deaths on the trovafloxacin arm and 34 on the ciprofloxacin arm. Copied below is sponsor's table D (page 59 of the study report):

Table D. Summary of Mortality			
	Clinically Evaluable Subjects		
	Alatrofloxacin ↓ Trovafoxacin (N=88)		Ciprofloxacin ↓ Ciprofloxacin (N=103)
Number of Deaths ^a	12 (14%)		17 (17%)
≤48 Hours	0		0
Day 3 to 7	2 (2%)		0
Day 8 to 15	3 (3%)		3 (3%)
Day 16 to 45	7 (8%)		14 (14%)
	Clinically Intent-to-Treat Subjects		
	Alatrofloxacin ↓ Trovafoxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=135)
Number of Deaths ^a	30 (24%)		34 (25%)
≤48 Hours	3 (2%)		3 (2%)
Day 3 to 7	11 (9%)		8 (6%)
Day 8 to 15	8 (6%)		7 (5%)
Day 16 to 45	8 (6%)		16 (12%)
a Number of deaths that occurred from initiation of study therapy. Ref.: Appendix I, Tables 9.1 and 9.2			

Medical Officer's Comment: Of note from table D is that most of the deaths on both treatment arms occurred after the conclusion of active therapy. The MO reviewed all deaths in the safety section of this review.

Clinical Failures:

The sponsor provided an analysis of the 20 trovafloxacin and 22 ciprofloxacin-treated subjects who were clinical failures at the EOT and carried forward as such to the EOS. This analysis has been copied from page 59 of the study report:

Eleven (11) of the 20 alatrofloxacin/trovafoxacin subjects designated as clinical failures were discontinued from treatment between Days 2 and 9 due to inadequate response. Three (3) subjects (Subjects 5106-0050, 5623-0323, and 5623-0682) who were clinical failures received optional aztreonam. Eighteen (18) subjects who were clinical failures received additional antibiotics for inadequate response. No subject was re-hospitalized or had hospitalization prolonged due to worsening of condition. Five subjects (Subjects 5174-0241, 5175-0719, 5175-0154, 5511-0618, and 5623-0682) died due to the disease under study.

Nine (9) of the 22 ciprofloxacin subjects designated as clinical failures were discontinued from treatment between Days 3 and 12 due to inadequate response. Of the subjects designated as

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clinical failures, one subject (Subject 5175-0163) received optional vancomycin, one subject (Subject 5546-0092) received optional clindamycin and vancomycin, and one subject (Subject 6367-0745) received optional aztreonam and clindamycin. Nineteen (19) ciprofloxacin subjects who were clinical failures received additional antibiotics for inadequate response and two subjects (Subjects 5173-0150 and 5175-0163) were re-hospitalized or had hospitalization prolonged due to worsening of condition. Four subjects (Subjects 5174-0242, 5407-0349, 6127-0786, and 5175-0163) died due to the disease under study.

Medical Officer's Comment: The MO reviewed all failures and found that 13/20 of the EOT failures on the trovafloxacin arm as well as 1 patient who was a relapse (EOS) were found to have had a baseline pathogen and thus were bacteriologically as well as clinically evaluable. On the ciprofloxacin arm, 13/22 EOT failures as well as 1/3 EOS relapses were in the same category. The MO elected to review these patients below:

Trovafloxacin (N = 14)

Subject Number	Baseline Pathogen (Source)	Days on Treatment	Subject Clinical Response	Pathogen Bacteriologic Outcome
51060050	<i>Pseudomonas aeruginosa</i> (sputum)	9	Failure	Eradication (documented by culture at EOT and EOS, with superinfection with <i>Serratia marcescens</i> .)
51190064	<i>Staphylococcus aureus</i> (sputum)	6	Failure	Presumed Persistence (patient died on day 6 after Vancomycin® started. No further cultures obtained)
51210230	<i>Escherichia coli</i> (blood)	15	Failure	Eradication (also had <i>Enterococcus faecalis</i> in blood repeatedly and MO determined that patient had an abdominal mass which appeared to be the cause of sepsis. Initial sputum not obtained but at day 7 until the EOS, the patient had persistent <i>Staphylococcus aureus</i> and intermittent <i>Pseudomonas aeruginosa</i> .)
51210232	<i>Haemophilus influenzae</i> (blood)	9	Failure	Presumed Persistence (MO agreed with determination).
51750154	<i>Proteus mirabilis</i> (LRT, sputum)	8	Failure	Eradication (at EOT and EOS, patient was changed to gentamicin at day 8).
51880192	<i>Staphylococcus aureus</i> (LRT, sputum)	3	Failure	Persistent (MO agreed. Patient had <i>Staphylococcus aureus</i> in the EOT sputum at day 3, as well as <i>Pseudomonas aeruginosa</i> . Alternative therapy with gentamicin and Nafcillin® were instituted.
51910039	<i>Staphylococcus aureus</i> (bronchoscopy, sputum)	10	Failure	Presumed Persistent (MO agreed. Patient received Timentin®, Vancomycin®, clindamycin, and metronidazole. Repeat cultures were not obtained).
53860251	<i>Pseudomonas aeruginosa</i> (lung, sputum)	14	Failure	Persistent (MO agreed. Patient had <i>Pseudomonas aeruginosa</i> in EOT and EOS specimens and was treated with ciprofloxacin)
55100610	<i>Moraxella catarrhalis</i> <i>Streptococcus pneumoniae</i> (LRT, lung)	5	Failure	Presumed Persistent: both isolates (MO agreed that by default would apply this outcome. However, in all specimens after day 5, the patient had <i>Enterobacteriaceae</i> isolated. Therapy was guided against these organisms with ultimate resolution)
55110618	<i>Klebsiella oxytoca</i> <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> (bronchoscopy)	2	Failure	All isolates Presumed Persistent (septic shock required the addition of multiple antimicrobials.)

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56230323	<i>Pseudomonas aeruginosa</i> (LRT)	10	Failure	Eradication (MO agreed. <i>Pseudomonas</i> was eradicated prior to the institution of other antimicrobials including ciprofloxacin).
56230682	<i>Pseudomonas aeruginosa</i> (LRT, sputum)	5	Failure	Eradication (MO agreed with EOT result, <i>Pseudomonas</i> was again present at the EOS and after multiple other anti-pseudomonal antimicrobials).
61270209	<i>Enterococcus faecalis</i> (blood) <i>Escherichia coli</i> (blood, lung) <i>Klebsiella pneumoniae</i> (blood, lung) <i>Streptococcus pneumoniae</i> (lung, sputum)	3	Failure	Presumed Persistence all isolates. (MO Agreed with outcome assessment. Patient was treated with multiple other antimicrobials)
50300265	<i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> (sputum)	9	Improvement Relapse	Eradication of <i>Escherichia coli</i> but Persistence of <i>Klebsiella pneumoniae</i> .

Ciprofloxacin ($N_c = 14$)

Subject Number	Baseline Pathogen (Source)	Days on Treatment	Subject Clinical Response	Pathogen Bacteriologic Outcome
51750163	<i>Staphylococcus aureus</i> (sputum)	15	Failure	Presumed Persistent (MO agreed. Patient was unable to produce a specimen and clindamycin was instituted).
51750717	<i>Klebsiella pneumoniae</i> <i>Streptococcus anginosus</i> (sputum)	10	Failure	Presumed Persistent (MO agreed. Patient was unable to produce a specimen and multiple antimicrobials were instituted).
51880191	<i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i> (sputum)	3	Failure	Eradication (MO agreed that pathogens were eradicated at the time of the institution of Unasyn® for inadequate response. No further specimens were obtained).
53860201	<i>Enterococcus faecalis</i> <i>Klebsiella pneumoniae</i> <i>Staphylococcus aureus</i> (sputum)	9	Failure	Presumed Persistent (MO agreed. Patient was unable to produce a specimen and oxacillin and rifampin were instituted).
53950338	<i>Enterobacter cloacae</i> (sputum, blood) <i>Acinetobacter calcoaceticus</i> (sputum)	7	Failure	Persistent (MO agreed. Patient was unable to produce a specimen and alternative antimicrobials were instituted).
54090357	<i>Enterobacter aerogenes</i> <i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i> (sputum)	10	Failure	Eradication of <i>Enterobacter</i> and <i>Escherichia coli</i> but persistence of <i>Pseudomonas</i> requiring gentamicin. MO agreed.
54090359	<i>Pseudomonas aeruginosa</i> (sputum)	10	Failure	Persistent (MO agreed. Patient required ticarcillin).
54670138	<i>Pseudomonas aeruginosa</i> (sputum)	9	Failure	Presumed Persistent (MO agreed in face of no repeat cultures and Primaxin® therapy).
55460092	<i>Klebsiella pneumoniae</i> (sputum)	10	Failure	Presumed Persistent (MO agreed)
56230309	<i>Haemophilus parainfluenzae</i> (LRT)	3	Failure	Presumed Persistent (MO agreed)
59030541	<i>Moraxella catarrhalis</i> <i>Citrobacter diversus</i> (not specified)	7	Failure	Eradication (MO agreed that the EOT specimen was negative. Patient then received cefotaxime for 8 days.)
63670745	<i>Pseudomonas aeruginosa</i> (lung, sputum)	14	Failure	Persistent (MO agreed. Patient received gentamicin and an anti-pseudomonal penicillin).
65430810	<i>Klebsiella pneumoniae</i> <i>Pseudomonas aeruginosa</i> (sputum)	12	Failure	Presumed Persistence of both isolates (MO agreed).

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51750020	<i>Pseudomonas aeruginosa</i> (LRT, sputum)	10	Cure Relapse	Persistent at EOT and EOS (MO agreed)

The MO agreed with the sponsor's determination of bacteriologic outcome in all cases. On the trovafloxacin arm, there were 3 patients with Pseudomonas aeruginosa who were clinical failures despite the eradication of this organism. During the PID review, the MO found that the sponsor determined this outcome based on an EOT culture. If it was negative on the day of stopping therapy or within a day, then the organism was "eradicated". The MO could not disagree with this approach as there was objective evidence of eradication at the EOT timepoint and a further EOS determination could not be made as these patients were then treated with other antimicrobials. On the trovafloxacin arm, this also occurred in a patient with Proteus mirabilis.

On the ciprofloxacin arm, there were 2 patient only who had documented eradication at the EOT in the face of clinical failure and prior to the institution of alternative therapies. In one case the patient had Haemophilus influenzae and Streptococcus pneumoniae, and in the other, Moraxella catarrhalis and Citrobacter diversus.

None of the baseline pathogens from patients that failed therapy were resistant to the study drugs, either at baseline or if re-cultured.

Cross-tabulation of Sponsor-Defined Clinical Response and Pathogen Outcome:

Among the bacteriologically evaluable subjects, sponsor-defined clinical response was consistent with sponsor-defined pathogen outcome at the end of treatment except for 12 alatrofloxacin/trovafloxacin subjects and seven ciprofloxacin subjects. The MO has copied and modified sponsor table E from page 68 of the study report below:

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Table 113.13

Cross-Tabulation of Clinical and Bacteriological Response at the EOT (as per the Sponsor: Table E) and the EOS (in Times New Roman font as per the MO)

Table E. Summary of Inconsistencies Between Sponsor-Defined Clinical Response and Pathogen Outcome at the End of Treatment Bacteriologically Evaluable Subjects			
Subject Number	Baseline Pathogen	Clinical Response	Pathogen Bacteriological Response
Alatrofloxacin/Trovafloxacin			
EOT/EOS			
5030-0265	<i>Klebsiella pneumoniae</i>	Improvement/Failed	Persistent/Persistent
5106-0050	<i>Pseudomonas aeruginosa</i>	Failure/Failure	Eradicated/Eradicated
5111-0108	<i>Acinetobacter calcoaceticus</i>	Improvement/Cure	Persistent/Presumed Eradicated
5121-0230	<i>Escherichia coli</i>	Failure/Failure	Eradicated/ Eradicated
5174-0016	<i>Pseudomonas aeruginosa</i> <i>Serratia marcescens</i>	Improvement/ Not Eval, no EOS	Persistent/ Not Eval., no EOS Persistent/ Not Eval., no EOS
5175-0154	<i>Proteus mirabilis</i>	Failure/Failure	Eradicated/ Eradicated
5211-0136	<i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i>	Improvement/Improvement	Persistent/Persistent Persistent/ Persistent
5396-0335	<i>Escherichia coli</i>	Improvement/Cure	Persistent/ Eradicated
5409-0346	<i>Pseudomonas aeruginosa</i>	Cure/ Not Eval, no EOS	Persistent/ Not Eval., no EOS
5409-0358	<i>Pseudomonas aeruginosa</i>	Improvement/Cure	Persistent/Eradicated
5623-0323	<i>Pseudomonas aeruginosa</i>	Failure/Failure	Eradicated/ Eradicated
5623-0682	<i>Pseudomonas aeruginosa</i>	Failure/ Failure	Eradicated/ Eradicated
Ciprofloxacin			
5175-0020	<i>Pseudomonas aeruginosa</i>	Cure/Failure	Persistent/Persistent
5188-0191	<i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i>	Failure/Failure	Eradicated/ Eradicated Eradicated/ Eradicated
5191-0040	<i>Pseudomonas aeruginosa</i>	Improvement/ Not Eval, no EOS	Persistent/ Not Eval., no EOS
5386-0252	<i>Pseudomonas aeruginosa</i>	Improvement/ Not Eval, no EOS	Persistent/ Not Eval., no EOS
5409-0357	<i>Enterobacter aerogenes</i> <i>Escherichia coli</i>	Failure/Failure	Eradicated/ Eradicated Eradicated/ Eradicated
5483-0125	<i>Staphylococcus aureus</i> ^a	Improvement/Not Eval, no EOS	Persistent/Not Eval., no EOS
5903-0541	<i>Moraxella catarrhalis</i> <i>Citrobacter diversus</i>	Failure/Failure	Eradicated/ Eradicated Eradicated/ Eradicated
a Resistant to study drug at baseline			

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Medical Officer's Comment: *All failures were reviewed previously. As stated on the previous page a determination of eradication in the face of failure could only have been made based on an objective culture report at the EOT. The MO determined that 2 trovafloxacin-treated and 3 ciprofloxacin-treated patients were not evaluable. Of those patients who were evaluable per the MO, there was no disagreement between the MO's and the sponsor's determinations of outcome.*

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Sponsor's Conclusion:

(Copied from page 77 of the study report and modified by the MO (in Times New Roman font))

Alatrofloxacin/trovafloxacin was comparable to ciprofloxacin for clinical success rate in subjects with nosocomial pneumonia.

One hundred twenty-nine (129) subjects were randomized to treatment with alatrofloxacin/trovafloxacin and 138 subjects were randomized to treatment with ciprofloxacin.

Of the randomized subjects, 127 subjects in the alatrofloxacin/trovafloxacin group and 137 subjects in the ciprofloxacin group received treatment; two randomized subjects in the alatrofloxacin/trovafloxacin group and one randomized subject in the ciprofloxacin group did not receive treatment. The two treatment groups were generally comparable with respect to characteristics at baseline, including medical history, use of prior and concomitant medications, severity factors (compromised respiratory function and need for mechanical ventilation), APACHE II score, and severity of pneumonia.

Eighty-eight (88) subjects in the alatrofloxacin/trovafloxacin group and 103 subjects in the ciprofloxacin group were clinically evaluable; 47 subjects in the alatrofloxacin/trovafloxacin group and 52 subjects in the ciprofloxacin group were bacteriologically evaluable. All treated subjects were included in analysis of adverse events.

Sponsor-defined clinical success rates (cure + improvement) supported equivalence of the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups at the end of treatment for both clinically evaluable and intent-to-treat subjects. Success rates were comparable between the two treatment groups at the end of study. Success rates among clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups were 77% (68/88) and 78% (79/101), respectively, at the end of treatment and 69% (50/72) and 68% (54/79), respectively, at the end of study and those among clinically intent-to-treat subjects were 63% (80/127) and 70% (94/135), respectively, at the end of treatment and 61% (77/127) and 67% (91/135), respectively, at the end of study. These findings were supported by marked decreases from baseline to the end of treatment and to the end of study in the presence of clinical and radiologic signs and symptoms of pneumonia in both treatment groups.

Among clinically evaluable subjects, 12 (14%) subjects in the alatrofloxacin/trovafloxacin group and 17 (17%) subjects in the ciprofloxacin group died within 45 days of initiation of study therapy. Among clinically intent-to-treat subjects, 30 (24%) subjects in the alatrofloxacin/trovafloxacin group and 34 (25%) subjects died within 45 days of initiation of study therapy.

Sponsor-defined pathogen eradication rates for the most commonly isolated pathogens were comparable among bacteriologically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups at the end of treatment and end of study.

Of the 15 evaluable alatrofloxacin/trovafloxacin subjects and 11 ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, six alatrofloxacin/trovafloxacin (40%) and four ciprofloxacin (36%) received optional aztreonam therapy (dual therapy). There appeared to be no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy in sponsor-defined clinical response at end of treatment or end of study. Subjects in

both treatment groups who received dual therapy had a lower rate of persistence and presumed persistence for *Pseudomonas aeruginosa* at the end of treatment, however, due to the small number of subjects no definitive conclusions could be drawn.

Of the subjects with an unfavorable clinical or bacteriological response who had baseline isolates with susceptibility testing performed both prior to and following treatment, none had pathogens that became resistant to trovafloxacin, ciprofloxacin, or aztreonam.

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Medical Officer's Efficacy Analysis:

In accordance with the previously described MO evaluability criteria, the MO excluded 40 additional patients from the clinically evaluable population because they had no EOS visit. Additionally, 4 patients were excluded because they received < 80% of the prescribed therapeutic regimen. This information has been presented in MO table 113.14, below:

**Table 113.14
Clinically Evaluable Population (as per the MO)**

Reason for exclusion	Trovafloxacin	Ciprofloxacin
Total Treated	127	137
Sponsor Evaluable	88	103
MO Excluded	18	26
No EOS Visit	16	24
< 80% Of regimen	2	2
Total Evaluated at EOS	70	77

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In the MO's analysis, the number of clinically evaluable patients at the EOT and the EOS were the same. The 70 clinically evaluable trovafloxacin patients represented 26.5% of the treated patients and the 77 ciprofloxacin patients represented 29.1%.

The MO's bacteriologically evaluable population was a subset of the clinically evaluable.

A by-center breakdown of the MO's evaluable population, is presented below in table 113.15:

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Table 113.15
Clinically Evaluable Population by Center (as per MO)

Center	Total Treated		Trovafoxacin		Ciprofloxacin	
	N = 264	(100%)	N = 70	100%	N = 77	100 %
5423	1	0.4	0	-	0	-
5467*	3	1.1	0	-	1	1.3
5483*	15	5.6	3	4.3	3	3.9
5508	1	0.4	1	1.4	0	-
5510	3	1.1	2	2.9	1	1.3
5511	3	1.1	2	2.9	0	-
5513	2	0.7	0	-	1	1.3
5515	1	0.4	0	-	1	1.3
5516	1	0.4	0	-	1	1.3
5541*	2	0.7	0	-	1	1.3
5546*	4	1.4	1	1.4	2	2.6
5623	18	6.7	7	10	5	6.5
5627	4	1.5	0	-	1	1.3
5628*	1	0.4	0	-	0	-
5834	3	1.1	2	2.9	0	-
5835	7	2.6	2	2.9	4	5.2
5837*	1	0.4	0	-	0	-
5903	2	0.7	1	1.4	1	1.3
5970*	1	0.4	0	-	0	-
5984*	1	0.4	0	-	0	-
5985*	3	1.1	0	-	1	1.3
5987*	2	0.7	0	-	0	-
6111	1	0.4	1	1.4	0	-
6112	1	0.4	1	1.4	0	-
6127*	7	2.6	1	1.4	2	2.6
6367*	3	1.1	0	-	2	2.6
6376*	1	0.4	0	-	0	-
5030	2	0.7	2	2.9	0	-
5034	3	1.1	0	-	1	1.3
5079*	5	1.8	3	4.3	2	2.6
5106*	4	1.5	1	1.4	0	-
5111*	8	3.0	2	2.9	1	1.3
5112*	14	5.2	3	4.3	4	5.2
5115*	2	0.7	0	-	1	1.3
5117*	1	0.4	0	-	0	-
5118*	2	0.7	0	-	1	1.3
5119*	8	3.0	3	4.3	3	3.9
5121*	5	1.8	3	4.3	2	2.6
5173*	5	1.8	1	1.4	3	3.9
5174*	6	2.2	2	2.9	2	2.6
5175*	19	7.1	8	11.4	6	7.8
5181*	1	0.4	0	-	1	1.3
5188*	11	4.1	2	2.9	3	3.9
5191*	8	3.0	1	1.4	2	2.6
5193*	1	0.4	0	-	0	-

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5211*	7	2.6	2	2.9	2	2.6
5249*	3	1.1	1	1.4	0	-
5384*	1	0.4	0	-	0	-
5386*	20	7.5	5	7.1	5	6.5
5395	1	0.4	0	-	1	1.3
5396	2	0.7	1	1.4	0	-
5407	2	0.7	0	-	1	1.3
5409	8	3.0	2	2.9	2	2.6
5410	7	2.6	0	-	1	1.3
6404	11	4.1	1	1.4	4	5.2
6455*	1	0.4	0	-	0	-
6543	7	2.6	3	4.3	2	2.6

*Designates US centers

As appreciated from the above table, no center had greater than 10% of the evaluable patients and most centers were able to provide only 1 or 2 evaluable patients. As in all indications, as the primary efficacy variable of clinical outcome was determined by the sponsor, the data were pooled for the analyses.

The demographic make-up of the FDA evaluable population can be seen in Table 113.16:

**Table 113.16
Demographic Characteristics of the FDA Evaluable Population:**

Characteristics		Trovafloxacin N = 70	Ciprofloxacin N = 77
Sex (Female)		32	35
(Male)		38	42
Age (years)	16 - 44	9	6
	45 - 64	11	11
	≥ 65	50	60
	Mean	69.8	72.1
Race:			
	Black	4	3
	White	60	68
	Hispanic	6	5
	Indian	0	1
Body weight (kg)	Mean	71.8	67.7
Smoking Status	Ex Smoker	27	29
	Never	31	29
	Smoker	12	27
	Missing	0	2
Mechanical Ventilation	Yes	18	16
	No	52	61
Compromised Respiration	Yes	15	24
	No	55	53
Severity if Illness			
	Mild/Moderate	50	52
	Severe	20	35
APACHE Score	Mean	13.1	13.4

The MO's evaluable populations are very similar in terms of the demographic variables of age, weight, sex, and race.

Both groups had a similar number of patients requiring ventilator assistance and presumably more severely ill. Specifically, 18/70 (25.7%) trovafloxacin-treated, MO evaluable patients received ventilator support as compared to 16/77 (20.7%) ciprofloxacin-treated, MO evaluable patients. The number of evaluable patients was small in this study and the difference of 1 or 2 patients leads to a large percentage point difference. The MO provided a separate efficacy analysis for this subgroup as well as for the subgroups of patients with mild/moderate disease, severe disease, and those that were both clinically and bacteriologically evaluable..

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EFFICACY:

**Table 113.17
Clinical Response by Patient (as per the MO):**

Timepoint	Trovafloxacin			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	70	50	71.4	76	54	70.1
EOS	70	48	68.6	77	52	67.5

The MO applied a 95% CI with continuity correction factor to these results and found the following:

EOT: Trovafloxacin versus Ciprofloxacin: -15.7%, 16.4% ($\Delta = 20$).

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EOS: Trovafloxacin versus Ciprofloxacin: -15.4%, 17.5% ($\Delta = 20$).

Thus the MO's results mirrored those of the sponsor (EOS: trovafloxacin 50/72 (69%) and 54/79 (68%) ciprofloxacin) and showed equivalence between trovafloxacin and the approved comparator agent at the MO TOC, the EOS.

Based on the MO's analysis, there were 22 failures at the EOS on the trovafloxacin arm (22/70{31.4%}) as compared to 25 on the ciprofloxacin arm (25/77 {32.5%}). Once again, these numbers are comparable to the sponsor's 22 failures at the EOS on the trovafloxacin arm and 25 on the ciprofloxacin arm. The patients who failed as per the MO include failures and relapses.

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Clinical Response by Disease Severity Status:

**Table 113.18
Clinical Response at EOS for Patients with Mild/Moderate Disease (as per MO):**

Timepoint	Trovafloxacin			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	50	40	80	51	41	78.8
EOS	50	38	76	52	39	75

EOT: Trovafloxacin versus Ciprofloxacin: -17.9%, 17.1% ($\Delta = 20$).

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EOS: Trovafloxacin versus Ciprofloxacin: -17.7%, 19.7% ($\Delta = 20$).

As noted previously, in the sponsor's analysis, the overall success rate was higher in this less severely ill population. (sponsor EOS: 39/51 (76%) trovafloxacin versus 40/53 (75%).

Table 113.19
Clinical Response at EOS for Patients with Severe Disease (as per MO):

Timepoint	Trovafloracin			Ciprofloracin		
	N	No. Cured	%	N	No. Cured	%
EOT	20	10	50	25	13	52
EOS	20	10	50	25	13	52

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Table 113.20

Clinical Response at EOS for Patients requiring Mechanical Ventilation Only (as per MO):

Timepoint	Trovafloracin			Ciprofloracin		
	N	No. Cured	%	N	No. Cured	%
EOT	18	10	55.6	16	8	50
EOS	18	10	55.6	16	8	50

CI's were not applied to these smaller groups of patients; that is in the patients with severe disease and in those requiring ventilatory support. However, trovafloracin appeared slightly numerically superior to ciprofloracin in this more severely ill subgroup, that is those patients on ventilators. Once again, these results were consistent with those of the sponsor.

Specifically, in patients with severe disease the sponsor found an EOS success rate of 11/21 (52%) trovafloracin versus 14/26 (54%) ciprofloracin.

As noted previously, in the sponsor's analysis, the overall success rate was higher in the less severely ill population (sponsor EOS: 39/51 (76%) trovafloracin versus 40/53 (75%). The results between the arms were comparable in both the MO's and the sponsor's analyses and indicate a 20 percentage point difference in success rates depending on disease severity and ventilatory status.

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Table 113.21

Clinical Response at EOS for Clinically and Bacteriologically Evaluable Patients (as per MO):

Timepoint	Trovafloracin			Ciprofloracin		
	N	No. Cured	%	N	No. Cured	%
EOT	37	24	64.9	36	24	66.7
EOS	37	23	62.2	36	23	63.9

EOT: Trovafloracin versus Ciprofloracin: - 26.3%, 22.7% ($\Delta = 20$).

EOS: Trovafloracin versus Ciprofloracin: - 26.6%, 23.2% ($\Delta = 20$).

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Clinical Response by Baseline Pathogen:

The MO elected to present clinical response by baseline pathogen as well as pathogen eradication rates for the EOS only. As stated in the introduction, the determination of bacteriologic outcome was based on either culture results or in the absence of a culture, the outcome was extrapolated from the clinical outcome. Neither variable was an individual, by-patient variable because there were patients who had more than 1 organism isolated from predominantly bronchoscopy samples.

Table 113.22
Clinical Response by Baseline Pathogen at the EOS (as per MO)

Pathogen	Trovafoxacin			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	6	5	83	7	6	86
<i>Moraxella catarrhalis</i>	1	0	0	2	1	50
<i>Streptococcus pneumoniae</i>	4	2	50	4	3	75
<i>Stenotrophomonas maltophilia</i>	2	2	100	-	-	-
<i>Haemophilus parainfluenzae</i>	4	4	100	2	1	50
<i>Klebsiella pneumoniae</i>	4	2	50	5	1	20
<i>Pseudomonas aeruginosa</i>	13	8	62	7	1	14.3
<i>Klebsiella oxytoca</i>	3	2	67	-	-	-
<i>Escherichia coli</i>	6	3	50	5	4	80
<i>Proteus mirabilis</i>	2	1	50	1	1	100
<i>Morganella morganii</i>	1	1	100	1	1	100
<i>Acinetobacter spp.</i>	1	1	100	2	2	100
<i>Staphylococcus aureus</i>	8	4	50	6	4	67
<i>Serratia marcescens</i>	1	1	100	1	1	100
<i>Enterococcus faecalis</i>	2	1	50	1	0	0
<i>Enterobacter cloace</i>	1	1	100	2	1	50
<i>Enterobacter aerogenes</i>	-	-	-	1	0	0
<i>Neisseria meningitidis</i>	1	1	100	-	-	-
<i>Providencia spp.</i>	1	1	100	-	-	-
<i>Aerococcus spp.</i>	-	-	-	1	1	100
<i>Citrobacter diversus</i>	-	-	-	1	0	0
<i>Corynebacterium spp.</i>	-	-	-	-	-	-
<i>Haemophilus parahemolyticus</i>	-	-	-	1	1	100
<i>Legionella pneumophila</i>	1	1	100	-	-	-
<i>Streptococcus anginosus</i>	-	-	-	1	0	0
Total	62	41	66.1	51	29	56.8

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The MO's results differed from those of the sponsor (EOS 59.4% trovafoxacin versus 54.8% ciprofloxacin) for this variable in that clinical response was slightly better for the trovafoxacin-treated patients as compared to the ciprofloxacin-treated group. Once again there was a much higher rate of clinical failure in patients with *Pseudomonas aeruginosa* as the baseline pathogen on the ciprofloxacin arm. A CI was not applied as this was not an individual variable.

Below, in MO table 113.23 is clinical response by baseline pathogen only for the requested pathogens:

Table 113.23
Clinical Response by Baseline Pathogen at the EOS (Clinically Evaluable Population/Requested Pathogens Only: as per MO)

Pathogen	Trovafoxacin			Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	6	5	83	7	6	86
<i>Escherichia coli</i>	6	3	50	5	4	80
<i>Klebsiella pneumoniae</i>	4	2	50	5	1	20
<i>Staphylococcus aureus</i>	8	4	50	6	4	67
<i>Pseudomonas aeruginosa</i>	13	8	62	7	1	14.3
Total	37	22	59.4	30	16	53.5

Thus indicating that when only the requested pathogens were evaluated, the clinical response of the trovafoxacin-treated patients was higher than that of the ciprofloxacin-treated patients. This result was similar to that seen in the sponsor's analysis and once again appears to be in part due to the numerically inferior activity of ciprofloxacin versus *Pseudomonas aeruginosa*.

Mortality:

The MO found that there were 8 deaths on the trovafloxacin arm (8/70 {11.6%}) as compared to 9 on the ciprofloxacin arm (9/77 {11.7%}). These were deaths that occurred within 45 days of the study. As stated previously, the MO elected to evaluate these patients in the safety portion of this review.

Bacteriologic Response:

Table 113.24
Pathogen Eradication Rates at the EOS (Bacteriologically Evaluable Population, as per MO)

Pathogen	Trovafloxacin			Ciprofloxacin		
	N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	6	5	83	7	7	100
<i>Moraxella catarrhalis</i>	1	0	0	2	2	100
<i>Streptococcus pneumoniae</i>	4	2	50	4	4	100
<i>Stenotrophomonas maltophilia</i>	2	2	100	-	-	-
<i>Haemophilus parainfluenzae</i>	4	4	100	2	1	50
<i>Klebsiella pneumoniae</i>	4	2	50	4	1	25
<i>Pseudomonas aeruginosa</i>	13	10	76.9	7	1	14.3
<i>Klebsiella oxytoca</i>	3	2	67	-	-	-
<i>Escherichia coli</i>	4	3	75	5	5	100
<i>Proteus mirabilis</i>	2	2	100	1	1	100
<i>Morganella morganii</i>	1	1	100	1	1	100
<i>Acinetobacter</i> spp.	1	1	100	1	0	0
<i>Staphylococcus aureus</i>	8	3	37.5	6	4	67
<i>Serratia marcescens</i>	1	1	100	1	1	100
<i>Enterococcus faecalis</i>	1	0	0	1	0	0
<i>Enterobacter cloacae</i>	1	1	100	2	1	50
<i>Enterobacter aerogenes</i>	-	-	-	1	1	100
<i>Neisseria meningitidis</i>	1	1	100	-	-	-
<i>Providencia</i> spp.	1	1	100	-	-	-
<i>Aerococcus</i> spp.	-	-	-	1	1	100
<i>Citrobacter diversus</i>	-	-	-	1	0	0
<i>Corynebacterium</i> spp.	-	-	-	1	1	100
<i>Haemophilus parahaemolyticus</i>	-	-	-	1	1	100
<i>Legionella pneumophila</i>	1	1	100	-	-	-
<i>Streptococcus anginosus</i>	-	-	-	1	0	0
Total	59	42	71.2	50	33	66

Based on the MO's analysis, the overall pathogen eradication rate of trovafloxacin was numerically superior to that of ciprofloxacin at the EOS. As stated above, the MO's outcome assessment was based either on repeat culture data or, in the absence of a culture, outcome was extrapolated from the EOT data as well as the clinical status of the individual patient.

Although the MO determined that not all the organisms found in table 113.24 were pathogens, for example, *Neisseria meningitidis*, the exclusion of a small number of organisms from each arm, would not ensure a major difference in outcome. The MO's results were similar to those of the sponsor to the degree that the pathogen eradication rate of trovafloxacin was superior to that of ciprofloxacin at the EOS. As noted in table 113.11, the sponsor's rates were EOS: trovafloxacin 44/61 (72.1%) as compared to ciprofloxacin 34/52 (55.3%). Thus the MO's results narrowed the numerical difference between the 2 arms.

The lower eradication rate of ciprofloxacin appeared to be attributable to the lower eradication rate of *Pseudomonas aeruginosa*.

Pathogen eradication rates for the requested pathogens only, can be seen below in table 113.25:

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Table 113.25
Pathogen Eradication Rates at the EOS (Bacteriologically Evaluable Population/Requested Pathogens Only: as per MO)

Pathogen	Trovafoxacin			Ciprofloxacin		
	N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	6	5	83	7	7	100
<i>Escherichia coli</i>	4	3	75	5	5	100
<i>Klebsiella pneumoniae</i>	4	2	50	4	1	25
<i>Staphylococcus aureus</i>	8	3	37.5	6	4	67
<i>Pseudomonas aeruginosa</i>	13	10	76.9	7	1	14.3
Total	35	23	65.7	29	18	62

The MO's results are the same as the sponsor's on the trovafoxacin arm and only 1 percentage point different on the ciprofloxacin arm. Overall, the 2 agents appeared numerically comparable in the eradication of *Haemophilus influenzae*. The number of *Escherichia coli* and *Klebsiella pneumoniae* isolates was too small to be able to draw any valid conclusions. The activity of trovafoxacin versus *Staphylococcus aureus* was marginal, whereas the activity of ciprofloxacin against *Pseudomonas aeruginosa* was very poor.

Bacteriologic Response in Subjects with *Pseudomonas aeruginosa* at baseline:

There were 13 trovafoxacin and 7 ciprofloxacin subjects in the MO evaluable population that had *Pseudomonas aeruginosa* as the baseline pathogen.

6/13 trovafoxacin patients received concurrent anti-pseudomonal coverage (5 aztreonam and 1 amikacin). 3 of the 6 were clinical failures with eradication of the baseline pathogen. Of the 3 patients who were clinical successes, there was persistence of the baseline pathogen in only 1 patient. Thus in 5 of the 6 patient on the trovafoxacin arm who received additional anti-pseudomonal coverage, eradication was seen in 80%.

Of the remaining 7 trovafoxacin patients, 2 patients were clinical failures with persistence of the baseline pathogen and 5 were clinical successes with persistence in only 1. Thus 3/7 (43%) patients who received monotherapy had persistence.

Based on the above, the sponsor's claim that additional anti-pseudomonal coverage may be helpful in the eradication of *Pseudomonas aeruginosa* in this population appeared to be accurate.

On the ciprofloxacin arm, 4/7 subjects received additional anti-pseudomonal coverage (1 aztreonam and 3 aminoglycosides). 2/4 (50%) were clinical failures with persistence and persistence was also noted in 1 of 2 cures. Thus of the 4 patients with additional anti-pseudomonal coverage, 3 of 4 (75%) had persistence.

Of the remaining 3 patients, all were failures with persistence (100%). Thus on this arm of the study, the addition of an additional anti-pseudomonal agent did not appear to affect bacteriologic outcome. Resistance was not documented in these patients and the poor activity of ciprofloxacin versus *Pseudomonas aeruginosa* cannot be explained.

Bacteriologic Response in Subjects with *Staphylococcus aureus* at baseline:

8 MO evaluable trovafoxacin subjects and 6 evaluable ciprofloxacin subjects had *Staphylococcus aureus* at baseline.

The patients are listed below with source, commensal pathogens, and outcome:

Trovafoxacin (N= 8)

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- #51120053: Orotracheal aspirate: *Staphylococcus aureus*: Cure with eradication.
- #51190064: Sputum: *Staphylococcus aureus*: Failure with persistence.
- #51880192: Orotracheal aspirate: *Staphylococcus aureus*: Failure with persistence.
- #51910039: Bronchial lavage: *Staphylococcus aureus*: Failure with persistence.
- #52110136: Nasotracheal aspirate: *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Improvement with persistence.
- #53860249: Sputum: *Staphylococcus aureus*, *Klebsiella oxytoca*: Cure with eradication.
- #55110618: Bronchial lavage: *Staphylococcus aureus*, *Klebsiella oxytoca*, and *Pseudomonas aeruginosa*. Failure with persistence.
- #56230318: Orotracheal aspirate: *Staphylococcus aureus*: Cure with eradication. Also had sputum with *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*, both eradicated.

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Ciprofloxacin (N=6):

- #51190225: Nasotracheal aspirate: *Staphylococcus aureus*: Cure with eradication.
- #51730152: Blood: *Staphylococcus aureus*: Cure with eradication.
- #51740013: Sputum: *Staphylococcus aureus* and *Haemophilus parainfluenzae*: Cure with eradication.
- #51750163: Sputum: *Staphylococcus aureus*: Failure with persistence.
- #53860201: Sputum: *Staphylococcus aureus* and *Enterococcus faecalis*: Failure with persistence.
- #65430537: Sputum: *Staphylococcus aureus*: Cure with eradication.

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Failure with persistence was seen in 4/8 (50%) of the trovafloxacin patients. Additionally, 1 of 4 (25%) of the clinical cures was associated with persistence. Thus 5/8 (62.5%) of isolates were associated with persistence. Once again the development of resistance was not an issue and the MO could not explain the higher clinical failure rate associated with the high rate of bacteriologic persistence seen on this arm.

Staphylococcus aureus was the sole isolate in 4 specimens, none of which were obtained from the lower respiratory tree. In 3 of the 4 of these cases, there was failure with persistence. If one excluded all specimens except lavage specimens then the eradication rate would be 1/8, if however, one only accepted specimens where *Staphylococcus aureus* was the sole pathogen, independent of the source, the eradication rate changed to 3 of 4 or 75%.

On the ciprofloxacin arm, 4/6 subjects were clinical cures with eradication (100%). There were 2 failures and in both there was persistence. Thus, eradication was seen in 67% of the cases and always associated with clinical success.

Staphylococcus aureus was the sole isolate in 4 specimens, none of which were obtained from the lower respiratory tree. In 3 of the 4 of these cases, there was cure with eradication. If one excluded all specimens except lavage specimens then no isolates would have been considered evaluable. If however, one only accepted specimens where *Staphylococcus aureus* was the sole pathogen, independent of the source, the eradication rate changed to 3 of 4 or 75%.

There appeared to be a good clinical correlation between eradication rates and clinical outcome in this subgroup of patients.

Cross-Tabulation of Clinical Response and Pathogen Outcome at the EOS:

There were few cases of incompatibility between clinical response and pathogen outcome in this trial. Specifically, there were 6 cases of clinical failure with bacteriologic eradication on the ciprofloxacin arm and 2 cases on the trovafloxacin arm. There were no cases of success with persistence on the ciprofloxacin arm and 2 cases on the trovafloxacin arm.

In all cases, there was no more than 1 bacterial isolate associated with the incongruity.

On the ciprofloxacin arm, the 6 failures were associated with 1 each of *Citrobacter diversus*, *Enterobacter aerogenes*, *Escherichia coli*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*.

On the trovafloxacin arm, the 2 failures were associated with 1 each of *Proteus mirabilis* and *Escherichia coli*. The 2 successes were associated with 1 each of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

No meaningful conclusions could be drawn from this data.

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Safety Review:

121/127 (95%: 458 events) trovafloxacin-treated subjects and 111/137 (81%: 405 events) ciprofloxacin-treated subjects had at least one AE, (all causality). This study included the intravenous administration of study drug for at least 3 days and therefore there appeared to be a large number of events associated with the intravenous insertion site. Specifically, this type of event was seen in 29/127 (23%) of the trovafloxacin-treated subjects and 24/137 (18%) of the ciprofloxacin-treated subjects.

The percentage of subjects reporting at least 1 treatment-related adverse event was 22% (28/127: 42 events), on the trovafloxacin arm, and 17% (23/137: 30 events), on the ciprofloxacin arm.

The most commonly reported adverse events on the trovafloxacin arm were related to the gastrointestinal system with nausea being reported most frequently.

On the ciprofloxacin arm, the system most affected was the respiratory tract.

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

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Table 113.26
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Trovafloracin	Ciprofloracin
Number of Subjects Treated	127 (100%)	137 (100%)
Subject-Days of Exposure	1100	1364
Subjects With At Least One Event	121 (95%)	111 (81%)
Number of Adverse Events	485	405
Subjects with Serious Adverse Events	46 (36%)	38 (28%)
Subjects with Severe Adverse Events	46 (36%)	40 (29%)
Subjects Discontinued Due to Adverse Events	19 (15%)	10 (7%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	4 (3%)	1 (<1%)
Subjects Discontinued Due to Objective Test Findings	3 (2%)	2 (1%)
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

Table 113.27
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Trovafloracin	Ciprofloracin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	127 (100%)	137 (100%)
Subjects With At Least One Event	121 (95%)	111 (81%)
Subjects Discontinued due to Adverse Event	19 (15%)	10 (7%)
ADVERSE EVENTS BY BODY SYSTEM:		
Appl./Inj./Incision/Insertion Site	29 (23%)	24 (18%)
Autonomic Nervous	5 (4%)	6 (4%)
Cardiovascular	47 (37%)	42 (31%)
Centr. & Periph. Nerv.	30 (24%)	25 (18%)
Endocrine	1 (<1%)	2 (1%)
Gastrointestinal	61 (48%)	47 (34%)
General	30 (24%)	32 (23%)
Hematopoietic	8 (6%)	2 (1%)
Liver/Biliary	3 (2%)	0
Metabolic/Nutritional	6 (5%)	3 (2%)
Musculoskeletal	7 (6%)	5 (4%)
Neoplasms	3 (2%)	1 (<1%)
Other Adverse Events	9 (7%)	8 (6%)
Psychiatric	26 (20%)	20 (15%)
Reproductive	2 (2%)	2 (1%)
Respiratory	43 (34%)	47 (34%)
Skin/Appendages	26 (20%)	30 (22%)
Special Senses	1 (<1%)	6 (4%)
Urinary System	19 (15%)	13 (9%)

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Table 113.28
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Trovafloxacin	Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	127 (100%)	137 (100%)
Subjects With At Least One Event	28 (22%)	23 (17%)
Subjects Discontinued due to Adverse Event	5 (4%)	0
ADVERSE EVENTS BY BODY SYSTEM:		
Appl//Inj./Insertion/Incision/Site	6 (5%)	7 (5%)
Cardiovascular	5 (4%)	2 (1%)
Centr. & Periph. Nerv.	4 (3%)	2 (1%)
Gastrointestinal	11 (9%)	6 (4%)
General	4 (3%)	3 (2%)
Psychiatric	2 (2%)	0
Reproductive	1 (<1%)	0
Respiratory	0	6 (4%)
Skin/ Appendages	3 (2%)	3 (2%)
Special Senses	0	1 (<1%)

Further breakdown of the treatment-related events, indicated that 3 (7%) of the events on the trovafloxacin arm were severe in nature, as compared to 0 on the ciprofloxacin arm. The 3 severe events on the trovafloxacin arm, were from the central and peripheral nervous systems (2), one event each confusion and involuntary muscle contraction and one from the gastrointestinal tract, diarrhea.

Table 113.29
Most Common AEs/Treatment-Related All Treated Patients (as per the MO)

# of subjects with at least 1 event	Trovafloxacin		Ciprofloxacin	
	N = 127		N = 137	
	28 (22%)		23 (17%)	
Nervous system	4	(3%)	2	(1%)
Headache	2	(2%)	1	(<1%)
GI System	11	(9%)	6	(4%)
Nausea	6	(5%)	1	(<1%)
Diarrhea	2	(2%)	2	(1%)
Vomiting	2	(2%)	1	(<1%)
Appl./Inj./Incision/Insertion Site	6	(5%)	7	(5%)
Site Reaction	4	(3%)	3	(2%)
Site Complication	2	(2%)	1	(<1%)
Cardiovascular	5	(4%)	2	(1%)
Phlebitis	5	(4%)	2	(1%)
General	4	(3%)	3	(2%)
Moniliasis	3	(2%)	3	(2%)
Reproductive	1	(<1%)	0	0
Vaginitis	1	(<1%)	0	0
Respiratory	0	0	6	(4%)
Respiratory Tract Infection	0	0	4	(3%)

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Deaths:

Overall (ITT population), there were 35 deaths on the trovafloxacin arm and 38 on the ciprofloxacin arm during the study. 6 deaths on each arm occurred while receiving therapy and were considered unrelated to the study drug by the investigator. 25 deaths on the trovafloxacin arm and 29 on the ciprofloxacin arm occurred after therapy but during the study period and were also considered unrelated to the study drugs. An additional 4 subjects on the trovafloxacin arm and 3 on the ciprofloxacin arm died > 30 days after the last dose of the study drug and these deaths were also considered unrelated to the study drugs.

The subjects who died during the study are reviewed below:

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Trovafloxacin (N = 35):

- # 51060050: 85 YO male died on study day 57 of renal failure, metabolic acidosis, respiratory failure, and cardiopulmonary arrest. This death was not attributed to the study drug.
- #51190227: 79 YO male died on study day 25 of cardiomyopathy, COPD, and congestive heart failure. This death was not attributed to the study drug.
- #50300265: 91 YO male with a history of tongue cancer, died on study day 31 of progression of his disease. This death was not attributed to the study drug
- #51060049: 72 YO male died on study day 2 of Gram (-) sepsis and respiratory failure. This death was not attributed to the study drug
- #51120224: 89 YO died of respiratory failure on study day 8. Death was attributed to a pulmonary embolism.
- #51180070: 95 YO female died on study day 8 of respiratory failure attributed to natural causes.
- #51190064: 78 YO male died on study day 6 of pulmonary edema and congestive heart failure. This death was not attributed to the study drug.
- #51730151: 69 YO male died on study day 2 of pneumonia and respiratory failure. This death was not attributed to the study drug.
- #51740016: 61 YO male died approximately 3 months after the completion of the study, of cardio-pulmonary arrest secondary to underlying atrial fibrillation.
- #51740241: 93 YO female died on study day 34 of cardio-pulmonary arrest secondary to pneumonia. This death was not attributed to the study drug.
- #51750017: 85 YO male died on study day 5 of ventricular tachycardia and cardiopulmonary arrest secondary to nosocomial pneumonia. This death was not attributed to the study drug.
- #51750154: 90 YO female died on study day 15 of pneumonia. This death was not attributed to the study drug.
- #51750719: 95 YO female died on study day 12 of pneumonia. This death was not attributed to the study drug.
- #51880004: 41 YO male died on study day 3 secondary to complications of a fatal head injury.

- #51910038: 78 YO male died on study day 4 of pneumonia. This death was not attributed to the study drug.
- #51910194: 76 YO male died on study day 3 of complications related to underlying interstitial lung disease
- #52110781: 90 YO male died on study day 6 of aspiration pneumonia. This death was not attributed to the study drug.
- #52490159: 80 YO male died on study day 2 of pulmonary edema. This death was not attributed to the study drug.
- #54070351: 75 YO male died on study day 21 of CHF. This death was not attributed to the study drug.
- #54090346: 66 YO female died on study day 17 of complications of peritonitis.
- #54100341: 51 YO female died on study day 7 of complications of an underlying intraperitoneal malignancy.
- #54100363: 49 YO female died on study day 22 of complications related to esophageal cancer.
- #54830113: 84 YO male died on study day 6 of respiratory failure related to underlying COPD.
- #55110618: 76 YO female died on study day 5 of septic shock. This death was not attributed to the study drug.
- #55460090: 98 YO male died on study day 8 of pneumonia. This death was not attributed to the study drug.
- #56230322: 76 YO male died on study day 29 of a gastrointestinal hemorrhage.
- #56230323: 74 YO female died on study day 37 of valvular cardiomyopathy and multisystem failure.
- #56230682: 64 YO male died on study day 51 of respiratory arrest and hemorrhage.
- #56270301: 75 YO male died on study day 7 of complications related to an underlying malignancy.
- #58350319: 64 YO male died on study day 47 of multiorgan failure secondary to surgical intervention.
- #59840281: 77 YO female died on study day 12 of sepsis secondary to an abdominal abscess.
- #61270209: 74 YO male died on study day 8 of ARDS. This death was not attributed to the study drug.
- #61270785: 45 YO male died on study day 8 of complications of an underlying brain tumor.
- #64010534: 81 YO female died on study day 3 of CHF secondary to underlying coronary artery disease.
- #64040804: 80 YO female died on study day 6 of acute heart failure.

Medical Officer's Comment: *The MO detected no clear pattern in the deaths above that could be attributed to the alatrofloxacin/trovafloxacin regimen. Approximately 8 patients died of complications related to the disease under study, nosocomial pneumonia, and therefore could be classified as therapeutic failures. This number however, was not unexpected.*

Ciprofloxacin (N = 38):

- #50340165: 91 YO male died on study day 6 of septic shock associated with underlying rectal carcinoma.
- #51060051: 70 YO male died on study day 2 of respiratory arrest secondary to pneumonia. This death was not attributed to the study drug.
- #51110081: 48 YO male died on study day 69 of CHF.
- #51120055: 78 YO male died on study day 6 of respiratory arrest. This death was not attributed to the study drug but to underlying Shy-Drager syndrome.
- #51750014: 87 YO female died on study day 25 of pneumonia (aspiration). This death was not attributed to the study drug.
- #51740242: 85 YO male died on study day 13 of cardiopulmonary arrest secondary to the disease under study. This death was not attributed to the study drug.
- #51750046: 94 YO female died on study day 5 of pneumonia. This death was not attributed to the study drug.
- #51750163: 78 YO female died on study day 62 of cardiac arrest.
- #51880190: 57 YO female died on study day 26 of necrotizing fasciitis.
- #51910040: 71 YO female died on study day 21 of complications related to a pulmonary embolism.
- #51910193: 73 YO male died on study day 9 of heart failure.
- #51930029: 37 YO female died on study day 19 of respiratory arrest secondary to underlying metastatic cancer.
- #52110134: 73 YO male died on study day 3 of complications related to septic shock and anoxic brain damage.
- #52110782: 71 YO male died on study day 3 of complications related to a pneumothorax, related to underlying pneumonia. This death was not attributed to the study drug.
- #53860246: 74 YO male died on study day 2 of respiratory arrest. This death was not attributed to the study drug.
- #53860250: 86 YO female died on study day 16 of cardiac arrest secondary to a CVA.
- #54070349: 42 YO female died on study day 11 of ARDS. This death was not attributed to the study drug.
- #54090345: 72 YO male died on study day 17 of respiratory failure secondary to COPD.
- #54090347: 54 YO female died on study day 6 secondary to sepsis and pneumonia. This death was not attributed to the study drug.
- #54090359: 77 YO male died on study day 29 of complications of bladder carcinoma.

- #54100362: 77 YO female died on study day 20 of pneumonia. This death was not attributed to the study drug.
- #54100364: 87 YO male died on study day 11 of CHF.
- #54830256: 81 YO female died on study day 23 of urospepsis.
- #55110619: 59 YO male died on study day 15 of septic shock. Secondary to *Staphylococcus aureus*.
- #55460092: 78 YO male died on study day 16 of aspiration pneumonia. This death was not attributed to the study drug.
- #56230317: 74 YO male died on study day 18 of bilateral pneumonia. This death was not attributed to the study drug.
- #56230324: 74 YO male died on study day 33 of sepsis.
- #58350330: 73 YO male died on study day 37 of peritoneal carcinomatosis.
- #59030541: 79 YO male died on study day 57 of COPD.
- #59879258: 73 YO female died on study day 32 of CHF.
- #61270211: 66 YO male died on study day 27 of lymphoma.
- #61270786: 66 YO female died on study day 15 of ARDS and pneumonia. This death was not attributed to the study drug.
- #63670745: 79 YO male died on study day 25 of multisystem organ failure.
- #63670746: 63 YO female died on study day 4 of pneumonia. This death was not attributed to the study drug.
- #63760709: 83 YO female died on study day 8 of pneumonia. This death was not attributed to the study drug.
- #64040803: 85 YO female died on study day 2 of acute heart failure.
- #64550789: 89 YO male died on study day 6 of pneumonia. This death was not attributed to the study drug.
- #65430810: 75 YO male died on study day 18 of acute heart failure.

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Medical Officer's Comment: *As on the trovafloxacin arm, the causes and number of deaths was not unexpected. Approximately 14 of the deaths appeared to be directly related to a pneumonia and occurred in the early days of the study.*

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Other Serious Adverse Events Related to the Study Drug:

2 patients from each treatment group had other serious adverse events which were related to the study drug. These are reviewed below:

Trovafloxacin (N = 2):

- #51110083: multifocal myoclonus in an 84 YO male with a history for renal failure, atrial fibrillation, CHF, and bilateral pleural effusions. The event occurred on study day 2 and resolved despite continuation of study drug.
- #53860208: respiratory failure in an 80 YO male on study day 4. This was 2 days after study drug was discontinued. Additionally, the patient developed recurrent pneumonia on study day 28 and this event was classified as being related to the study drug. The patient was hospitalized, and the event resolved.

Ciprofloxacin (N = 2)

- #51730150: atrial fibrillation on study day 6 requiring hospitalization. Event resolved and was attributed to underlying CHF. On study day 21, 9 days post-therapy, the patient developed worsening pneumonia attributed to the study drug. The patient was hospitalized, and the pneumonia resolved.
- #51750163: worsening pneumonia, possible deep vein thrombosis on day 29. Attributed by the investigator to the study drug. Both resolved with hospitalization. Also urosperis on day 43 with failure to thrive, attributed to the study drug and culminating in death.

Medical Officer's Comment: The MO did not find any untoward events that could be definitively attributed to either study drug. Interestingly, there were no complaints of dizziness in this non-ambulatory population.

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Clinical Laboratory Abnormalities:

2 subjects, one on each arm, were discontinued from study drug due to laboratory abnormalities. The MO copied the sponsor's narratives of these patients below:

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Subject 5174-0241 Alatrofloxacin/Trovafloxacin

This subject, a 93 year-old white female with a history of congestive heart failure and impaired renal function and a primary diagnosis of nosocomial pneumonia, was treated with intravenous alatrofloxacin 300 mg for ten days. The subject had SGOT and SGPT values that were within the normal ranges at baseline. On Day 7, the subject was discontinued due to increased SGOT and SGPT values that were above the normal range. On Day 14, the subject's SGOT and SGPT values had decreased, however, the SGPT value was still above the normal range. On Day 30, both the SGOT and SGPT values were within the normal range.

	<u>SGOT (U/L)</u>	<u>SGPT (U/L)</u>
Baseline		
Day 7		
Day 14		
Day 30		
Normal Range		

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Medical Officer's Comment: *The MO agreed that there did not appear to be any other cause for this patient's increased LFTs. As noted in previous studies, these elevations do occur sporadically with shorter course of therapy, although consistently when the duration of therapy is prolonged (21 days).*

Subject 5386-0198 Ciprofloxacin

This subject, a 56 year-old white male with a history of coronary artery disease, hyperlipidemia, and hypertension and a primary diagnosis of nosocomial pneumonia, was treated with intravenous ciprofloxacin 400 mg for four days and oral ciprofloxacin 750 mg BID for three days. The subject had SGOT and SGPT values that were above the normal range at baseline. On Day 5, the subject's SGOT and SGPT values increased further above the normal range. On Day 17, the SGOT and SGPT values had decreased, however, the SGPT value was still above the normal range.

	<u>SGOT (U/L)</u>	<u>SGPT (U/L)</u>
Baseline		
Day 5		
Day 17		
Normal Range		

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Medical Officer's Comment: *Once again the MO determined no other cause for this increase.*

Other than the above, SGOT elevations were found in 7 (6%) of the trovafloxacin-treated subjects and 6 (5%) of the ciprofloxacin-treated subjects. SGPT elevations were found in 9 (8%) of the trovafloxacin-treated subjects and 7 (6%) of the ciprofloxacin treated subjects. All of these events resolved post-therapy.

Additionally, 9 (8%) of the trovafloxacin-treated subjects and 6 (5%) of the ciprofloxacin-treated subjects had increased serum creatinine values. The MO did not discern any patterns or find the above unusual for this much iller population that that seen in previous trials.

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Conclusions:

As per the Sponsor: Alatrofloxacin (300 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for a total treatment duration of 10 to 14 days and intravenous ciprofloxacin (400 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (750 mg twice daily) for a total treatment duration of 10 to 14 days were comparable for the sponsor-defined clinical success rate at the end of treatment for both intent-to-treat and evaluable

subjects. (EOT: 68/88 (77%) trovafloxacin versus 79/101 (78%) ciprofloxacin and EOS: 50/72 (69%) trovafloxacin versus 54/79 (68% ciprofloxacin: clinically evaluable population).

Sponsor-defined pathogen eradication rates for many of the most commonly isolated pathogens were comparable among bacteriologically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups at the end of treatment and end of study isolated at baseline. Of the 15 evaluable alatrofloxacin/trovafloxacin subjects and 11 ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, six alatrofloxacin/trovafloxacin (40%) and four ciprofloxacin (36%) received optional aztreonam therapy (dual therapy). There appeared to be no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy in sponsor-defined clinical response at end of treatment or end of study, however, due to the small number of subjects no definitive conclusions could be drawn.

The percentage of subjects discontinued from treatment due to adverse events was 15% in the alatrofloxacin/trovafloxacin group and 7% in the ciprofloxacin group. Five (5) subjects in the alatrofloxacin/trovafloxacin group and no subjects in the ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all and treatment-related adverse events was 95% and 22%, respectively, for subjects in the alatrofloxacin/trovafloxacin group and 81% and 17%, respectively, for subjects in the ciprofloxacin group. The most commonly reported treatment-related adverse event was nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and respiratory tract infection (3%) for subjects in the ciprofloxacin group.

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As per the Reviewer:

The MO's results were comparable to those of the sponsor, as were the clinically evaluable populations. The MO agreed with the sponsor's determinations of outcome, overall, in this trial, and thus accepted all of these determinations as well as those determinations applying to evaluability. The only differences were in the time of the application of the TOC, i.e. MO at EOS as opposed to sponsor TOC at the EOT, and in the MO's exclusion of "cures" who received less than 80% of the prescribed regimen.

Specifically as to the appropriate duration of therapy, most cases of true nosocomial pneumonia require 10-14 days of antimicrobial therapy if not 21, as is common in the general practice of medicine. The MO was reluctant therefore to accept a regimen of less than 8 days of therapy, this led to the ultimate exclusion of 4 patients, 2 from each arm.

The MO's evaluable population consisted of 70 patients on the trovafloxacin arm and 77 on the ciprofloxacin arm. The demographic characteristics of the 2 populations were very similar in terms of age, weight, sex, smoking status, and severity of illness.

At the EOS, the MO found a clinical success rate of 48/70 (68.6%) trovafloxacin versus 52/77 (67.5%) ciprofloxacin. These results revealed equivalence when a 95 % CI was applied, and were very similar to the sponsor's results. The MO's results differed from those of the sponsor at the EOT (Sponsor: 77% trovafloxacin versus 78% ciprofloxacin; MO: 71.4% trovafloxacin versus 70.1% ciprofloxacin), in that the sponsor's was 7% higher at the EOT for their clinically evaluable population with a 10 percentage point relapse rate at the EOS. This is compared to the MO's results, which revealed a much smaller "relapse/failure" rate between the EOT and the EOS.

For all subgroups analyzed, including patients with mild/moderate disease (EOS: success rate trovafloxacin 38/50 (76%) versus ciprofloxacin 39/53 (75%), patients with severe disease (EOS: success rate trovafloxacin 10/20 (50%) versus ciprofloxacin 13/25 (52%), patients requiring mechanical ventilation (EOS: success rate trovafloxacin 10/18 (55.6%) versus ciprofloxacin 8/16 (50%), and patients who were both clinically and bacteriologically evaluable (EOS: success rate trovafloxacin 23/37 (62.2%) versus ciprofloxacin 23/36 (63.9%), the MO found results comparable with those found by the sponsor in similar analyses. The MO ascertained that the effectiveness of trovafloxacin was equivalent to that of

ciprofloxacin in patients with mild/moderate disease and that it was numerically comparable if not equal for the other subgroups. As in the sponsor's analysis, the MO also found that those patients with mild/moderate disease had a higher clinical success rate by an almost 20 percentage point difference compared to those with severe disease.

Overall pathogen eradication rates were comparable between the 2 arms at 42/59 (71.2%) trovafloxacin versus 33/55 (66%) ciprofloxacin. This included all organisms designated as pathogens by the sponsor. Overall rates only for the requested pathogens were 23/35 (65.7%) trovafloxacin versus 18/29 (62.5%) ciprofloxacin. The MO determined that all of the above rates were comparable although, when an overall rate was utilized, it appeared that the MO's rate was more valid in terms of it's being representative of true pathogens without any contaminants.

Pathogen eradication rates based on follow-up cultures for those requested in labeling were as follows:

Trovafloxacin:

Haemophilus influenzae: 5/6 (83%)
Escherichia coli: 3/4 (75%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 3/8 (37.5%)
Pseudomonas aeruginosa: 10/13 (76.9%)

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Ciprofloxacin:

Haemophilus influenzae: 7/7 (100%)
Escherichia coli: 5/5 (100%)
Klebsiella pneumoniae: 1/4 (25%)
Staphylococcus aureus: 4/6 (67%)
Pseudomonas aeruginosa: 1/7 (14.3%)

The MO determined that the 2 agents were numerically comparable in their eradication of *Haemophilus influenzae* and that the numbers of evaluable *Escherichia coli* and *Klebsiella pneumoniae* isolates were too small to be able to draw any valid conclusions. Additionally, trovafloxacin appeared superior to ciprofloxacin in the eradication of *Pseudomonas aeruginosa*. Trovafloxacin's activity versus *Staphylococcus aureus* appeared inferior to that of ciprofloxacin but again the number of isolates was small.

The MO agreed with the sponsor's statement that "additional anti-pseudomonal coverage may be helpful in the eradication of *Pseudomonas aeruginosa* in this population."

As the primary efficacy variable was clinical response at the EOS, the MO elected to utilize clinical response by pathogen as the primary determinant of microbiologic efficacy. It should be noted that bacterial eradication rates were often presumptively assigned according to the clinical outcome and not based on culture results because follow-up cultures cannot always be obtained or they may contain of bacteria of uncertain significance, i.e. contaminants versus pathogens. Below are the clinical response rates by pathogen, for those organisms requested by the sponsor:

Trovafloxacin:

Haemophilus influenzae: 5/6 (83.3%)
Escherichia coli: 3/6 (50%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 4/6 (50%)
Pseudomonas aeruginosa: 8/13 (62%)

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Ciprofloxacin:

Haemophilus influenzae: 6/7 (86%)
Escherichia coli: 4/5 (80%)
Klebsiella pneumoniae: 1/5 (20%)
Staphylococcus aureus: 4/6 (67%)
Pseudomonas aeruginosa: 1/7 (53.5%)

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From the above it is evident that success rates were comparable in those patients with *Haemophilus influenzae* at baseline. With regards to *Escherichia coli*, trovafloxacin was numerically inferior to ciprofloxacin and the opposite was true with regards to *Klebsiella pneumoniae*. Response rates were not radically different for patients with *Pseudomonas aeruginosa* and *Staphylococcus aureus* at baseline, with ciprofloxacin numerically superior to trovafloxacin in patients with *Staphylococcus aureus* and trovafloxacin superior to ciprofloxacin in patients with *Pseudomonas aeruginosa*.

From the safety review, the MO found that overall mortality was similar in both arms of the study and that causes of death were similar on both arms. There were fewer to no episodes of dizziness or headache in this population of non-ambulatory patients as compared to the previously reviewed indications. Nausea was the most common AE seen in the trovafloxacin-treated patients as compared to respiratory events in the ciprofloxacin patients.

There were a similar number of patients on each arm with LFT and/or creatinine elevations and a single patient on each arm where these were determined to be severe. The elevations returned to normal in both instances.

The MO concluded that trovafloxacin was equivalent to ciprofloxacin 400 mg IV q12h in the treatment of nosocomial pneumonia and further that no safety issues were identified in the review of this single pivotal study.

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Study 154-137:**TITLE:**

Randomized, multicenter, open trial comparing intravenous alatrofloxacin followed by oral trovafloxacin with intravenous ceftazidime followed by oral ciprofloxacin with optional gentamicin and vancomycin for the treatment of nosocomial pneumonia.

Study Dates: September 6, 1995 - August 21, 1996

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Objective: The objective of this Phase III, open study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin (with optional vancomycin) compared to intravenous ceftazidime followed by oral ciprofloxacin (with optional vancomycin, gentamicin, clindamycin, and/or metronidazole), for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

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List of Principal Investigators:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
France	5414	Jean-Francois Muir, MD
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	5955	Laurent Holzapfel, MD
	5956	Pierre Zuck, MD
	5957	Jean Marty, MD
	5958	Jean Louis Pourriat, MD
	5961	Jean Michel Coulaud, MD
	5962	Christian Brambilla, MD
5963	Pierre-Yves Lallement, MD	
Australia	5935	Michael Whitby, MD
	5936	Brent Richards, MD
	5937	Peter James McDonald, MD
	5940	Anthony Bell, MD
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	5945	David Barrie McGeachie, MD
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	5978	Thomas Henneberg, MD
	5979	Claudia Spies, MD
	6342	Friedrich Eckart Isemer, MD
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	5924	Mervyn Singer, MD
	5926	Christopher Andrews, MD
	5930	Pushpinder Singh Mangat, MD
Canada	5795	Doria Grimard, MD
	5800	Gordon Ford, MD
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	6072	George Pylupchuk, MD
	6073	Ronald Grossman, MD
	6075	Irving Salit, MD
Belgium	5437	Jean-Louis Vincent, MD
	5964	Michel Staroukine, MD
	5966	M. DeHovre, MD
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	5973	Raymond Zakhia, MD
Finland	5952	Esa Rintala, MD
Greece	5871	Harry Bassaris, MD
Italy	6357	Tommaso Todisco, MD
	6557	Miele Nazareno, MD
	6569	Paolo Battocchi, MD

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Study Design: Study 154-137 was a randomized, open, comparative, multicenter trial (conducted at non-US sites only), of alatrofloxacin administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (to complete 10 to 14 days of total treatment), versus intravenous ceftazidime administered for 2 to 7 days followed by oral ciprofloxacin (to complete 10 to 14 days of total treatment), for the treatment of nosocomial pneumonia requiring initial intravenous therapy. In subjects unable to tolerate oral medication (intubated patients), the total duration of intravenous therapy could have been extended to 14 days. In addition, in subjects with documented methicillin-resistant *Staphylococcus aureus*, vancomycin may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added to the ceftazidime/ciprofloxacin treatment regimen only. For subjects with documented *Pseudomonas* infection, gentamicin may have been added to the ceftazidime/ciprofloxacin treatment regimen. Although not originally specified by protocol, subjects in the alatrofloxacin/trovafloxacin group with documented *Pseudomonas aeruginosa* at baseline who were subsequently treated with gentamicin were considered evaluable for efficacy by the sponsor.

Protocol Overview:

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Copied below from the electronic submission, appendix A of the original protocol is the sponsor's schedule of visits and procedures:

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SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number Study day: Allowable Window	1 Day 1 (-24 hours)	2 Day 4 (Day 3-7)	3 Day 14 (Day 12-16)	4 Day 30 (Day 28-35)
Treatment Period	Day 1 to Day 10 to Day 14		Day 15 to Day 35	
Follow-up period				
Informed consent	X			
Demographic Information	X			
Targeted Physical Exam	X			
APACHE II Score	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Dosing Record		X	X	
Clinical Signs & Symptoms	X	X	X	X
Chest X-ray	X		X	abn
Microbiology				
sputum Gram stain	X	X	X	X2
culture & sensitivity	X	X	X	X2
blood culture	X	X3	X4	
Serology	X			X
Safety laboratory tests				
haematology	X	X	X	abn
biochemistry	X	X	X	abn
urinalysis	X		X	abn
Pregnancy test1	X			
Adverse events				
routine events		X	X	X
serious adverse events		X	X	X
Investigator's assessment of clinical response5			X	X

abn = abnormal at previous visit or clinically significant adverse event
 1 to be done by local site for women of child bearing potential
 2 to be done if clinically indicated
 3 to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure
 4 to be done if a positive culture was obtained at visit 2.
 5 to be done at the time of discontinuation, if applicable

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As can be appreciated from the above schedule, at the baseline assessment (Visit 1, Day 1), all subjects were to have had a medical history and clinical and radiological findings consistent with nosocomial pneumonia, requiring initial intravenous therapy, acquired at least 48 hours after a hospitalization for reasons other than respiratory infection. Nonambulatory institutionalized (nursing home) subjects who were admitted to a hospital for suspected gram negative pneumonia were also eligible for enrollment.

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The following characteristics were to have been present:

- New infiltrate(s) on chest x-ray;

and

- At least one of the following

- Cough or increasing severity of coughing.
- Acute changes in the quality of sputum.
- Body temperature $>38^{\circ}\text{C}$ (100.4°F) or $<36.1^{\circ}\text{C}$ (97°F).
- Auscultatory findings such as rales or evidence of pulmonary consolidation.
- Leukocytosis (blood leukocyte count $>10,000/\text{mm}^3$ or $>15\%$ bands).

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All patients who met the clinical diagnosis of NP at V1 and who gave informed consent and met all additional inclusion criteria and none of the exclusion criteria were eligible for randomization.

V1 assessments included collection of demographic information, medical history and physical examination (including APACHE II score), concomitant medication use, antibiotic therapy within the last 7 days, and vital signs (pulse, respiration, blood pressure, and temperature). The illness leading to the patient's hospitalization was recorded as well as the type of NP the patient had (post-surgical, suspected aspiration, occurring in a mechanically ventilated subject, or other causes). Clinical assessment of signs and symptoms of nosocomial pneumonia included sputum characteristics, cough, dyspnea, chills/rigors, pleuritic chest pain, lung sounds, and chest X-ray (PA and lateral views). In addition, a standard panel of blood (including culture), and urine tests were performed. Initial serology testing for evidence of infection with *Legionella spp.* was performed. Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per low power field [LPF], squamous epithelial cells per LPF) of sputum were performed. If a satisfactory specimen could not be obtained the investigator could have induced sputum with nebulised saline solution or physiotherapy. If this technique was unsuccessful the investigator could have used such techniques as transtracheal aspiration, bronchial brushings or biopsy material obtained by bronchoscopy.

Susceptibility to the study drugs, trovafloxacin, ciprofloxacin, and ceftazidime was determined for all potentially significant organisms isolated from respiratory specimens, that were considered adequate. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. If no pathogen was detected on baseline culture or if a pathogen was resistant to study medication, study therapy could continue, at the discretion of the investigator.

At Visit 2 (V2: Day 3 to 7), a patient's need for continued intravenous therapy was assessed, (daily from study day 3 to 7). Subjects were switched to oral therapy if the following situations applied:

- resolution of fever;
- improvement of symptoms;
- no progression of x-ray changes.

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Efficacy observations were performed during this visit, including clinical assessment of signs and symptoms of nosocomial pneumonia to assess response to study therapy; bacteriologic response was assessed through respiratory samples. Blood cultures were repeated only if they had been positive at the previous visit. In addition to efficacy observations, safety was assessed through recording of concomitant medications, vital signs, study drug dosing, adverse events, and laboratory (hematology and biochemistry), evaluations.

At Visit 3 (V3: Day 14; EOT) efficacy observations were performed including clinical assessment of signs and symptoms of nosocomial pneumonia to assess response to study therapy; bacteriologic response was assessed through respiratory samples. Blood cultures were repeated only if they had been positive at the previous visit; a chest X-ray was also performed. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory (hematology, biochemistry, and urinalysis), evaluations. The investigators provided an evaluation of clinical response.

At Visit 4 (V4: Day 30; EOS), efficacy observations were performed including clinical assessment of signs and symptoms of nosocomial pneumonia to assess response to study therapy; bacteriologic response was assessed through respiratory samples. Blood cultures were repeated only if they had been positive at the previous visit. If the V3 CxR had not resolved to the subject's baseline, a final X-ray was done at this visit. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, and adverse events. Laboratory evaluations were performed if a clinically significant abnormality was present as V3 or if the subject was experiencing a clinically significant adverse event. A final serology was performed and the investigators provided a final evaluation of clinical response.

Medical Officer's Comment: *Study 154-137 was identical to study 113 with the exception that this was an open study and that the intravenous comparator agent was ceftazidime and not ciprofloxacin. Additionally, additional anti-pseudomonal coverage was provided with gentamicin instead of aztreonam. The MO elected to present only those details specific to this study in the ensuing review and to refer back to the introduction of the MOR for the general details.*

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Compliance:

This study was conducted in compliance with local or central Institutional Review Board (IRB) and informed consent regulations.

Concomitant Illnesses and Medications:

Please see MOR of study 154-113, page 392, for the MO's comment.

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Discontinuation of Study Therapy:

Please see MOR of study 154-113, page 392.

Protocol Amendments:

The protocol was amended twice. Once, on June 14, 1995 for the Australian centers only, to reflect the addition to the exclusion criteria of the exclusion of all patients on chronic immunosuppressive therapy including those patients on > 10 mg/day of systemic corticosteroids. Additionally excluded were patients with moderate to severe hepatic or renal dysfunction and patients on concomitant theophylline or warfarin, unless monitored closely. The schedule of visits was amended to reflect the monitoring of all laboratory parameters every 72 hours while on alatrofloxacin and every 7 days while receiving trovafloxacin.

The second amendment on December 15, 1995 applied to all centers and reflected the ability to add clindamycin or metronidazole to the ceftazidime/ciprofloxacin arm of the study in patients with suspected anaerobic infections, the extension of the duration of treatment to 14 days, a standardized dose reduction regimen for patients on ceftazidime and ciprofloxacin who had renal dysfunction, the addition of the APACHE scoring system for all patients at V1, and the application of a 95% CI and p-values as a method for comparison of efficacy.

Precautions:

Please see MOR of study 154-113, page 393.

Study Population:

It was expected that up to 320 subjects were to be randomized to one of two treatment groups, with each center enrolling approximately 8 subjects.

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Inclusion and Exclusion Criteria:

Medical Officer's Comment: *The criteria were the same as those used in study 154-113. For MO comment, please see page 394 of the MOR.*

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Randomization and Blinding:

Medical Officer's Comment: *Please see MOR page 394. This study was unblinded.*

Dosage Form and Administration (Copied from pages 21 and 22 of the study report):

Study drug medication was not blinded. Intravenous alatrofloxacin (equivalent to 300 mg trovafloxacin) for intravenous administration was provided in vials of 5 mg/mL (100 mg/20 mL) to be diluted to 1.5 mg/mL with 5% dextrose (D5W). Intravenous ceftazidime was provided in vials containing 2 g to be diluted in 50 mL sodium chloride intravenous infusion.

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Subjects received one of the following intravenous treatment regimens:

Alatrofloxacin 300 mg in 200 mL of D5W administered as a 60-minute infusion once daily in the morning (3 x 100 mg vials).

Ceftazidime 2 g in 50 mL sodium chloride for intravenous infusion administered twice daily as a 30-minute infusion.

Subjects unable to tolerate oral medication (e.g., ventilated subjects) or subjects with severe nosocomial pneumonias at baseline, defined as bacteremia or requiring mechanical ventilation or high fractional O₂ (>35% to maintain PO₂ at >60), may have received up to a total of 14 days of intravenous therapy.

When the investigator had determined a subject's resolution of fever with an improvement of symptoms and no new X-ray findings, the subject was switched from intravenous to oral therapy. Study drug for oral administration was in the form of trovafloxacin tablets and ciprofloxacin tablets and was packaged in blister packs. After 2 to 7 days of intravenous treatment with randomized study medication subjects received one of the following treatments orally:

Trovafloxacin 200 mg/day as a single active dose (2 x 100 mg tablet) administered in the morning.

Ciprofloxacin 1500 mg/day in two equally divided doses (1 x 750 mg tablet) once in the morning and once in the evening.

Subjects were to receive the appropriate oral therapy to complete a total maximum treatment duration of 10 to 14 days.

Subjects with *Pseudomonas* infection, methicillin-resistant *Staphylococcus aureus*, and/or anaerobic infection may have received optional antibiotic therapy, as follows:

Optional gentamicin

For subjects with documented *Pseudomonas* infection at baseline, treatment with open-label gentamicin, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in the ceftazidime/ciprofloxacin regimen. Treatment with gentamicin was to continue for a maximum of 14 days.

Optional Vancomycin

For subjects with documented methicillin-resistant *Staphylococcus aureus* infection at baseline, treatment with open-label vancomycin, at medically appropriate and approved doses, was to be initiated within 3 days of the start of study treatment for subjects in either treatment regimen. Treatment with vancomycin was to continue for a maximum of 14 days.

Optional Clindamycin / Metronidazole

For subjects randomized to ceftazidime/ciprofloxacin who had suspected anaerobic nosocomial pneumonia at baseline, treatment with clindamycin or metronidazole, at medically appropriate and approved doses was to be initiated for a maximum of 14 days.

In renally impaired subjects (creatinine clearance ≤ 50 mL/min/1.73 m²) the dosages of both ceftazidime and ciprofloxacin required adjustment. If during the study the estimated creatinine clearance dropped below 5 mL/min/1.73 m² (Cockcroft-Gault equation; Appendix G - Protocol) the subject was to be withdrawn from treatment.

At intervals during treatment or at the time of premature discontinuation of study therapy, appropriate entries for tablets taken and returned were completed on the case report form (CRF) and the Pfizer Drug Inventory Record (PDIR). If doses were missed, the reason was to be recorded on the CRF.

Medical Officer's Comment: *With the exception that this study was unblinded, the overall design is the same as in study 154-113. The addition of concomitant antimicrobials was pathogen driven and was allowed only when a culture result was available.*

Compliance: Please see the MOR page 395.

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Microbiologic Methods:

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 24 of the study report)

Criteria	Trovafoxacin		Ciprofloxacin		Ceftazidime	
	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) (5 μg Disk)	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) 5 μg Disk	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) 30 μg Disk
Susceptible	≤ 2	≥ 15	≤ 2	≥ 15	≤ 8	≥ 18
Intermediate	4		4			
Resistant	≥ 8	≤ 10	≥ 8	≤ 10	≥ 32	≤ 14

Note: Trovafoxacin 5 μg disks were never approved for clinical trial use and were subsequently replaced with 10 μg disks. Results using the 10 μg disks were not available during the study report period.

Susceptibility breakpoints for trovafoxacin were tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. MIC and zone diameter (mm) for ciprofloxacin and ceftazidime are based on NCCLS criteria.

Clinical and Bacteriological Response:

Please see the MOR page 396.

Safety Assessments, Adverse Events, Clinical Laboratory Tests:

Please the MOR page 397.

Data Analysis:

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Please see the introduction to the MOR, page 382 for an overview of the sponsor's subsets.

Clinical Evaluability Criteria:

See the introduction to the MOR, page 383, for a review of the sponsor's criteria and the MO's comments.

Criteria for Bacteriological Evaluability:

See the introduction to the MOR, page 383, for a review of the sponsor's criteria and the MO's comments.

Primary and Secondary Endpoints for Efficacy:

See the introduction to the MOR, page 383, for a review of the sponsor's endpoints and the MO's comments.

Definitions of Response:

See the introduction to the MOR, page 383, for a review of the sponsor's definitions and the MO's comments.

Interim Analyses:

No interim analyses were performed.

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Demographics:

As per the sponsor, 275 patients signed consent, 2 of these however, were withdrawn prior to randomization because they did not meet the study entry criteria. Thus 272 subjects were randomized and treated (135/274 (49.2%) to receive alatrofloxacin/trovafloxacin and 140/272 (51.8%) to receive ceftazidime/ciprofloxacin). All randomized subjects received treatment. (Total treated = 272).

The MO has recreated sponsor's Table 1.1, the Disposition of Enrolled subjects.

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**Table 137.1
Subject Disposition, All Enrolled Patients (As per the Sponsor)**

	274 2	Alatro/Trovafloxacin 300 mg → 200 mg	Ceftazidime/Ciprofloxacin 2 gm bid → 750 mg bid
Subjects with Signed Consent	274		
Withdrawn Prior to Randomization	2		
Randomized		135	140
Randomized, But Not Treated		0	0
All Treated Subjects		135 (100%)	140 (100%)
Withdrawn During Treatment		47 (35%)	39 (28%)
Completed Treatment		88 (65%)	101 (72%)
Withdrawn During Follow-up		17 (13%)	22 (16%)
Completed Study		86 (64%)	89 (64%)
Completed Treatment and Study		71 (53%)	79 (56%)
Withdrawn During Treatment and Study		32 (24%)	29 (21%)

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Medical Officer's Comment:

The MO realized that 135 + 140 = 275 randomized patients instead of 272 as stated by the sponsor. The MO queried the sponsor as to this discrepancy on 10/9/97. The sponsor provided a written response on 10/24/97. They stated that there were 274 subjects with signed consent of which 2 were withdrawn. Therefore there were 272 subjects randomized with signed consent but there were also 3 subjects randomized who did not sign consent. Thus there were 275 randomized subjects.

There were a larger number of patients withdrawn during treatment on the trovafloxacin arm as compared to the ciprofloxacin arm. 19/47 (14%) of the discontinuation on the trovafloxacin arm were considered related to the study drug and included 7 withdrawals (5%) for an AE, 11 for an insufficient response (8%), and 1 because of a laboratory abnormality. 28/47 discontinuations on this arm were considered unrelated to the study drug and included 8 withdrawals because of an AE, 9 deaths, 5 "other", 1 protocol violation, 1 did not meet randomization criteria, and 4 laboratory abnormalities.

On the ceftazidime/ciprofloxacin arm, 16/39 discontinuations from treatment (11%) were considered related to the study drug. 15 of these were due to insufficient response and 1 to an adverse event. Of the 23/39 discontinuations unrelated to ceftazidime/ciprofloxacin therapy, 4 were due to an AE, 2 patients did not meet randomization criteria, 3 "other," 12 deaths, and 2 laboratory abnormalities.

Of the 53 trovafloxacin patients withdrawn from treatment, 15/47 completed the study as compared to 10/39 of the ceftazidime/ciprofloxacin patients.

Discontinuation from treatment or the study had no predetermined effect on evaluability. Evaluability was determined solely by the previously described criteria.

Copied below is the sponsor's table of all randomized patients and the study evaluation groups:

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Table 137.2
Study Evaluation Groups/All Randomized Patients as per the Sponsor (Modified by MO)

	Alatro/Trovafloxacin	Ceftazidime/Ciprofloxacin
All Randomized Subjects	135 (100%)	140 (100%)
All Treated Subjects	135 (100%)	140 (100%)
Subjects with Inappropriate Baseline Diagnosis	3 (2%)	1 (<1%)
Clinically Intent- to- Treat Subjects	132 (98%)	139 (>99%)
Subjects with Negative Baseline Culture	66 (49%)	58 (41%)
Bacteriologically ITT Subjects	66 (49%)	81 (58%)
Clinically Evaluable Subjects	103 (76%)	109 (78%)
Clinically evaluable with baseline pathogen	53 (39%)	66 (47%)
Clinically Not Evaluable Subjects	29 (21%)	30 (21%)
Insufficient Therapy	21 (16%)	11 (8%)
No post-baseline clinical assessment	18 (13%)	16 (11%)
Prior Antibiotic therapy	0	0
Concomitant Antibiotic therapy	3 (2%)	7 (5%)
No post-baseline clinical assessment in evaluable analysis window	18 (13%)	16 (11%)
Other	3 (2%)	6 (4%)
Clinically evaluable at EOS	85 (63%)	89 (64%)
Clinically evaluable at EOS with baseline pathogen	42 (31%)	56 (40%)
Bacteriologically Evaluable Subjects	52 (39%)	66 (47%)
Bacteriologically Not Evaluable Subjects	51 (38%)	43 (31%)
No Baseline Pathogen	50 (37%)	43 (31%)
No post-baseline cultures or outside window	1 (<1%)	2 (1%)
Bacteriologically Evaluable at EOS	41 (30%)	55 (39%)
Baseline Blood Cultures Performed	126 (93%)	132 (94%)
Analyzed for Safety		
Adverse Events	135 (100%)	140 (100%)
Laboratory Data	119 (88%)	124 (89%)

* Subjects may have had more than one reason to have been unevaluable

Medical Officer's Comment: From table 137.2, it can be appreciated that on the alatrofloxacin/trovafloxacin arm there were 29/132 (21.9%) randomized and treated subjects with an appropriate baseline diagnosis who were clinically unevaluable at the EOT and an additional 18/132 (13.6%) clinically unevaluable at the EOS, thus there were a total of 47/132 (35.6%) that were clinically unevaluable.

On the ceftazidime/ciprofloxacin arm, there were 30/139(21.5%) randomized and treated subjects with an appropriate baseline diagnosis, who were clinically unevaluable at the EOT and an additional 20/139 (14.3%) subjects clinically unevaluable at the EOS. Thus, on the ceftazidime/ciprofloxacin arm there were 50/139 (35.9%) subjects who were clinically unevaluable.

Additionally, the bacteriologically evaluable population was a subset of the clinically evaluable and the bacteriological ITT population, which are both subsets of the clinical ITT population.

Copied and modified below is sponsor's Table 1.3 from the Esub, which depicts the number of subjects randomized and treated by center.

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Table 137.3
Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor)

Center	Total Randomized N = 275 (100%)		Alatrofloxacin/Trovafloxacin				Ceftazidime/Ciprofloxacin			
			Randomized and Treated N = 135 (100%)		Randomized and Treated N = 135 (100%)		Randomized and Treated N = 140 (100%)		Randomized and Treated N = 140 (100%)	
5414	12	4.3	6	4.4	6	4.4	6	4.9	6	4.9
5437	1	0.3	0	-	0	-	1	0.7	1	0.7
5439	5	1.8	2	1.9	2	1.9	3	2.5	3	2.5
5795	1	0.3	1	0.7	1	0.7	0	-	0	-
5800	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5869	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5871	40	14.5	20	14.8	20	14.8	20	14.9	20	14.9
5877	14	5.0	8	5.9	8	5.9	6	4.9	6	4.9
5924	12	4.3	6	4.4	6	4.4	6	4.9	6	4.9
5926	21	7.6	11	8.1	11	8.1	10	7.5	10	7.5
5930	1	0.3	0	-	0	-	1	0.7	1	0.7
5935	6	2.4	2	1.9	2	1.9	4	2.8	4	2.8
5936	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5937	2	0.7	0	-	0	-	2	1.4	2	1.4
5940	1	0.3	1	0.7	1	0.7	0	-	0	-
5942	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5945	5	1.8	2	1.9	2	1.9	3	2.5	3	2.5
5948	3	1.0	2	1.9	2	1.9	1	0.7	1	0.7
5952	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5953	12	4.3	6	4.4	6	4.4	6	4.9	6	4.9
5955	27	9.8	13	9.6	13	9.6	14	5.1	14	5.1
5956	5	1.8	3	2.2	3	2.2	2	1.4	2	1.4
5957	6	2.9	3	2.2	3	2.2	3	2.5	3	2.5
5958	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5961	1	0.3	1	0.7	1	0.7	0	-	0	-
5962	1	0.3	0	-	0	-	1	0.7	1	0.7
5963	2	0.7	0	-	0	-	2	1.4	2	1.4
5964	1	0.3	1	0.7	1	0.7	0	-	0	-
5966	9	3.2	5	3.7	5	3.7	4	2.8	4	2.8
5972	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5973	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
5975	11	4.0	6	4.4	6	4.4	5	3.6	5	3.6
5977	4	1.6	2	1.9	2	1.9	2	1.4	2	1.4
5978	14	5.0	7	5.9	7	5.9	7	5.0	7	5.0
5979	6	2.4	2	1.9	2	1.9	4	2.8	4	2.8
5996	1	0.3	1	0.7	1	0.7	0	-	0	-
6072	3	1.0	2	1.9	2	1.9	1	0.7	1	0.7
6073	6	2.4	3	2.2	3	2.2	3	2.5	3	2.5
6075	5	1.8	3	2.2	3	2.2	2	1.4	2	1.4
6342	3	1.0	1	0.7	1	0.7	2	1.4	2	1.4
6357	4	1.6	2	2.2	2	2.2	2	1.4	2	1.4
6557	1	0.3	0	-	0	-	1	0.7	1	0.7
6569	1	0.3	1	0.7	1	0.7	0	-	0	-

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Medical Officer's Comment: *It can be appreciated from table 137.3, that no center had > 10% of the except for one center, #5871, which had approximately 15%. That center was in Greece and the MO elected to review those patients separately as well as in conjunction with the other patients. Otherwise, patients were well distributed over the 43 centers listed.*

At this point and because of the overall concurrence between the MO and the sponsor as to the design and implementation of this trial, the MO elected to review a selected sample of patients. This random sample was generated by the FDA statistician, Dr. Nancy Silliman, and is representative in terms of demographic content with the randomized population. This list was generated and reviewed in a blind manner.

Alatrofloxacin/Trovafloxacin (N = 17):

- #57950577: 72 YO female, smoker, who was neither clinically nor bacteriologically evaluable. The patient died on the second study day of her underlying COPD, aggravated by NP. No organisms were isolated from the blood or the sputum, and the CxR revealed probable fluid overload. The Reviewer agreed that this patient was not evaluable because of the lack of confirmatory evidence of a NP.
- 58710073: 57 YO female, never smoked, clinically evaluable only. The patient received a 14 day course of therapy for a new left lower lobe infiltrate. The initial sputum sample had no growth and the patient was unable to produce a sample at the EOT and EOS. The patient was assessed as a cure at the EOT and at the EOS. The Reviewer agreed.
- #58710422: 61 YO male, smoker, who was clinically and bacteriologically evaluable. The patient received 7 days of therapy. The initial CxR revealed right lower lobe consolidation. The initial sputum sample as well as those obtained at the time of withdrawal revealed *Pseudomonas aeruginosa*. The patient was changed to imipenem, and was classified as a failure with persistence. Reviewer agreed.
- #59260083: 74 YO female, never smoked, neither clinically nor bacteriologically evaluable. This patient received 2 days of therapy. Initial sputum was induced but had no growth and the CxR was normal. Blood cultures were negative and sepsis was ruled out. The patient died on day 3 of her underlying disease processes which included a CVA and renal failure. Reviewer agreed that this patient was unevaluable because of lack of radiographic evidence of NP.
- #59450133: 73 YO male, smoker, clinically evaluable only. This patient received 12 days of therapy and was classified as a cure at both the EOT and EOS. The CxR revealed bilateral new atelectasis, and the initial sputum as well as blood cultures were negative. Reviewer agreed.
- #59520095: 72 YO male never smoked, clinically evaluable only after 14 days of study drug. Sputum cultures at the start of the study as well as at the EOT were notable for the absence of a bacterial pathogen and positive only for *Candida albicans*. Initial CxR revealed bibasilar new infiltrates. No other antimicrobial was utilized either prior to the study or concomitantly. The Reviewer agreed with the evaluability of this patient as well as with the outcome of cure at the EOS.
- #59550221: 18 YO male, never smoked, clinically and bacteriologically evaluable after 12 days of therapy. Initial CxR revealed "pneumonia". Initial specimens for culture were obtained bronchoscopically and revealed *Staphylococcus aureus*, *Haemophilus influenzae*, and *Bacteroides melaninogenicus*. Blood cultures were negative. Sputum obtained at day 7 revealed eradication of all isolates and at the EOS the patient was unable to produce a specimen. The patient was classified as a cure at the EOT and EOS with eradication of all pathogens. Reviewer agreed.
- #59550227: 70 YO female, never smoked, clinically and bacteriologically evaluable after 3 days of therapy as a failure with persistence of the original isolate, *Pseudomonas aeruginosa*. Notable is that the isolate had a MIC of 1 mcg/mL which was determined to be resistant to the study drug. The patient was treated with ceftazidime and fosfomycin through day 14. CxR revealed patchy bilateral lower lobe

infiltrates, The Reviewer agreed that this patient was an evaluable failure and that the patient was carried forward appropriately.

- *#59550245: 50 YO male, never smoked, clinically and bacteriologically evaluable after 3 days of therapy as a failure with presumed persistence of the original sputum isolate, Enterobacter aerogenes. CxR revealed left lower lobe infiltrate. The patient received a 10 day course of ceftriaxone and netilmicin for inadequate response and had resolution of the pneumonia. Reviewer agreed with the evaluability of this patient and determined that he was carried forward as a failure.*
- *#59559246: 71 YO female, smoker, clinically evaluable only, after 14 days of therapy as a cure. Sputum revealed only Neisseria meningitidis and the CxR revealed questionable lower lobe interstitial infiltrates. These early infiltrates improved with antimicrobial therapy and therefore the Reviewer agreed with the evaluability of this patient based on the initial CxR and with the outcome assessment.*
- *#59550268: 28 YO male, smoker, clinically and bacteriologically evaluable after 12 days of therapy. Initial specimens for culture were obtained bronchoscopically and revealed Morganella morganii and Staphylococcus aureus. An EOT sputum specimen revealed eradication of both organisms and the patient was unable to produce a specimen at the EOS. The CxR revealed left upper lobe infiltrate and early lower lobe infiltration. Reviewer agreed with the evaluability and outcome assessment of this patient.*
- *#59550290: 57 YO male, ex-smoker, clinically evaluable only as a cure at the EOT and EOS. The patient received 12 days of study drug for new left and right lower lobe infiltrates, without bacteriologic confirmation, which completely resolved by the EOT without any other antimicrobial coverage. Reviewer agreed.*
- *#59550291: 49 YO male, smoker, clinically and bacteriologically evaluable after 11 days of study drug as a cure at the EOT. The patient did not have an EOS visit. CxR revealed a right lower and a left upper lobe infiltrate. Initial bronchoscopic specimen revealed Haemophilus influenzae, which was eradicated, in follow-up specimens. The reviewer excluded this patient because there was no EOS visit.**
- *#59560229: 92 YO male, ex-smoker, clinically evaluable only after 16 days of therapy as a cure at the EOS. This patient had a right middle lobe pneumonia which resolved by the EOS. There was no EOT visit and all sputum specimens were negative. Reviewer agreed with the evaluability and outcome assessments of the sponsor.*
- *#60750459: 89 YO female, ex-smoker, clinically and bacteriologically evaluable after 12 days of study drug. Initial blood cultures were notable for the growth of Escherichia coli and the initial sputum culture was negative. CxR revealed bilateral lower lobe patchy infiltrates. Reviewer agreed with evaluability and outcome assessments in this patient because of the initial CxR and the lack of additional antimicrobial therapy.*
- *#63570484: 67 YO female, ex-smoker, clinically and bacteriologically evaluable after 11 days of therapy. Initial CxR revealed consolidation of the right upper and middle lobes. Initial specimen for culture was obtained bronchoscopically, and revealed Pseudomonas aeruginosa which was persistent at the EOT. The patient was classified as a cure at the EOT with presumed eradication of the baseline pathogen, There was no EOS visit. Reviewer excluded the patient because of the lack of an EOS visit (transferred to nursing home), and therefore no appropriate follow-up. **
- *#65690509: 89 YO female never smoked, clinically evaluable only after 12 days of therapy. CxR revealed left upper lobe consolidation. Initial sputum well as all follow-up specimens were negative as were the blood cultures. The patient was classified as a cure at the EOT and EOS. Reviewer agreed.*

** Denotes patients excluded by MO for other reasons.*

Ceftazidime/Ciprofloxacin (N = 11):

- #54390220: 60 YO male, smoker, neither clinically nor bacteriologically evaluable after 13 days of therapy. CxR revealed ARDS without a bacterial isolate. The patient did not receive alternative antimicrobials. The Reviewer agreed with the unevaluability of this patient because of the lack of confirmatory evidence of a NP.
- #58000582: 42 YO male, smoker, clinically and bacteriologically evaluable after 15 days of therapy as an improvement at the EOT and a failure at the EOS. The patient presented with a left lower lobe infiltrate on initial CxR, which improved and had growth of *Escherichia coli* in the initial culture obtained bronchoscopically. The isolate was eradicated in the face of clinical improvement at the EOT and no further specimens were obtainable. The patient received an additional 5 days of ciprofloxacin from days 15 – 19. Reviewer agreed that this patient was a clinical failure with eradication of the baseline pathogen.
- #58710080: 83 YO male, ex-smoker, clinically evaluable only after 11 days of therapy for a new right middle lobe infiltrate that resolved. The patient was assessed as a cure at both the EOT and EOS. Reviewer agreed.
- #58710433: 53 YO male, never smoked, clinically and bacteriologically evaluable after 6 days of therapy for a new left lower lobe infiltrate. Initial sputum revealed *Enterobacter aerogenes* which was persistent. The patient received aztreonam and Primaxin® after discontinuation of the study drugs. Classified as a failure with persistence. Reviewer agreed.
- #59240046: 72 YO male, never smoked, neither clinically nor bacteriologically evaluable after 2 days of study drug for diffuse bilateral interstitial pneumonia by CxR (ARDS). Initial sputum revealed both *Haemophilus influenzae* and *Streptococcus pneumoniae*. The *Haemophilus* was resistant to ceftazidime and the study drugs were stopped. The patient was changed to benzylpenicillin and he died at day 5 of multiorgan failure. Reviewer agreed that this patient was unevaluable because of lack of radiographic evidence of NP.
- #59530249: 71 YO male ex-smoker, neither clinically nor bacteriologically evaluable after 2 days of therapy. Initial CxR was read, as compatible with NP and *Pseudomonas aeruginosa* and *Candida albicans* were isolated bronchoscopically. The patient died of respiratory failure and septic shock on the day of withdrawal. Reviewer agreed that this patient was unevaluable because he did not receive the minimum duration of therapy necessary to be evaluable as a failure and there was no way of independently verifying the CxR.
- #59560231: 82 YO female, ex-smoker, clinically evaluable only after 12 days of therapy as an EOS cure. The patient was treated for a new left upper infiltrate without a bacterial pathogen. Reviewer agreed with evaluability and outcome assessments as per the sponsor.
- #59570280: 81 YO male, never smoked, clinically and bacteriologically evaluable after 13 days of therapy as a cure at the EOT and EOS with presumed eradication of the baseline bronchoscopically obtained isolate, *Proteus vulgaris*. Had new left lower lobe consolidation at onset which completely resolved. Reviewer agreed.
- #59570281: 30 YO male, never smoked, neither clinically nor bacteriologically evaluable after 1 day of therapy. CxR revealed left lower lobe infiltrate and bronchoscopically obtained specimen revealed *Staphylococcus aureus* and *Streptococcus pneumoniae*. Reviewer agreed because of absence of confirmatory evidence of NP.
- #59730318: 83 YO male, ex-smoker, clinically and bacteriologically evaluable after 12 days of therapy as a failure with presumed persistence of the baseline sputum isolates (*Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*). CxR revealed basilar consolidation of the

right lower lobe. The patient was changed to cefuroxime and aztreonam on day 12, but die during the post-study period of multiorgan failure.

- #60750457: 84 YO male, never smoked, neither clinically nor bacteriologically evaluable after 1 day of therapy for a "severe" right upper lobe pneumonia. No bacterial pathogens were isolated from blood or sputum and the patient died on study day 1 of respiratory failure secondary to pneumonia. Reviewer agreed that this patient was unevaluable because he did not receive enough therapy to be evaluable as a failure.

Medical Officer's Comment: As can be appreciated from the synopses of the above 28 patients, there was general concordance between the MO and the sponsor both in terms of evaluability and outcome assessments. The only exception was in 2 trovafloxacin-treated patients who would have been excluded from the MO's evaluable population because they had no EOS visit.

The MO was satisfied however, that all cases evaluated were seen in patients already hospitalized, that all failures were carried forward and that the sponsor generally adhered to the protocol. Additionally, the MO verified that the recordation of data from the CRFs to the PIDs was appropriate. Specifically, there was concurrence in all CxR and culture reports. Because of the above, the MO elected to accept the sponsor's determinations of evaluability and outcome in all cases. The only exceptions to the above were the exclusion from the MO's evaluable population of those 18 alatrofloxacin/trovafloxacin and 20 ceftazidime/ciprofloxacin patients who did not have an EOS visit and therefore did not meet the MO's evaluability criteria. An additional 3 alatrofloxacin/trovafloxacin and 2 ceftazidime/ciprofloxacin patients were excluded from the sponsor's EOT analysis because they had no EOT visit. These patients were included in the sponsor's EOS analysis and were also included in the MO's evaluable population.

2 patients were excluded from the MO's population because they were classified as cures after 6 and 7 days of therapy only and therefore did not meet the pre-specified minimum duration of therapy necessary to be evaluable as per the MO (#59360110: alatrofloxacin/trovafloxacin and #59750407: ceftazidime/ciprofloxacin).

The patients who did not have an EOS visit are listed by study arm below:

Alatrofloxacin/Trovafloxacin (N = 18):

- #58710078: improvement
- #58770360: cure
- #59260041: improvement
- #59360111: cure
- #59530250: cure
- #59550275: cure
- #59550291: cure
- #59550350: cure
- #59560230: cure
- #59570277: cure
- #59570237: cure
- #59580277: cure
- #59570278: cure
- #59580237: cure
- #59640321: improvement
- #59660311: improvement
- #60730474: cure
- #63420382: cure
- #63570484: cure

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Ceftazidime/Ciprofloxacin (N = 20)

- #58690026: *improvement*
- #58710079: *improvement*
- #58710425: *improvement*
- #58710438: *improvement*
- #58770358: *cure*
- #59240013: *cure*
- #59240015: *cure*
- #59240038: *cure*
- #59260042: *cure*
- #59260081: *cure*
- #59260084: *cure*
- #59350161: *cure*
- #59410148: *cure*
- #59560232: *improvement*
- #59580239: *improvement*
- #59660338: *cure*
- #59660340: *cure*
- #59790361: *cure*
- #60750458: *cure*
- #63570482: *cure*

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The 5 additional patients who did not have an EOT visit are listed below:

Alatrofloxacin/Trovafloxacin (N=5)

- #59450136: *cure*
- #59560229: *cure*
- #59750386: *cure*
- #58690025: *cure*
- #59340016: *cure*

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Ceftazidime/Ciprofloxacin (N = 3)

- #59560231: *cure*
- #63420381: *cure*
- #54390241: *cure*

Sponsor's Evaluable Population: As per the sponsor, of the 135 alatrofloxacin/trovafloxacin and 140 ceftazidime/ciprofloxacin subjects who were randomized, 3 alatrofloxacin/trovafloxacin and 1 ceftazidime/ciprofloxacin subjects had an inappropriate baseline diagnosis and were excluded from the ITT and evaluable analyses.

Of the 132 alatrofloxacin/trovafloxacin and 139 ceftazidime/ciprofloxacin clinical ITT patients, 29 alatrofloxacin/trovafloxacin and 30 ceftazidime/ciprofloxacin patients were not clinically evaluable at the EOT therefore, 103 alatrofloxacin/trovafloxacin-treated subjects and 109 ceftazidime/ciprofloxacin-treated subjects were clinically evaluable at the EOT.

The most common reasons for exclusion from the clinical efficacy analyses can be seen in table 113.2.

66/132 alatrofloxacin/trovafloxacin ITT subjects and 81/109 ceftazidime/ciprofloxacin ITT subjects were included in the bacteriological ITT analysis. The remaining patients (66 and 58 per arm respectively), had negative baseline cultures.

Of the 88 clinically evaluable as per the sponsor, alatrofloxacin/trovafoxacin patients, and the 103 ceftazidime/ciprofloxacin patients, 51 and 43 per arm respectively, were not included in the bacteriologically evaluable analysis. Therefore, 52 alatrofloxacin/trovafoxacin-treated subjects and 66 ceftazidime/ciprofloxacin subjects were bacteriologically evaluable.

Baseline Characteristics:

88/135 alatrofloxacin/trovafoxacin-treated subjects (65%) were male and 497(35%) were female and 99/140 ceftazidime/ciprofloxacin-treated subjects (71%) were male and 41 (29%) were female. Treated subjects in the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin treatment groups were generally comparable with respect to age, race, weight, and smoking classification.

The distribution of treated subjects according to smoking classification was similar between the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin treatment groups (28% and 36% ex-smoker, 37% and 35% never smoked, and 34% and 29% smoker, respectively.

The primary diagnosis for clinically-intent-to-treat subjects was nosocomial-acquired pneumonia. The median duration (range) since onset of pneumonia was 2 days (0 – 12 days) for subjects in the alatrofloxacin/trovafoxacin group and 2 days (1-19 days) for subjects in the ceftazidime/ciprofloxacin group.

There were no marked differences between subjects in the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin groups with respect to medical history at baseline.

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Copied below, from page 34 of the study report, is Sponsor's Table A:

Table A. Summary of Baseline Characteristics and Selected Underlying Diseases and Syndromes at Baseline (All Treated Subjects)				
Baseline Characteristic	Alatrofloxacin ↓ Trovafoxacin (N=135)		Ceftazidime ↓ Ciprofloxacin (N=140)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	61.7		63.6	
Minimum				
Maximum				
16-44	25	(19%)	20	(14%)
45-64	43	(23%)	42	(30%)
≥65	67	(50%)	78	(56%)
Smokers	46	(34%)	41	(29%)
Asthma	4	(3%)	7	(5%)
Chronic Obstructive Lung Disease	25	(19%)	26	(19%)
Congestive Heart Failure	17	(13%)	28	(20%)
Diabetes Mellitus	16	(12%)	21	(15%)
Hepatic Disease	6	(4%)	5	(4%)
Impaired Renal Function	16	(12%)	22	(16%)
Ref.: Tables 2.1.1 and Appendix I, Table 1				

Of the clinically evaluable subjects in the alatrofloxacin/trovafoxacin treatment group, 28 (27%) had post-surgical pneumonia as compared to 33 (30%) of the subjects in the ceftazidime/ciprofloxacin group. Additionally, 31 (30%) and 24 (22%) subjects, respectively, had nosocomial pneumonia resulting from suspected aspiration, 21 (20%) and 28 (26%) subjects, respectively, had nosocomial pneumonia resulting

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from mechanical ventilation, and 23 (22%) and 24 (22%) subjects, respectively, had nosocomial pneumonia resulting from "other" reasons. (Subjects may have had more than one reason for nosocomial pneumonia.)

Severity Factors and APACHE II Scores at Baseline:

Of the clinically evaluable subjects 56/103 (54%) alatrofloxacin/trovafoxacin-treated subjects and 60/109 (55%) of the ceftazidime/ciprofloxacin treated subjects had severe disease. 48/103 (47%) and 54/109 (50%) respectively, had compromised respiratory function (included all subjects who were mechanically ventilated or required a fractional oxygen concentration of ≥ 0.35 to maintain an arterial oxygen tension of ≥ 60 mm Hg.).

41/103 (40%) of the alatrofloxacin/trovafoxacin-treated subjects and 37/109 (34%) of the ceftazidime/ciprofloxacin-treated subjects required mechanical ventilation.

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The mean APACHE score at baseline for both the alatrofloxacin/trovafoxacin-treated patients was 12.66 at baseline as compared to 13.59 for the ceftazidime/ciprofloxacin-treated group.

Duration of Treatment:

On the alatrofloxacin/trovafoxacin arm, the subjects were treated for a median number of 6 days with alatrofloxacin and 6 days with trovafoxacin. The total median number of days of treatment was 10 (range 1 - 23). On the ceftazidime/ciprofloxacin arm, the subjects were treated with a median number of 7 days intravenously and 7 days orally. The total median number of days of therapy was 12 on this arm (range 1 - 19).

Medical Officer's Comment: It appeared as if the ceftazidime/ciprofloxacin-treated subjects were marginally more severely ill at baseline and that they received 1 - 2 day longer courses of therapy.

Concomitant Medications:

Protocol-specified Antimicrobials:
(Copied from page 36 of the study report):

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Among treated subjects, 12 alatrofloxacin/trovafoxacin and 32 ceftazidime/ciprofloxacin subjects received additional protocol-specified therapy with gentamicin (for documented baseline *Pseudomonas* infection), vancomycin (for documented baseline methicillin-resistant *Staphylococcus aureus*), clindamycin, and/or metronidazole (for suspected anaerobic infections). (Subjects in the alatrofloxacin/trovafoxacin group may have received vancomycin; subjects in the ceftazidime/ciprofloxacin group may have received gentamicin, vancomycin, clindamycin, and/or metronidazole.) The use of these protocol-specified adjunctive antibiotics did not impact subject evaluability or clinical or bacteriologic outcome as long as they were used appropriately for the indicated baseline pathogen or had no impact on the baseline pathogen.

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• Additional Therapy with Gentamicin

Eight (8) subjects in the alatrofloxacin/trovafoxacin group and 17 subjects in the ceftazidime/ciprofloxacin group received additional therapy with gentamicin. Of the clinically evaluable subjects with a baseline pathogen of *Pseudomonas aeruginosa*, 5/8 subjects in the alatrofloxacin/trovafoxacin group and 10/17 subjects in the ceftazidime/ciprofloxacin group received gentamicin as adjunctive therapy. The alatrofloxacin/trovafoxacin subjects were assessed as fully evaluable despite this deviation from protocol. The median number of days that subjects in the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin groups were treated with gentamicin was 5 and 6 days, respectively.

Medical Officer's Comment: *The MO agreed that the use of adjunctive gentamicin therapy for patients with documented Pseudomonas aeruginosa infections was allowable since it was specified in a protocol amendment a priori. The use of other anti-pseudomonal agents was not specified, however, the MO elected to consider these patients as evaluable because the use of one or another aminoglycoside is clearly dependent upon regional differences in hospital sensitivity patterns.*

- **Additional Therapy with Vancomycin**
Five (5) subjects in the alatrofloxacin/trovafloracin group and 17 subjects in the ceftazidime/ciprofloxacin group received additional therapy with vancomycin. The median number of days that subjects in the alatrofloxacin/trovafloracin and ceftazidime/ciprofloxacin groups were treated with vancomycin was 11 and 9 days, respectively.
- **Additional Therapy with Clindamycin and/or Metronidazole**
One subject in the ceftazidime/ciprofloxacin group received additional therapy with metronidazole for 9 days.

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Medical Officer's Comment: *From the sponsor's submission, it was apparent that more patients in the ceftazidime/ciprofloxacin treatment group received protocol-specified concomitant antimicrobials. This increased usage should have created a "worst case" scenario in favor of that arm.*

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Other Medications:

135/135 (100%) subjects in the alatrofloxacin/trovafloracin group and 140/140 (100%) subjects in the ciprofloxacin group received concomitant medications during study therapy. The most commonly used medications during therapy were analgesics, antibacterial drugs, anticoagulants, diuretics, electrolyte and water replacement, hypnotics, oxygen treatment, and ulcer-healing drugs.

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Concomitant Antimicrobials:

During the study, 69 subjects in the alatrofloxacin/trovafloracin group and 84 subjects in the ceftazidime/ciprofloxacin group received antibiotics or other anti-microbials other than study drug for the following reasons:

- inadequate response (23, alatrofloxacin/ trovafloracin; 28, ceftazidime/ciprofloxacin),
- early discontinuation of study drug due to an adverse event (3, alatrofloxacin/trovafloracin; 1, ciprofloxacin)
- other reasons (43, alatrofloxacin/trovafloracin; 55, ceftazidime/ciprofloxacin).

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These numbers included subjects whose last dose of prior antibiotic therapy was taken on Day 1 of the study.

Medical Officer's Comment: *The MO performed a separate audit on the CRFs of those patients on concomitant, non-protocol-specified antimicrobials and found that alatrofloxacin/ trovafloracin patients treated for other reasons were not clinically evaluable. Of the alatrofloxacin/trovafloracin patients who received alternative antimicrobials for other reasons, the most common reason was the development of a new and different infectious process. This is an expected phenomenon in this group of patients. On the ceftazidime/ciprofloxacin arm, 21 subjects were not clinically evaluable. Once again, the use of the category "other" predominantly referred to other infectious processes.*

All cases where antimicrobials were utilized for "inadequate response" was carried forward as failures. Additionally, all of the "other" category of patients who received antimicrobials for a pulmonic process were carried forward as failures.

From the audit of all patients who received concomitant antimicrobial therapy, the MO disagreed with the sponsor's assessment of evaluability or outcome in the following patient:

Alatrofloxacin/Trovafloxacin (N=1):

- #58770392: *Evaluable cure with presumed eradication of one of the presumed baseline pathogens, Streptococcus pneumoniae (as per the sponsor). The patient also had Staphylococcus aureus isolated from the baseline specimen. The patient received 14 days of study drug as well as vancomycin between days 6-14 for the development of MRSA. The sponsor has not provided MIC results. The sponsor determined that as the patient had radiographic resolution in conjunction with sterilization that an outcome of clinical cure was appropriate. However, the MO determined that this patient was unevaluable. This decision was mad because of the known activity of vancomycin versus Streptococcus pneumoniae. Additionally, the vancomycin was started on study day 6 even though, as per protocol, it may be utilized within the first 3 days of the documentation of MRSA. As no MIC information was provided, the appropriateness of the institution at this time cannot be determined.*

(Note: additional 9 alatrofloxacin/trovafloxacin patients and 7 ceftazidime/ciprofloxacin patients with outcomes of cure or improvement would have been excluded by the MO because of concomitant antimicrobial usage. However, all patients were excluded previously because of the absence of an EOS visit or in the case of 1 ceftazidime/ciprofloxacin patient because of the assignment of an assessment of cure prior to the allowed minimum duration of therapy.)

Based on the above, the MO excluded an additional patient from the clinically evaluable population on the alatrofloxacin/trovafloxacin arm of the study and added 2 patients. Thus, the MO found that there were 85 clinically evaluable patients at the EOS.

On the ceftazidime/ciprofloxacin arm, the MO excluded 20 patients because of "no EOS visit." The MO found that there were 89 clinically evaluable patients at the EOS.

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Protocol Deviations:

(Copied from page 38 of the study report)

Deviations from protocol were noted for 37 subjects, two of whom had more than one deviation, during the study. These deviations were categorized as follows.

- Inclusion criteria deviations included three subjects who did not give written informed consent, two subjects who did not have radiological evidence of nosocomial pneumonia at baseline, one subject who had a baseline chest x-ray performed on Day 2, one subject who had a pulmonary embolism rather than nosocomial pneumonia, one subject with no signs and symptoms consistent with nosocomial pneumonia, and one subject who was admitted to the hospital with nosocomial pneumonia but had been in the hospital for 4 days with an infective exacerbation of chronic obstructive pulmonary disease 3 days earlier.
- Exclusion criteria deviations included one subject with known hypersensitivity to study drugs, two subjects with known hypersensitivity to penicillin, one subject who received an investigational drug within 4 weeks of enrollment, two subjects who had evidence of drug or alcohol abuse or dependence, and two subjects who had a history of epilepsy.
- Study drug administration deviations included five subjects with *Pseudomonas* in the alatrofloxacin/trovafloxacin arm who received gentamicin, five subjects who received concomitant gentamicin without evidence of *Pseudomonas* infection, ten subjects who received concomitant vancomycin without having evidence of methicillin-resistant *Staphylococcus aureus* infection, one subject who received ceftazidime for 18 days, and one subject who received alatrofloxacin/trovafloxacin for 23 days.

With the exception of subjects who were not evaluable due to inappropriate baseline diagnosis and subjects who were not evaluable due to inappropriate use of optional antibiotics, none of the protocol deviations discussed above affected subject evaluability.

Subjects with protocol deviations are listed in the following table.

Inclusion Criteria	5439-0218 ^a ; 5926-0083; 5942-0145; 5956-0232; 5962-0261; 5966-0309; 5966-0339; 6075-0461; 6357-0482
Exclusion Criteria	5924-0047; 5926-0059; 5957-0281; 5979-0361; 5926-0010; 5930-0049; 5953-0256; 5439-0218 ^a
Study Drug Administration	5871-0422; 5439-0217; 5439-0219; 5439-0220; 5439-0241; 5800-0581; 5924-0037; 5926-0057; 5935-0143; 5945-0136; 5953-0251; 5953-0254; 5955-0248; 5955-0292; 5955-0349; 5958-0237; 5958-0239; 5961-0285 ^b ; 5966-0338; 6357-0481; 6357-0484
a Subject 5439-0218 had an inclusion and an exclusion criteria deviation. b Subject 5961-0285 had two study drug administration deviations.	

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Medical Officer's Comment: *The MO agreed with the exclusion of the patients as described by the sponsor with the exception of the patients listed previously who received concomitant antimicrobial therapy.*

Sponsor's Efficacy Analysis:

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Sponsor-Defined Clinical Response:

Table 137.4

Sponsor-Defined Clinical Response/Clinically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.1)

Timepoint	Alatrofloxacin/Trovafloxacin N= 103	Ceftazidime/Ciprofloxacin N = 109
Number of patients evaluated at EOT	100 (100%)	107 (100%)
Cure	54 (54%)	52 (49%)
Improvement	20 (20%)	23 (21%)
Failure	26 (26%)	32 (30%)
Success (Cure + Improvement)	74 (74%)	75 (70%)
Number of patients evaluated at EOS	85 (100%)	89 (100%)
Cure	54 (64%)	48 (67%)
Improvement	2 (2%)	4 (1%)
Failure	26 (31%)	32 (28%)
Relapse	3 (4%)	5 (4%)
Success (Cure + Improvement)	56 (66%)	52 (58%)

The sponsor provided the following CIs without continuity correction factor:

EOT: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 8.3%, 16.1% ($\Delta = 20$)
 EOS: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 5.9%, 21.8% ($\Delta = 20$)

The sponsor stated that: sponsor-defined clinical success rates (cure + improvement) supported equivalence between the 2 treatment arms at the EOT (74% and 70%, respectively) and were comparable between the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin treatment groups at the end of study (66% and 58%, respectively).

Of note, the results for center #5871, which enrolled 15% of the patients, were as follows: Trovafloxacin EOT: 11/18 (61%) and EOS: 10/17 (59%); Ceftazidime/ciprofloxacin: EOT: 10/16 (63%) and EOS 7/13 (54%). These results are consistent with those of the general population and support the pooling of the centers.

Medical Officer's Comment: *The MO agreed with the sponsor's determination that the 2 agents were equivalent at the EOT but the ceftazidime/ciprofloxacin combination appeared numerically less effective at the EOS. CIs with continuity correction factor, were provided by the FDA statistician, Dr. Nancy Silliman:*

EOT: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 9.3%, 17.1% ($\Delta = 20$)
 EOS: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: - 8.1%, 23% ($\Delta = 20$)

Based on the FDA CI, the alatrofloxacin/trovafloxacin combination was superior to the ceftazidime/ciprofloxacin combination at the EOS (MO TOC).

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The results seen in the ITT population were relatively similar, with an overall success rate at the EOT of 82/129 (64%) for the trovafloxacin-treated patients as compared to 88/136 (65%) for the ceftazidime/ciprofloxacin-treated patients (CI: -13.5%, 11.2% with continuity correction factor ($\Delta = 20$). Thus indicating equivalence of ciprofloxacin at this early timepoint.

At the EOS, the overall success rate was 80/132 (61%) trovafloxacin versus 84/139 (60%) ciprofloxacin, (CI: -12.2%, 12.5% with continuity correction factor ($\Delta = 20$). It therefore appeared as if trovafloxacin was equivalent to ciprofloxacin in this broader population at the MO TOC, the EOS.

The MO noted that the results from this trial were similar to those seen in the US study, 154-113, where the trovafloxacin EOT clinical response rate was 68/88 (78%) and the ciprofloxacin clinical response rate was 79/101 (78%). Thus the 2 agents were also equivalent at this early timepoint in that study. Clinical response was marginally lower in the current study.

At the EOS in 154-113, the trovafloxacin clinical response rate was 50/72 (69%) as compared to the ciprofloxacin arm, 54/79 (68%). In this study the response rate of both arms was lower, by 7 percentage points on the alatrofloxacin/trovafloxacin arm and by 10 percentage points on the ceftazidime/ciprofloxacin arm. The MO was unable to explain the lower rates in this trial especially for the ceftazidime/ciprofloxacin arm, except to postulate that the population on that arm was marginally more severely ill, and that the use of ceftazidime as the intravenous comparator agent had an effect. Although, the 2 populations appeared similar demographically, the overall number of severely ill patients on both arms was higher in this study (50%)

Although clinical response by severity of illness can be found below, the MO found that patients on ceftazidime/ciprofloxacin with mild/moderate disease had a lower response rate as compared to the alatrofloxacin/trovafloxacin-treated patients and that the clinical response rates in the more severely ill population were very similar. This as compared to study 154-113 where ciprofloxacin-treated patients had a higher clinical response rate in patients with mild/moderate disease and a similar response rate in patients with severe disease.

Clinical Response by Baseline Severity:

Table 137.5

Sponsor-Defined Clinical Response/Clinically Evaluable Population with Mild/Moderate Disease at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Alatrofloxacin/Trovafoxacin N= 47	Ceftazidime/Ciprofloxacin N = 49
Number of patients evaluated at EOT	44 (100%)	47 (100%)
Cure	29 (66%)	26 (59%)
Improvement	10 (23%)	9 (26%)
Failure	5 (11%)	12 (15%)
Success (Cure + Improvement)	39 (89%)	35 (74%)
Number of patients evaluated at EOS	40 (100%)	42 (100%)
Cure	33 (83%)	29 (69%)
Improvement	1 (3%)	1 (2%)
Failure	5 (13%)	12 (29%)
Relapse	1 (3%)	0
Success (Cure + Improvement)	34 (85%)	30 (71%)

Medical Officer's Comment: 95% CI with continuity correction factor for the EOT was - 3.6%, 32% and for the EOS, it was - 6.5%, 33.6% ($\Delta = 20$). Thus equivalence was not supported in this subgroup, but rather trovafoxacin was more effective. The clinical success rates were approximately the same at the EOT and the EOS on both arms of this study and the alatrofloxacin/trovafoxacin combination was numerically superior to the ceftazidime/ciprofloxacin at both timepoints. This did not occur in study 154-113 where the 2 arms were comparable for this subgroup of patients, and the comparators success rate was numerically superior to trovafoxacin's at the EOT (83% trovafoxacin versus 85% ciprofloxacin). At the EOS in study 154-113 the 2 arms were approximately equivalent (EOS trovafoxacin 76% versus 75% ciprofloxacin).

The superior success rate on the trovafoxacin arm in this trial can be explained by the open nature of this study. The much lower rate on the ceftazidime/ciprofloxacin arm can potentially be explained only by the inclusion of a more severely ill population as well as by the use of ceftazidime as a comparator agent.

Below is the sponsor's table of clinical response for those patients with "severe" disease. Patients were defined as having severe disease if they required mechanical ventilation or a fractional inspired oxygen concentration of ≥ 0.35 to maintain an arterial oxygen tension of 60 mmHg.

Table 137.6

Sponsor-Defined Clinical Response/Clinically Evaluable Population with Severe Disease at EOT and EOS: (Modified by MO from Sponsor Table 5.1.4)

Timepoint	Alatrofloxacin/Trovafoxacin N= 56	Ceftazidime/Ciprofloxacin N = 60
Number of patients evaluated at EOT	56 (100%)	60 (100%)
Cure	25 (45%)	26 (43%)
Improvement	10 (18%)	14 (23%)
Failure	21 (38%)	20 (33%)
Success (Cure + Improvement)	35 (63%)	40 (67%)
Number of patients evaluated at EOS	45 (100%)	47 (100%)
Cure	21 (47%)	19 (40%)
Improvement	1 (2%)	3 (6%)
Failure	21 (47%)	20 (46%)
Relapse	2 (4%)	5 (11%)
Success (Cure + Improvement)	22 (49%)	22 (47%)

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Medical Officer's Comment: 95 % CI with continuity correction factor at the EOT was – 23.3%, 15% and at the EOS, - 20.5%, 25 % ($\Delta = 20$). The validity of the CIs is suspect given the small numbers involved. From this table, it can be appreciated that the 2 treatment arms were numerically similar for this subgroup of patients and that overall response was approximately 20 percentage points less at both the EOT and the EOS. Similar results were found in study 154-113 where the EOT response was 66% for both arms and the EOS clinical response rate was 52% for the trovafloxacin arm and 54% for the ciprofloxacin.

Sponsor-Defined Clinical Response for Clinically and Bacteriologically Evaluable subjects:

Table 137.7
Sponsor-Defined Clinical Response/Clinically and Bacteriologically Evaluable Population at EOT and EOS: (Modified by MO from Sponsor Table 5.1.3)

Timepoint	Trovafloxacin N= 52	Ciprofloxacin N = 66
Number of patients evaluated at EOT	50 (100%)	66 (100%)
Cure	21 (42%)	25 (38%)
Improvement	13 (26%)	16 (24%)
Failure	16(32%)	25(38%)
Success (Cure + Improvement)	34 (68%)	41 (62%)
Number of patients evaluated at EOS	41 (100%)	56 (100%)
Cure	23 (56%)	23 (41%)
Improvement	0	4 (7%)
Failure	16 (39%)	25 (45%)
Relapse	2(5%)	4 (7%)
Success (Cure + Improvement)	23 (56%)	27 (48%)

Medical Officer's Comment: 95% CI with continuity correction factor at the EOT was –15.3%, 25%, and at the EOS was – 14.3%, 30% ($\Delta = 20$). It appeared, as if in this subpopulation, that there was a numerical superiority of trovafloxacin to ceftazidime/ciprofloxacin at both timepoints, as compared to study 154-113 where there was a slight numerical superiority of ciprofloxacin to trovafloxacin at the EOT, however, this difference was no longer apparent at the EOS. Overall, the results of this subpopulation were about 10 percentage points lower than those for all clinically evaluable patients.

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Clinical Response by Baseline Pathogen:

Table 137.8

Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically Evaluable Population: Modified 5.3.1 by MO)

Pathogen		Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	7	7	100	7	5	71
	EOS	5	4	80	6	4	67
<i>Moraxella catarrhalis</i>	EOT	1	0	0	2	2	100
	EOS	1	0	0	2	1	50
<i>Streptococcus pneumoniae</i>	EOT	6	5	83	3	0	0
	EOS	4	3	75	3	0	0
<i>Stenotrophomonas maltophilia</i>	EOT	1	0	0	-	-	-
	EOS	1	0	0	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	1	0	0	3	2	67
	EOS	1	0	0	3	2	67
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	4	2	50
	EOS	4	2	50	3	1	33
<i>Pseudomonas aeruginosa</i>	EOT	8	4	50	17	9	53
	EOS	5	1	20	14	5	36
<i>Klebsiella oxytoca</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Escherichia coli</i>	EOT	6	6	100	11	5	45
	EOS	6	5	83	11	5	45
<i>Proteus mirabilis</i>	EOT	1	1	100	-	-	-
	EOS	1	0	0	-	-	-
<i>Morganella morganii</i>	EOT	2	2	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Acinetobacter baumannii</i>	EOT	4	1	25	1	1	100
	EOS	4	1	25	1	1	100
<i>Staphylococcus aureus</i>	EOT	17	14	82	20	12	60
	EOS	13	10	77	15	6	40
<i>Serratia marcescens</i>	EOT	3	2	67	3	1	33
	EOS	2	1	50	3	1	33
<i>Enterococcus faecalis</i>	EOT	2	1	50	3	2	67
	EOS	1	0	0	2	1	50
<i>Enterobacter cloacae</i>	EOT	4	1	25	6	3	50
	EOS	4	1	25	6	3	50
<i>Enterobacter aerogenes</i>	EOT	1	0	0	3	0	0
	EOS	1	0	0	3	0	0
<i>Neisseria meningitidis</i>	EOT	2	2	100	3	1	33
	EOS	2	2	100	3	1	33
<i>Bacteroides melaninogenicus</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter diversus</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Hafnia alvei</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter freundii</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Legionella pneumophila</i>	EOT	2	2	100	2	2	100
	EOS	3	2	67	2	2	100
<i>Proteus vulgaris</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Acinetobacter calcoaceticus</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	0	0
<i>Streptococcus mitis</i>	EOT	1	1	100	-	-	-
	EOS	-	-	-	-	-	-
<i>Streptococcus agalactiae</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	0	0
Total	EOT	76	56	73.6	94	53	56.3
	EOS	61	49	80.3	73	45	47.9

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* The MO omitted all non-specified isolates from this table.

Medical Officer's Comment: The results in table 137.8 were very different from those in table 137.4, with a clinical response in the 70% range at the EOT which increased by the EOS to 80.3% for the alatrofloxacin/trovafloxacin-treated patients as compared to a much lower 56.3% at the EOT and 47.9% at the EOS for the ceftazidime/ciprofloxacin-treated patients.

The MO elected to evaluate the requested pathogens separately to see if any difference in results was obtained.

CI's were not applied to this variable as each patient could have had more than 1 bacterial isolate.

Table 137.9
Sponsor-Defined Clinical Response by Baseline Pathogen at the EOT and EOS (Clinically evaluable Population/Requested Pathogens Only: Modified 5.3.1 by MO)

Pathogen		Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	7	7	100	7	5	71
	EOS	5	4	80	6	4	67
<i>Escherichia coli</i>	EOT	6	6	100	11	5	45
	EOS	6	5	83	11	5	45
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	4	2	50
	EOS	4	2	50	3	1	33
<i>Staphylococcus aureus</i>	EOT	17	14	82	20	12	60
	EOS	13	10	77	15	6	40
<i>Pseudomonas aeruginosa</i>	EOT	8	4	50	17	9	53
	EOS	5	1	20	14	5	36
Total	EOT	42	33	78.5	59	33	56
	EOS	33	22	66.6	49	21	42.8

Medical Officer's Comment: When only clinical response by requested pathogen was assessed, the clinical response rates are essentially unchanged at the EOT although slightly lower. At the EOS however, the clinical response rates on both arms decreased proportionately and as expected. In this study, it appeared as if both agents had similar and relatively low clinical response rates in patients with *Pseudomonas aeruginosa* as compared to study 154-113 where trovafloxacin had better activity in a similar subgroup (EOS 62% clinical success trovafloxacin versus 25% ciprofloxacin), and that trovafloxacin also had a higher success rate in patients with *Staphylococcus aureus*, as compared to study 154-113 where ciprofloxacin had a higher clinical response rate in patients with this organism (EOS 50% trovafloxacin versus 67% ciprofloxacin).

The sponsor stated that (copied from page 47 of the study report):

When sponsor-defined clinical success rates were evaluated by baseline pathogen, higher clinical success rates were observed at both the end of treatment and the end of study among subjects in the alatrofloxacin/trovafloxacin group with baseline isolates of *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus pneumoniae* compared to subjects in the ceftazidime/ciprofloxacin group.

Sponsor-defined clinical success rates were comparable at both the end of treatment and the end of study among subjects with baseline isolates of *Haemophilus influenzae* and *Pseudomonas aeruginosa*. A comparable percentage of subjects in both the alatrofloxacin/trovafloxacin (62%, 5/8) and ceftazidime/ciprofloxacin (59%, 10/17) treatment groups received adjunctive gentamicin for the treatment of baseline *Pseudomonas aeruginosa*. Of those subjects with clinical success for *Pseudomonas aeruginosa*, 3/4 alatrofloxacin/trovafloxacin subjects and 5/10 ceftazidime/ciprofloxacin subjects received adjunctive gentamicin. Of these four subjects receiving alatrofloxacin/trovafloxacin with clinical success for *Pseudomonas aeruginosa* at end of treatment, three were not evaluable at the end of study (2 subjects [Subjects 5926-0041 and 5958-0254] due to concomitant use of antibiotics for

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reasons other than nosocomial pneumonia and 1 subject [Subject 6357-0484] died of a cardiac arrest). One subject (Subject 5414-0270) in the ceftazidime/ciprofloxacin subgroup relapsed with *Pseudomonas aeruginosa* nosocomial pneumonia. There was no evidence of the development of resistance in any of the failures in either subgroup.

C_s were not applied to this variable as each patient could have had more than 1 bacterial isolate.

Clinical Response by Ventilator Status:

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The MO requested that the sponsor provide an assessment of clinical response for this subpopulation.

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Table 137.10

Sponsor-Defined Clinical Response/Clinically Evaluable Population requiring Mechanical Ventilation at EOT and EOS

Timepoint	Alatrofloxacin/Trovafloxacin N= 41	Ceftazidime/Ciprofloxacin N = 37
Number of patients evaluated at EOT	41 (100%)	37 (100%)
Cure	20 (50%)	15 (36.4%)
Improvement	6 (31.2%)	8 (27.3%)
Failure	15 (18.8%)	14 (36.4%)
Success (Cure + Improvement)	26 (63.4%)	23 (62.2%)
Number of patients evaluated at EOS	32 (100%)	30 (100%)
Cure	16 (50%)	13 (50%)
Improvement	-	1 (3.3%)
Failure	15 (46.9%)	14 (46.7%)
Relapse	1 (3.1%)	2 (6.7%)
Success (Cure + Improvement)	16 (50%)	14 (46.7%)

Medical Officer's Comment: As expected, clinical response was worse overall in this apparently more ill population by about 20 percentage points at both the EOT and the EOS. Alatrofloxacin/trovafloxacin appeared numerically superior to ceftazidime/ciprofloxacin at the MO TOC, the EOS. These results are comparable to those in study 154-113, where the clinical response rates at the EOT were 66.7% trovafloxacin versus 63.6% ciprofloxacin and at the EOS, 55.6% and 50% per arm respectively.

Signs and Symptoms:

(Copied from page 50 of the study report)

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The percentage of clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups with moderate or severe signs and symptoms of nosocomial pneumonia at baseline was as follows: dyspnea (48% and 51%, respectively), cough (52% and 48%, respectively), pleuritic chest pain (3% and 9%, respectively), chills/rigor (14% and 17%, respectively), and increased sputum volume (64% and 68%, respectively). In both treatment groups, the percentage of subjects with these signs and symptoms of nosocomial pneumonia decreased from baseline to the end of treatment and further decreases were observed at the end of study. In general, among subjects who continued to display these signs or symptoms, the severity was decreased. Similar trends were observed among clinically intent-to-treat subjects.

The percentage of clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups with additional signs and symptoms present at baseline, including fever, focal abnormal auscultatory findings (FAAF), and diffuse abnormal auscultatory findings (DAAF) was as follows: documented fever (72% in each group), FAAF (83% and 80%, respectively), and DAAF (44% and 50%, respectively). The percentage of subjects with these

signs and symptoms decreased from baseline to the end of treatment, with further decreases generally noted at the end of study. Similar trends were observed among clinically intent-to-treat subjects.

In addition, among the clinically evaluable subjects who were febrile within 24 hours of the baseline visit, the mean ($\pm$ standard deviation) time to afebrile was 6.30 days ($\pm$ 5.85) and 6.29 days ($\pm$ 6.03) for subjects in the alatrofloxacin/trovafoxacin (n=70) and ceftazidime/ciprofloxacin (n=73) groups, respectively. Among the clinically intent-to-treat subjects, the mean ($\pm$ standard deviation) time to afebrile was 6.08 days ($\pm$ 5.58) and 6.60 days ($\pm$ 6.11) for subjects in the alatrofloxacin/trovafoxacin (n=79) and ceftazidime/ciprofloxacin (n=87) groups, respectively. A summary of the percentage of subjects with mild, moderate, or severe clinical signs and symptoms of nosocomial pneumonia at baseline, end of treatment, and end of study is presented in the following table.

Table C. Summary of Clinical Signs and Symptoms

	Alatrofloxacin ↓ Trovafoxacin			Ceftazidime ↓ Ciprofloxacin		
	Baseline	EOT	EOS	Baseline	EOT	EOS
	Percentage of Clinically Evaluable Subjects With Clinical Signs and Symptoms					
Sign/Symptom^a						
Dyspnea	68%	30%	17%	69%	25%	20%
Cough	75%	33%	18%	72%	39%	20%
PCP	16%	7%	1%	19%	6%	1%
Chills/Rigors	23%	3%	1%	29%	<1%	2%
ISV	83%	40%	20%	88%	36%	22%
Fever	72%	13%	9%	72%	10%	11%
FAAF	83%	22%	10%	80%	15%	8%
DAAF	44%	16%	9%	50%	24%	11%
	Baseline	EOT	EOS	Baseline	EOT	EOS
	Percentage of Clinically Intent-to-Treat Subjects With Clinical Signs and Symptoms					
Sign/Symptom^a						
Dyspnea	68%	33%	16%	70%	30%	20%
Cough	74%	39%	17%	73%	40%	23%
PCP	14%	5%	1%	17%	6%	1%
Chills/Rigors	22%	3%	1%	24%	3%	2%
ISV	83%	44%	20%	90%	39%	26%
Fever	67%	16%	8%	70%	13%	11%
FAAF	82%	28%	10%	80%	19%	8%
DAAF	48%	26%	8%	51%	26%	15%

EOT= End of Treatment; EOS = End of Study; PCP = Pleuritic Chest Pain; ISV = Increased Sputum Volume; FAAF= Focal Abnormal Auscultatory Findings; DAAF= Diffuse Abnormal Auscultatory Findings
 a Not all subjects were evaluated for all signs/symptoms at all timepoints.
 Ref.: Tables 5.8.1a, 5.8.1b, 5.8.2a, and 5.8.2b

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Medical Officer's Comment: As can be appreciated from sponsor's Table C, the decrease in signs and symptoms was comparable between the 2 study arms.

Radiographic Changes (Copied from pages 50 and 51 of the study report):

Four clinically evaluable subjects in the alatrofloxacin/trovaflaxacin group and three clinically evaluable subjects in the ceftazidime/ciprofloxacin group had a chest x-ray that was not obtained within the evaluable window at baseline (Day -1 to Day 1). All other clinically evaluable subjects (alatrofloxacin/trovaflaxacin, 99 and ceftazidime/ciprofloxacin, 106) had x-rays obtained within the appropriate window at baseline. Of these, 58 (56%) alatrofloxacin/trovaflaxacin subjects and 67 (61%) ceftazidime/ciprofloxacin subjects had unilateral abnormalities and 41 (40%) alatrofloxacin/trovaflaxacin subjects and 39 (36%) ceftazidime/ciprofloxacin subjects had bilateral abnormalities. Ten (10) subjects (10%) in the alatrofloxacin/trovaflaxacin group and 12 subjects (11%) in the ceftazidime/ciprofloxacin group had abnormalities in ≥ 3 lobes at baseline. The mean number of lobes involved at baseline was 1.5 for subjects in both treatment groups. The majority of subjects in both treatment groups with positive baseline x-ray findings showed improvement (better or complete resolution) from baseline to the end of treatment (84%, alatrofloxacin/trovaflaxacin; 80%, ceftazidime/ciprofloxacin) and to the end of study (87%, alatrofloxacin/trovaflaxacin; 88%, ceftazidime/ciprofloxacin).

Medical Officer's Comment: *As expected, the radiographic findings followed the clinical. The MO concurred with the sponsor's analysis.*

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Bacteriological Response:

As per the sponsor, the pathogen eradication rates were derived by collapsing pathogen outcomes of eradication and presumed eradication for a response of eradication, and by collapsing the outcomes of persistence and presumed persistence for a response of persistence. That is, the results were not necessarily based on actual repeat positive culture results. The sponsor stated that (copied from page 51 of the study report):

The pathogens isolated at baseline were those expected in a population of subjects with nosocomial pneumonia. Among the bacteriological evaluable subjects, sponsor-defined pathogen eradication rates for the most frequently isolated baseline pathogens were compared between the two treatment groups both at the end of treatment and study.

Higher eradication rates for the baseline pathogens *Staphylococcus aureus* and *Streptococcus pneumoniae* were seen both at the end of treatment and end of study in the alatrofloxacin/trovaflaxacin compared with the ceftazidime/ciprofloxacin groups.

For *Staphylococcus aureus*, the higher eradication rate at the end of treatment (75%, 12/16 versus 60%, 12/20) became more pronounced at the end of study (92%, 11/12 versus 50%, 6/12) in the alatrofloxacin/trovaflaxacin group compared with the ceftazidime/ciprofloxacin group.

For *Streptococcus pneumoniae*, all isolates in the alatrofloxacin/trovaflaxacin group were either eradicated or presumed eradicated (end of treatment 3/3, end of study 1/1) compared with the presumed persistence of all isolates (end of treatment and end of study 0/3 eradicated) in the ceftazidime/ciprofloxacin group.

Lower eradication rates for the baseline pathogens *Pseudomonas aeruginosa* and *Enterobacter cloacae* were seen both at the end of treatment and end of study in the alatrofloxacin/trovaflaxacin compared with the ceftazidime/ciprofloxacin groups.

For *Pseudomonas aeruginosa*, the eradication rate at the end of treatment (25%, 2/8 versus 53%, 9/17) and end of study (20%, 2/5 versus 54%, 7/13) was lower in the alatrofloxacin/trovaflaxacin compared to the ceftazidime/ciprofloxacin group, respectively. This is in contrast to the comparable clinical success rate for *Pseudomonas aeruginosa* in both treatment groups (Table I). Adjunctive use of gentamicin as specified in the protocol occurred in 5/8 and 10/17 of the subjects in the alatrofloxacin/trovaflaxacin and ceftazidime/ciprofloxacin groups, respectively. Of those subjects receiving gentamicin, the eradication rate of *Pseudomonas aeruginosa* was 2/5 (40%) and 4/10 (40%) for the alatrofloxacin/trovaflaxacin and ceftazidime/ciprofloxacin groups,

respectively, at the end of treatment. There was no evidence of the development of resistance in any of the persistent *Pseudomonas aeruginosa* pathogens in either treatment group.

For *Enterobacter cloacae*, the eradication rate at the end of treatment (25%, 1/4 versus 100%, 6/6) and end of study (50%, 2/4 versus 100%, 5/5) was lower in the alatrofloxacin/trovafloracin group compared to the ceftazidime/ciprofloxacin group, respectively. In the alatrofloxacin/trovafloracin group, 2/4 isolates were persistent at the end of treatment compared with 0/4 at end of study (2/4 were presumed persistent). Comparable eradication rates were seen for *Escherichia coli* and *Haemophilus influenzae* at the end of treatment and end of study in both the alatrofloxacin/trovafloracin and ceftazidime/ciprofloxacin groups.

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Table 137.11
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically Evaluable Population: Modified 5.4.1 by MO)

Pathogen		Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
		N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	EOT	7	6	86	7	6	86
	EOS	5	4	80	6	5	83
<i>Moraxella catarrhalis</i>	EOT	-	-	-	2	2	100
	EOS	-	-	-	2	1	50
<i>Streptococcus pneumoniae</i>	EOT	5	5	100	3	0	0
	EOS	3	3	100	2	0	0
<i>Stenotrophomonas maltophilia</i>	EOT	1	0	0	-	-	-
	EOS	1	0	0	-	-	-
<i>Haemophilus parainfluenzae</i>	EOT	1	1	100	3	3	100
	EOS	1	1	100	3	3	100
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	4	2	50
	EOS	4	2	50	2	1	50
<i>Pseudomonas aeruginosa</i>	EOT	8	2	25	17	9	53
	EOS	5	1	20	13	7	54
<i>Klebsiella oxytoca</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Escherichia coli</i>	EOT	6	6	100	11	9	82
	EOS	6	6	100	9	9	100
<i>Proteus mirabilis</i>	EOT	1	0	0	-	-	-
	EOS	1	0	0	-	-	-
<i>Morganella morganii</i>	EOT	2	2	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Acinetobacter baumannii</i>	EOT	4	2	50	1	1	100
	EOS	4	2	50	1	1	100
<i>Staphylococcus aureus</i>	EOT	16	12	75	20	12	60
	EOS	12	11	92	12	6	50
<i>Serratia marcescens</i>	EOT	3	2	67	3	2	67
	EOS	2	2	100	3	2	67
<i>Enterococcus faecalis</i>	EOT	2	1	50	2	2	100
	EOS	1	0	0	-	-	-
<i>Enterobacter cloacae</i>	EOT	4	1	25	6	6	100
	EOS	4	2	50	5	5	100
<i>Enterobacter aerogenes</i>	EOT	1	0	0	3	0	0
	EOS	1	0	0	2	0	0
<i>Neisseria meningitidis</i>	EOT	2	2	100	-	-	-
	EOS	2	2	100	-	-	-
<i>Bacteroides melaninogenicus</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter diversus</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	1	100
<i>Hafnia alvei</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Citrobacter freundii</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Legionella pneumophila</i>	EOT	2	2	100	2	2	100
	EOS	3	2	67	2	2	100
<i>Proteus vulgaris</i>	EOT	-	-	-	2	1	50
	EOS	-	-	-	2	1	50
<i>Pseudomonas fluorescens</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Acinetobacter calcoaceticus</i>	EOT	-	-	-	1	0	0
	EOS	-	-	-	1	0	0
<i>Streptococcus mitis</i>	EOT	1	1	100	-	-	-
	EOS	1	1	100	-	-	-
<i>Streptococcus agalactiae</i>	EOT	-	-	-	1	1	100
	EOS	-	-	-	1	0	0
TOTAL	EOT	72	45	62.5	93	57	61.3
	EOS	58	42	72.4	71	46	64.7

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Medical Officer's Comment: The MO agreed with the sponsor's analysis of the data as it pertained to their evaluable population. Interestingly, in this open trial, alatrofloxacin/trovafloxacin's activity versus *Pseudomonas aeruginosa* was much lower than expected and as compared with study 154-113 where there was an eradication rate of 77% at the EOT and 63.6% at the EOS. Additionally, the activity against *Staphylococcus aureus* was much higher (113: 55% EOT, 38% EOS).

Overall eradication rates were not comparable to clinical response rate and additionally, were opposite to those seen in study 154-113. Eradication rates increased at the EOS on both arms, potentially because of the exclusion from the EOS from the evaluable population of most of the patients that the MO considered unevaluable either because of no EOS visit or because of concomitant antimicrobials. Please note that as in previous studies, the sponsor's evaluable population is not the same at the EOT and the EOS.

The overall eradication rate for the alatrofloxacin/trovafloxacin arm of this study was similar to that seen at the EOS in study 154-113 (72.1%), however the ceftazidime/ciprofloxacin rate was lower at the EOT and higher at the EOS (72.2%EOT, 55.3% EOS).

The eradication rates only for the requested pathogens can be seen below:

Table 137.12
Sponsor-Defined Pathogen Eradication Rates at the EOT and EOS (Bacteriologically evaluable Population/Requested Pathogens Only: Modified 5.4.1 by MO)

Pathogen		Trovafloxacin			Ceftazidime/Ciprofloxacin		
		N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	EOT	7	6	86	7	6	86
	EOS	5	4	80	6	5	83
<i>Escherichia coli</i>	EOT	6	6	100	11	9	82
	EOS	6	6	100	9	9	100
<i>Klebsiella pneumoniae</i>	EOT	4	2	50	4	2	50
	EOS	4	2	50	2	1	50
<i>Staphylococcus aureus</i>	EOT	16	12	75	20	12	60
	EOS	12	11	92	12	6	50
<i>Pseudomonas aeruginosa</i>	EOT	8	2	25	17	9	53
	EOS	5	1	20	13	7	54
Total	EOT	41	28	68.2	59	38	64.4
	EOS	32	24	75	42	28	66.6

Medical Officer's Comment: These rates are comparable to those seen in table 137.11 and the EOT results are comparable to those seen in study 154-113 (EOT: trovafloxacin 63.6% and ciprofloxacin 63.4%). However, the alatrofloxacin/trovafloxacin EOS eradication rate is approximately 10 percentage points higher than that of ceftazidime/ciprofloxacin, and to the trovafloxacin overall eradication rate seen in study 154-113 (EOS: trovafloxacin 65.7% and ciprofloxacin 63.5%).

Bacteriologic Response in Subjects with *Pseudomonas aeruginosa* at Baseline:
 (Copied from page 54 of the study report)

Of the eight evaluable alatrofloxacin/trovafloxacin subjects and 17 ceftazidime/ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, five alatrofloxacin/trovafloxacin subjects (63%) and ten ceftazidime/ciprofloxacin (59%) subjects received optional gentamicin therapy (dual therapy).

There was no difference in clinical outcomes between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy; however, due to the small number of subjects no definitive conclusions could be drawn.

Medical Officer's Comment: The MO independently audited the 8 alatrofloxacin/trovafloxacin and 17 ceftazidime/ciprofloxacin subjects who had *Pseudomonas aeruginosa* isolated at baseline. The MO found that 7/8(87.5%) trovafloxacin patients with *Pseudomonas aeruginosa* at baseline received an aminoglycoside, either per protocol gentamicin or amikacin as compared to 12/17 (70.5%) ceftazidime/ciprofloxacin patients.

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Please note that the MO counted any evaluable patient who received any aminoglycoside at any time during the study.

Of the 7 patients who received gentamicin or amikacin (1) on the trovafloxacin arm, only 4 were followed to the EOS and at that point, 3 were clinical failures with persistence of the *Pseudomonas*, and 1 was a clinical cure with presumed eradication (persistence at EOT). The EOT results revealed failure with persistence in the same 3 patients as well as 2 clinical cures with eradication and 2 improvements with persistence. The 1 patient who received NO aminoglycoside, was a clinical failure at the EOT, with persistence, and was carried forward as such.

On the ceftazidime/ciprofloxacin arm, of the 12 patients who received an aminoglycoside, 9 were followed through to the EOS. Of these patients, 5 were clinical failures with persistence, 1 was a failure with eradication, 2 were clinical improvements with eradication, and 1 was clinically cured with eradication.

Of the remaining 3 patients on this arm, who received an aminoglycoside but who were not followed through to the EOS, 2 were clinical cures with eradication at the EOT and 1 was a clinical improvement with eradication at the EOT.

Of the 5 patients who received no adjunctive aminoglycoside therapy, 2 were failures with eradication and 1 was a failure with persistence at the EOS. The remaining 2 patients were cures with eradication.

Based on the above, the MO agreed with the sponsor that the number of patients evaluated was too small to make any firm statements. However, that the MO agreed to that the statement appended by the sponsor to the draft labeling ("As with other antibiotics, treatment of nosocomial infections due to *Pseudomonas aeruginosa* infections, may require combination therapy.") was accurate. The MO was sufficiently impressed by the very poor activity of trovafloxacin versus *Pseudomonas aeruginosa* seen in this open trial, to suggest rewording of the above statement to reflect the definite need for the addition of a second antipseudomonal agent when treating a NP secondary to this organism.

The overall eradication rate from both trials for the trovafloxacin arm, was 11/18 (sponsor evaluable, EOS: 61.1%) as compared to the ciprofloxacin eradication rate of 9/21 (42.8%), which is very low considering the lack of the development of resistance in these trials. The MO could not explain these very disparate results.

Bacteriologic Response in Subjects with *Staphylococcus aureus* at Baseline:

The MO requested that the sponsor provide a separate listing of patients with this organism at baseline, the source, and if it was a sole pathogen or not. From these listings, the MO found that 17 alatrofloxacin/trovafloxacin patients had *Staphylococcus aureus* at baseline as compared to 20 ceftazidime/ciprofloxacin patients.

13/17 (76.4%) of the alatrofloxacin/trovafloxacin patients and 15/20 (75%) of the ceftazidime/ciprofloxacin patients were followed through the EOS (MO TOC).

On the alatrofloxacin/trovafloxacin arm, 3 of the 13 were clinical failures, 2 with eradication, and one with persistence. The remaining 10 patients were clinical cures and the pathogen was eradicated in all cases.

On the ciprofloxacin arm, 8 of the 15 were clinical failures with persistence in all 8. One patient was a relapse with persistence and in all the remaining cases there was clinical cure with eradication.

The conclusion drawn from the above is that alatrofloxacin/trovafloxacin was more effective in eradicating *Staphylococcus aureus* than ceftazidime/ciprofloxacin and that there was general consistency between a clinical outcome of cure and a bacteriologic outcome of eradication.

Of the 4 patients on the trovafloxacin arm who were not seen at the EOS but only at the EOT, 2 were cures with persistence and 2 were improvements with eradication.

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Of the 5 ciprofloxacin patients who were not seen at the EOS but only at the EOT, 3 were clinical cures with eradication and 2 were clinical improvements, one with eradication, and 1 with persistence.

Superinfecting Pathogens and Colonizing Organisms:

As per the sponsor, 5 patients on the alatrofloxacin/trovafoxacin arm and 8 subjects on the ceftazidime/ciprofloxacin arm had superinfecting pathogens at the EOS requiring further therapy. 30 (29%) trovafoxacin-treated subjects were found to have colonizing organisms not requiring treatment as compared to 29 (27%) ciprofloxacin subjects. The sponsor's text has been copied from page 56 of the study report. Please note that patients with *Pseudomonas aeruginosa* were already reviewed in the previous section.

Eleven (11) superinfecting pathogens (one isolate of *Pseudomonas putida* from the bronchi; three isolates of *Pseudomonas aeruginosa* and one isolate of *Klebsiella pneumoniae* from the lung; and one isolate each of *Escherichia coli* and *Klebsiella pneumoniae*; and four isolates of *Pseudomonas aeruginosa* from sputum or induced sputum) were isolated from five subjects (5%) in the alatrofloxacin/trovafoxacin group and 14 superinfecting pathogens (one isolate of *Streptococcus pneumoniae* isolate from the bronchi; one isolate each of *Staphylococcus aureus* and *Acinetobacter baumannii*, and one isolate of *Pseudomonas aeruginosa* (via transtracheal aspiration) from the lung; three isolates each of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and one isolate each of *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Enterococcus faecalis*, and *Candida* species from sputum) were isolated from eight subjects (7%) in the ceftazidime/ciprofloxacin group.

Medical Officer's Comment: The MO verified the above information and agreed that the sponsor's statement was accurate.

Subjects with Positive Blood Cultures at Baseline (copied from page 58 of the study report):

Among bacteriologically intent-to-treat subjects, seven subjects in the alatrofloxacin/trovafoxacin group and nine subjects in the ceftazidime/ciprofloxacin group had a positive blood culture at baseline and at least one follow-up blood culture during the study. With the exception of one isolate of *Staphylococcus aureus* in the ceftazidime/ciprofloxacin treatment group, which was persistent, all follow-up blood cultures in both treatment groups showed eradication of baseline blood pathogens, as presented in the following table.

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Table D. Summary of Sponsor-Defined Pathogen Eradication Rates For Baseline Pathogens Isolated from Blood (Bacteriologically Intent-to-Treat Subjects)^a

	Alatrofloxacin ↓ Trovafoxacin	Ceftazidime ↓ Ciprofloxacin
	Number of Pathogens ^b	
<i>Staphylococcus aureus</i>	0/0	3/4
<i>Pseudomonas aeruginosa</i>	0/0	1/1
<i>Escherichia coli</i>	2/2	0/0
<i>Streptococcus pneumoniae</i>	1/1	0/0
<i>Enterobacter cloacae</i>	0/0	1/1
<i>Klebsiella pneumoniae</i>	0/0	1/1
<i>Enterococcus faecalis</i>	1/1	0/0
<i>Serratia marcescens</i>	1/1	0/0
<i>Morganella morganii</i>	1/1	0/0
<i>Klebsiella sp</i>	0/0	1/1
<i>Streptococcus mitis</i>	1/1	0/0
<i>Bacteroides sp</i>	0/0	1/1
<i>Enterobacter sp</i>	0/0	1/1

a Subjects with a positive baseline blood culture and at least one follow-up blood culture during study.
 b Percents displayed only when denominator is ≥15.
 Ref.: Table 5.4.4

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In addition, three bacteriologically intent-to-treat subjects in the alatrofloxacin/trovafoxacin group and three subjects in the ceftazidime/ciprofloxacin group had positive baseline blood cultures and no follow-up blood cultures. Two subjects in the alatrofloxacin/trovafoxacin group were clinically cured and one subject died after 5 days of treatment. One subject in the ceftazidime/ciprofloxacin group was clinically improved, one subject was discontinued from treatment after receiving two days of treatment due to *Haemophilus influenzae* isolated in sputum, and one subject received additional antibiotics due to insufficient response.

Medical Officer's Comment: The MO agreed with the sponsor's statements and tables.

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Mortality:

The sponsor stated that amongst the clinically evaluable alatrofloxacin/trovafloxacin patents, there were 15 (15%) deaths within 45 days of the initiation of study therapy as compared to 14 (13%) on the ceftazidime/ciprofloxacin arm.

Amongst the clinically ITT subjects, there were 32 (24%) deaths on the alatrofloxacin/trovafloxacin arm and 29 (21%) on the ceftazidime/ciprofloxacin arm. Copied below is sponsor's table E (page 59 of the study report):

Table E. Summary of Subject Mortality				
Clinically Evaluable Subjects				
	Alatrofloxacin ↓ Trovafloxacin (N=103)		Ceftazidime ↓ Ciprofloxacin (N=109)	
Number of Deaths ^a	17	(17%)	15	(14%)
≤48 Hours	0		0	
Day 3 to 7	3	(3%)	1	(<1%)
Day 8 to 15	7	(7%)	4	(4%)
Day 16 to 45	5	(5%)	9	(8%)
Day 46 to 60	2	(2%)	1	(<1%)
Clinically Intent-to-Treat Subjects				
	Alatrofloxacin ↓ Trovafloxacin (N=132)		Ceftazidime ↓ Ciprofloxacin (N=139)	
Number of Deaths ^a	35	(27%)	30	(22%)
≤48 Hours	5	(4%)	2	(1%)
Day 3 to 7	7	(5%)	10	(7%)
Day 8 to 15	12	(9%)	7	(5%)
Day 16 to 45	8	(6%)	10	(7%)
Day 45 to 60	2	(2%)	1	(<1%)
Missing	1	(<1%)	0	

^a Number of deaths that occurred from initiation of study therapy.
 Ref.: Appendix I, Tables 9.1 and 9.2

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Medical Officer's Comment: Of note is that most of the deaths on the alatrofloxacin/trovafloxacin arm occurred during active therapy as compared to the ceftazidime/ciprofloxacin arm where they occurred after the conclusion of active therapy. The MO reviewed all deaths in the safety section of this review.

Clinical Failures:

The sponsor provided an analysis of the 26 alatrofloxacin/trovafloxacin and 32 ceftazidime/ciprofloxacin-treated subjects who were clinical failures at the EOT and carried forward as such to the EOS. In addition, the MO copied the sponsor's analysis of relapses because these patients were considered failures by the MO. This analysis has been copied from page 59 of the study report:

Ten (10) of the 26 alatrofloxacin/trovafloxacin subjects designated as clinical failures were discontinued from treatment between Days 2 and 10 due to inadequate response. Of the subjects designated as clinical failures, four received optional treatment with vancomycin and two (Subjects 5871-0422 and 5961-0285) received gentamicin in violation of the protocol (See Section 7). Twenty-three (23) subjects received additional antibiotics for inadequate response. Four (4) subjects were re-hospitalized or had hospitalization prolonged due to worsening of condition. Five (5) subjects who were clinical failures died due to the disease under study.

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Fifteen (15) of the 32 ceftazidime/ciprofloxacin subjects designated as clinical failures were discontinued from treatment between Days 3 and 13 due to inadequate response. Of the subjects designated as clinical failures, four received optional vancomycin, five received optional gentamicin, and one received optional gentamicin and vancomycin. Twenty-five (25) ceftazidime/ciprofloxacin subjects received additional antibiotics for inadequate response. Two (2) subjects, who were clinical failures and died, had their cause of death attributed to the disease under study.

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In addition to the clinically evaluable subjects discussed above, 21 alatrofloxacin/trovafloxacin subjects and 16 ceftazidime/ciprofloxacin subjects who were not clinically evaluable were designated as clinical failures in the intent-to-treat analysis.

Clinical Relapse. Among clinically evaluable subjects who were clinical successes at the end of treatment, three subjects in the alatrofloxacin/trovafloxacin group and five subjects in the ceftazidime/ciprofloxacin group were designated as clinical relapses at the end of study.

All three subjects in the alatrofloxacin/trovafloxacin group who were designated as clinical relapse received additional antibiotics for inadequate response. None were re-hospitalized or had hospitalization prolonged due to worsening of condition.

All five subjects in the ceftazidime/ciprofloxacin group who were designated as clinical relapses received additional antibiotics for inadequate response. One subject was re-hospitalized or had hospitalization prolonged due to worsening of condition, and one subject (Subject 5942-0145) received optional vancomycin.

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Medical Officer's Comment: The MO reviewed all failures, and found that on the alatrofloxacin/trovafloxacin arm, 16 of the 26 patients who were designated as clinical failures and two of the three subjects who were designated as clinical relapses had pathogens isolated at baseline (18 total). Eight (8) of the 16 subjects with a baseline pathogen and a clinical response of failure and one of the two with a baseline pathogen and a clinical response of relapse had repeat cultures that showed persistence of *Acinetobacter baumannii*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Proteus mirabilis*, and *Staphylococcus aureus*.

On the ceftazidime/ciprofloxacin arm, 25 of the 32 patients who were designated as clinical failures and four of the five subjects who were designated as clinical relapses had pathogens isolated at baseline (29 total). Six (6) of the 25 subjects with a baseline pathogen and a clinical response of failure and two of the four subjects with a baseline pathogen and a clinical response of relapse had repeat cultures that showed persistence of *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, and *Staphylococcus aureus*.

Of the subjects with an unfavorable clinical and/or bacteriological response who had baseline pathogens isolated with susceptibility testing performed both prior to and following treatment, none had pathogens that became resistant to trovafloxacin ($\geq 8 \mu\text{g/mL}$), ceftazidime ($\geq 32 \mu\text{g/mL}$), or ciprofloxacin ($\geq 8 \mu\text{g/mL}$).

Subjects with Resistant Organisms at Baseline (copied from pages 61 and 62 of the study report):

A number of subjects in both treatment groups isolated resistant organisms at baseline, which are listed in the following table (the table includes all pathogens isolated at baseline that were resistant to the study drug used as judged by sensitivities performed by the central laboratory). For subjects with baseline pathogens resistant to the study drug the clinical success rate at the end of treatment was 1/5(20%) for alatrofloxacin/trovafloxacin compared with 7/12(58%) with ceftazidime/ciprofloxacin.

Table F. Summary of Sponsor-Defined Clinical Response (ITT) and Bacteriological Response (ITT) at the End of Treatment for Those Subjects ^a with a Resistant Baseline Isolate				
Subject Number	Organism (Source)	MIC (µg/mL)	Bacteriological Response	Clinical Response
Alatrofloxacin/trovafloxacin (MICs stated are to trovafloxacin with resistance being ≥8µg/mL)				
5871-0071	<i>Acinetobacter baumannii</i> (Sputum)	16	PP	Failure
5871-0548	<i>Acinetobacter baumannii</i> (Sputum)	8	E	Failure
5871-0552	<i>Acinetobacter baumannii</i> (Sputum)	8	P	Failure
5955-0245	<i>Enterobacter aerogenes</i> (Sputum)	32	PP	Failure
5978-0365	<i>Escherichia Coli</i> (Blood)	>64	E	Cure
Ceftazidime/ciprofloxacin (MICs stated are to ceftazidime with resistance being ≥32µg/mL) ^{**}				
5871-0427 ^v	<i>Staphylococcus aureus</i> (Sputum)	>128	P	Failure
5871-0433	<i>Enterobacter aerogenes</i> (Sputum)	>128	P	Failure
5871-0439	<i>Enterobacter aerogenes</i> (Sputum)	>128	P	Failure
5871-0439	<i>Pseudomonas aeruginosa</i> (Sputum)	32	E	Failure
5871-0439	<i>Staphylococcus aureus</i> (Blood)	>128	E	Failure
5877-0389	<i>Acinetobacter sp</i> (Sputum)	32	PE	Improvement
5877-0389	<i>Enterococcus faecalis</i> (Sputum)	>128	PE	Improvement
5926-0066	<i>Staphylococcus aureus</i> (Sputum)	>128	PE	Cure
5936-0112	<i>Staphylococcus aureus</i> (Sputum)	>128	PE	Cure
5942-0145	<i>Acinetobacter calcoaceticus</i> (Sputum)	>128	P	Cure
5942-0148	<i>Enterococcus faecalis</i> (Sputum)	64	PE	Cure
5948-0126	<i>Staphylococcus aureus</i> (Sputum)	>128	PE	Cure
5953-0253	<i>Enterobacter cloacae</i> (Sputum)	128	PE	Cure
5966-0309	<i>Enterococcus faecalis</i> (Sputum)	32	E	Failure
6357-0481	<i>Enterobacter aerogenes</i> (Sputum)	>128	PP	Failure
MIC = Minimum Inhibitory Concentration; P = Persistent; E = Eradicated; PP = Presumed Persistent; PE = Presumed Eradicated				
^a One subject (Subject 5955-0349) does not appear in this table because the pathogen was resistant at baseline to ciprofloxacin but not to ceftazidime.				
^v Received optional therapy with vancomycin.				

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Medical Officer's Comment: Interestingly, there were a higher number of bacterial isolates with baseline resistance in this trial as compared to study 154-113 where there were none. The higher number of patients with ciprofloxacin resistance probably is representative of the fact that this is an approved agent that is widely used in all the participating countries.

Of concern to the MO were the isolates of *Staphylococcus aureus* that were MR and that developed during the trial. The MO requested a separate listing of these patients on 10/14/97. This listing had not been provided at the time of approval.

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Cross-tabulation of Sponsor-Defined Clinical Response and Pathogen Outcome:

Among the bacteriologically evaluable subjects, sponsor-defined clinical response was consistent with sponsor-defined pathogen outcome at the end of treatment except for 14 alatrofloxacin/trovafloxacin subjects and 15 ciprofloxacin subjects. The MO has copied and modified sponsor table G from page 68 of the study report below:

Table 137.13

Cross-Tabulation of Clinical and Bacteriological Response at the EOT (as per the Sponsor: Table G) and the EOS (in Times New Roman font as per the MO)

Table G. Summary of Inconsistencies Between Sponsor-Defined Clinical Response and Pathogen Outcome at the End of Treatment (Bacteriologically Evaluable Subjects)			
Subject Number	Baseline Pathogen	Clinical Response	Pathogen Bacteriological Response
Alatrofloxacin/Trovafloxacin		EOT/EOS	
5414-0269	<i>Haemophilus parainfluenzae</i> <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i> <i>Serratia marcescens</i>	Failure/Failure	Eradication/ Eradicated Eradication/ Eradicated Eradication/ Eradicated Eradication/ Eradicated
5871-0440 ^v	<i>Klebsiella pneumoniae</i> <i>Staphylococcus aureus</i>	Failure/Failure	Eradication/ Eradicated Eradication/ Eradicated
5871-0548	<i>Acinetobacter baumannii</i> ^a	Failure/Failure	Eradication/ Eradicated
5871-0552	<i>Enterobacter cloacae</i>	Failure/ Failure	Eradication/ Eradicated
5926-0041	<i>Pseudomonas aeruginosa</i>	Improvement/Not Eval., no EOS	Persistent/ Not Eval., no EOS
5953-0216	<i>Enterobacter cloacae</i>	Cure/ Cure	Persistent/ Pres. Eradicated
5953-0254 ^o	<i>Pseudomonas aeruginosa</i>	Improvement/ Cure	Persistent/ Pres. Eradicated
5955-0224	<i>Haemophilus influenzae</i> <i>Proteus mirabilis</i>	Improvement/ Failure	Persistent/ Persistent Persistent/ Persistent
5955-0267	<i>Staphylococcus aureus</i>	Cure/ Cure	Persistent/ Eradicated
5955-0274	<i>Staphylococcus aureus</i>	Cure/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5957-0278	<i>Staphylococcus aureus</i>	Cure/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5966-0311	<i>Serratia marcescens</i>	Improvement/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5975-0401	<i>B. streptococcus</i> Group C	Cure/ Cure	Persistent/ Pres. Eradicated
5978-0365	<i>Klebsiella pneumoniae</i>	Cure/ Cure	Persistent/ Persistent
Ceftazidime/Ciprofloxacin			
5414-0270	<i>Pseudomonas</i>	Improvement/Relapse	Persistent/ Persistent

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	<i>aeruginosa</i>		
5414-0294	<i>H. parainfluenzae</i> <i>S. marcescens</i>	Failure/Failure	Eradication/ Eradicated Eradication/ Eradicated
5800-0582	<i>Escherichia coli</i>	Failure/ Failure	Eradication/ Eradicated
5871-0079	<i>Staphylococcus aureus</i>	Improvement/ Not Eval., no EOS	Persistent/ Not Eval., no EOS
5871-0439 ^v	<i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i>	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
5926-0011	<i>Staphylococcus aureus</i>	Failure/ Failure	Eradication/ Eradicated
5935-0143 ^{g,v}	<i>Escherichia coli</i>	Failure/Failure	Eradication/ Eradicated
5942-0145 ^v	<i>Acinetobacter calcoaceticus</i> ^a	Cure/ Failure	Persistent/Pres. Persistent
5953-0251 ^{g,v}	<i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i>	Improvement/Cure	Persistent/ Eradicated Persistent/ Eradicated
5955-0222 ^g	<i>Pseudomonas aeruginosa</i>	Cure/Improvement	Persistent/ Eradicated
5955-0223	<i>Haemophilus influenzae</i>	Failure/ Failure	Eradication/ Eradicated
5957-0279 ^g	<i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i>	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
5966-0309	<i>Enterobacter cloacae</i> <i>Enterococcus faecalis</i>	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
5972-0325	<i>Enterobacter cloacae</i> <i>Citrobacter diversus</i>	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated
6073-0475	<i>Enterobacter cloacae</i> <i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i>	Failure/ Failure	Eradication/ Eradicated Eradication/ Eradicated Eradication/ Eradicated
a Resistant to study drug at baseline v Received optional therapy with vancomycin. g Received optional therapy with gentamicin. Ref.: Table 5.7.1 and Appendix I, Tables 8 and 8a			

Medical Officer's Comment: All failures were reviewed previously. As stated on the previous page a determination of eradication in the face of failure could only have been made based on an objective culture report at the EOT. The MO determined that 4 trovafloxacin-treated and 1 ceftazidime/ ciprofloxacin-treated patients were not evaluable. Of those patient who were evaluable per the MO, there was no disagreement between the MO's and the sponsor's determinations of outcome. On the alatrofloxacin/trovafloxacin arm there were 4 EOS failures with eradication as compared to 10 on the ceftazidime/ciprofloxacin arm. There was 1 cure with persistence on the alatrofloxacin/trovafloxacin arm as compared to 0 EOS inconsistencies in this group on the ceftazidime/ciprofloxacin arm.

Sponsor's Conclusion:

(Copied from page 71 of the study report and modified by the MO (in Times New Roman font))

Alatrofloxacin/trovafloxacin was clinically effective in the treatment of subjects with nosocomial pneumonia and statistically equivalent to ceftazidime/ciprofloxacin for sponsor-defined clinical success rates.

One hundred thirty-five (135) subjects were randomized to treatment with alatrofloxacin/trovafloxacin and 140 subjects were randomized to treatment with ceftazidime/ciprofloxacin. All of the randomized subjects in both treatment groups received

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treatment. The two treatment groups were generally comparable with respect to characteristics at baseline, including medical history, use of prior and concomitant medications, severity factors (compromised respiratory function and need for mechanical ventilation), APACHE II score, and severity of nosocomial pneumonia.

One hundred three (103) subjects in the alatrofloxacin/trovafloxacin group and 109 subjects in the ceftazidime/ciprofloxacin group were clinically evaluable; 52 subjects in the alatrofloxacin/trovafloxacin group and 66 subjects in the ceftazidime/ciprofloxacin group were bacteriologically evaluable. All treated subjects were included in analysis of adverse events.

Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates at the end of treatment supported equivalence of the two treatment regimens for both clinically evaluable and intent-to-treat subjects.

Success rates among clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups were 74% (74/100) and 70% (75/107) (CI: -8.3, 16.1), respectively, at the end of treatment and 66% (56/85) and 58% (52/89), respectively, at the end of study and those among clinically intent-to-treat subjects were 64% (82/129) and 65% (88/136) (CI: -12.7, 10.4), respectively, at the end of treatment and 61% (80/132) and 60% (84/139), respectively, at the end of study. The clinical success in the subgroup of subjects both clinically and bacteriologically evaluable also supported equivalence of the two treatment regimens.

When sponsor-defined clinical success rates were evaluated by baseline pathogen, higher clinical success rates were observed among clinically evaluable subjects at both the end of treatment and the end of study among subjects in the alatrofloxacin/trovafloxacin group with baseline isolates of *Staphylococcus aureus* compared to subjects in the ceftazidime/ciprofloxacin group (end of treatment: 82% (14/17) and 60% (12/20), respectively; end of study: 77% (10/13) and 40% (6/15), respectively).

Sponsor-defined clinical success rates among clinically evaluable subjects were comparable at the end of treatment and end of study among subjects with baseline isolates of *Pseudomonas aeruginosa* (end of treatment: 50% (4/8) and 53% (9/17), respectively; end of study: 20% (1/5) and 36% (5/14), respectively). Similar results were noted among clinical intent-to-treat subjects.

Absolute eradication rates were higher for *Staphylococcus aureus* and *Streptococcus pneumoniae*, lower for *Pseudomonas aeruginosa* and *Enterobacter cloacae*, and comparable for *Escherichia coli* and *Haemophilus influenzae* in the alatrofloxacin/trovafloxacin compared with the ceftazidime/ciprofloxacin groups, respectively. For *Staphylococcus aureus*, the end of treatment eradication rates were 75% (12/16) and 60% (12/20) in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups, respectively. All *Streptococcus pneumoniae* isolates were eradicated in the alatrofloxacin/trovafloxacin compared with none in the ceftazidime/ciprofloxacin group. The eradication rate of *Pseudomonas aeruginosa* at the end of treatment was 25% (2/8) and 53% (9/17) in the alatrofloxacin/trovafloxacin compared with the ceftazidime/ciprofloxacin groups, respectively. However, sponsor-defined clinical response was comparable at end of treatment at 50% (4/8) and 53% (9/17) in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups, respectively. In those subjects receiving adjunctive therapy with gentamicin for *Pseudomonas aeruginosa*, the eradication rate was comparable at 40% (2/5) and 40% (4/10) for the alatrofloxacin/trovafloxacin group compared with the ceftazidime/ciprofloxacin group, respectively. There was no evidence of the development of resistance in any persistent isolate of *Pseudomonas aeruginosa*.

Of the eight evaluable alatrofloxacin/trovafloxacin subjects and 17 ceftazidime/ciprofloxacin subjects with *Pseudomonas aeruginosa* isolated at baseline, five alatrofloxacin/trovafloxacin subjects (63%) and ten ceftazidime/ciprofloxacin (59%) subjects received optional gentamicin therapy (dual therapy). There was no difference in clinical outcomes between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy; however, due to the small number of subjects no definitive conclusions could be drawn.

In bacteriological intent-to-treat subjects, the eradication rates among the most frequently isolated pathogens at baseline were similar to those of the clinically evaluable subset. Of note were two subjects with penicillin-resistant *Streptococcus pneumoniae* in the alatrofloxacin/trovafloxacin group who were clinically cured with eradication. There were seven and nine subjects with baseline septicemia and a post-baseline blood culture in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups, respectively. All were eradicated except for one isolate of *Staphylococcus aureus* in the ceftazidime/ciprofloxacin treatment group, which was persistent.

Among clinically evaluable subjects, 15 (15%) subjects in the alatrofloxacin/ trovafloxacin group and 14 (13%) subjects in the ceftazidime/ciprofloxacin group died within 45 days of initiation of study therapy. Among clinically intent-to-treat subjects, 32 (24%) subjects in the alatrofloxacin/trovafloxacin group and 29 (21%) subjects died within 45 days of initiation of study therapy. The date of death was missing but had occurred after the end of study following discharge from hospital for one subject (Subject 5926-0065) in the alatrofloxacin/trovafloxacin group.

Medical Officer’s Efficacy Analysis:

In accordance with the previously described MO evaluability criteria, the MO excluded 38 additional patients from the clinically evaluable population because they had no EOS visit. Additionally, 2 patients were excluded because they received < 80% of the prescribed therapeutic regimen. However, the MO changed the evaluability status on an additional 3 patients, thus the total number of MO evaluable patients, approximated that of the sponsor at the EOS. This information has been presented in MO table 137.14, below:

**Table 137.14
Clinically Evaluable Population (as per the MO)**

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
Total Treated	135	140
Sponsor Evaluable EOT	103	109
Sponsor Evaluable EOS	85	89
MO Evaluable at EOT	80	86
MO Evaluable at EOS	85	89
MO Excluded at EOS	18	20
No EOS Visit	18	20
< 80% Of regimen	1	1
Concomitant Antimicrobials	1	1
Re-included in Analysis	2	1
Total Evaluable at EOS	85	89

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* 5 Alatrofloxacin/trovafloxacin patients and 3 ceftazidime/ciprofloxacin patients had no EOT but are included in the EOS analysis thus justifying the increase in evaluable patients at the EOS.

The 85 clinically evaluable alatrofloxacin/trovafloxacin patients represented 63% of the randomized patients and the 89 ceftazidime/ciprofloxacin patients represented 63.6%. The total MO evaluable population of 174 patients represented 63.3% of the total randomized.

The MO’s bacteriologically evaluable population was a subset of the clinically evaluable.

A by-center breakdown of the MO’s evaluable population, is presented below in table 137.15:

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**Table 137.15
Clinically Evaluable Population at EOS by Center (as per MO)**

Center	Total Randomized N = 275 (100%)		Alatrofloxacin/Trovafloxacin		Ceftazidime/Ciprofloxacin	
			N = 85	100 %	N = 89	100 %
5414	12	4.3	5	5.9	6	6.7
5437	1	0.3	0	-	1	1.1
5439	5	1.8	0	-	1	1.1
5795	1	0.3	0	-	0	-
5800	3	1.0	1	1.2	2	2.2
5869	4	1.6	2	2.4	0	-
5871	40	14.5	17	20	13	14.6
5877	14	5.0	5	5.9	4	4.5
5924	12	4.3	4	3.5	0	-
5926	21	7.6	7	8.2	5	6.7
5930	1	0.3	0	-	0	-
5935	6	2.4	1	1.2	3	3.4
5936	4	1.6	0	-	1	1.1
5937	2	0.7	0	-	2	2.2
5940	1	0.3	0	-	0	-
5942	4	1.6	0	-	1	1.1
5945	5	1.8	2	2.4	2	2.2
5948	3	1.0	1	1.2	1	1.1
5952	3	1.0	1	1.2	2	2.2
5953	12	4.3	5	5.9	5	5.6
5955	27	9.8	9	10.6	10	11.2
5956	5	1.8	2	2.4	1	1.1
5957	6	2.9	0	-	2	2.2
5958	3	1.0	0	-	0	-
5961	1	0.3	1	1.2	0	-
5962	1	0.3	0	-	0	-
5963	2	0.7	0	-	2	2.2
5964	1	0.3	0	-	0	-
5966	9	3.2	2	2.4	2	2.2
5972	4	1.6	0	-	1	1.1
5973	3	1.0	1	1.2	1	1.1
5975	11	4.0	5	5.9	4	4.4
5977	4	1.6	1	1.2	2	2.2
5978	14	5.0	6	7.1	7	7.9
5979	6	2.4	1	1.2	1	1.1
5996	1	0.3	1	1.2	0	-
6072	3	1.0	1	1.2	1	1.1
6073	6	2.4	1	1.2	2	2.2
6075	5	1.8	2	2.4	0	-
6342	3	1.0	0	-	2	2.2
6357	4	1.6	1	1.2	0	-
6557	1	0.3	0	-	1	1.1
6569	1	0.3	1	1.2	0	-

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The demographic make-up of the FDA evaluable population can be seen in Table 137.16:

**Table 137.16
Demographic Characteristics of the FDA Evaluable EOS Population:**

Characteristics		Alatrofloxacin/Trovafloxacin N = 85	Ceftazidime/Ciprofloxacin N = 89
Sex (Female)		27	28
(Male)		58	61
Age (years)	16 –44	23	13
	45 – 64	27	34
	≥ 65	35	42
	Mean	58.3	62.4
Race:	Arab	1	0
	White	82	86
	Asian	2	0
	East Indian	0	1
	Chinese	0	1
	Fijian	1	1
Body weight (kg)	Mean	70.8	62.4
Smoking Status	Ex Smoker	20	33
	Never	33	29
	Smoker	31	27
	Missing	1	0
Mechanical Ventilation	Yes	33	31
	No	52	56
Compromised Respiration	Yes	40	43
	No	42	45
	Missing	2	1
Severity if Illness	Mild/Moderate	39	41
	Severe	46	48
APACHE Score	Mean	12.3	13.6

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The MO's evaluable populations were very similar in terms of the demographic variables of age, weight, sex, and race. However, and as pointed out previously in the sponsor's efficacy analysis, the ceftazidime/ciprofloxacin population appeared to be more severely ill as compared to the trovafloxacin population. This can be appreciated from the higher APACHE score, although the numbers of patients requiring mechanical ventilation or with respiratory compromise are similar. The MO requested that the sponsor determine if there was statistical significance in the difference between APACHE scores between the treatment arms. The sponsor responded that the above values were representative of 75 and 72 of the patients per arm respectively, and that the difference was not statistically significant.

As in study 154-113, the MO provided a separate efficacy analysis for the subgroups of patients who were mechanically ventilated and for those with compromised respiration, as well as for patients with mild/moderate disease, severe disease, and those that were both clinically and bacteriologically evaluable.

EFFICACY:

**Table 137.17
Clinical Response by Patient (as per the MO):**

Timepoint	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	80	54	67.5	86	54	62.8
EOS	85	54	63.5	89	51	57.3

The MO applied a 95% CI with continuity correction factor to these results and found the following:

EOT: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: -11%, 20.4% ($\Delta = 20$).

EOS: Alatrofloxacin/Trovafloxacin versus Ceftazidime/Ciprofloxacin: -9.4%, 21.8% ($\Delta = 20$).

Thus the MO's results differed from those of the sponsor. In the MO's analysis, trovafloxacin appeared to have superior efficacy at the EOT and at the EOS. In the sponsor's analysis, there was equivalence at the EOT timepoint.

Based on the MO's analysis, there were 32 failures at the EOS on the alatrofloxacin/trovafloxacin arm (32/85 {37.6%}) as compared to 38 on the ceftazidime/ciprofloxacin arm (38/89 {42.6%}). The patients who failed as per the MO include failures and relapses. The number of failures in the MO's analysis was comparable to the number in the sponsor's analysis (EOS: 29 and 37 per arm respectively) and the slight increase on both arms was caused by the MO's change in outcome on 3 patients and 1 patient per arm respectively.

Clinical Response by Disease Severity Status:

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**Table 137.18
Clinical Response at EOS for Patients with Mild/Moderate Disease (as per MO):**

Timepoint	alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	36	31	86.1	39	27	69.2
EOS	39	33	84.6	41	29	70.7

As noted previously, in the sponsor's analysis, the overall success rate was higher in this less severely ill population. The MO's and the sponsor's results were comparable (EOS: 85% versus 71% per arm respectively), and were also comparable to the sponsor's results in study 154-113 (EOS: 39/51 (76%) trovafloxacin versus 40/53 (75%). CIs were not applied to any of these analyses because of the small numbers of patients; however, the results were consistent between the studies and between the sponsor and the MO. Overall, alatrofloxacin/trovafloxacin appeared numerically superior to the comparator arms in both studies.

**Table 137.19
Clinical Response at EOS for Patients with Severe Disease (as per MO):**

Timepoint	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	44	23	52.3	47	27	57.4
EOS	46	21	45.7	48	22	45.8

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The MO's results were again comparable to those of the sponsor (49% versus 47%) in this more severely ill population. As in the previously reviewed study (154-113), there was a significant drop in efficacy in this subgroup. However, the 2 arms appeared to be numerically comparable.

Table 137.20

Clinical Response at EOS for Patients requiring Mechanical Ventilation Only (as per MO):

Timepoint	Alatrofloxacin/Trovafoxacin			Ceftazidime/Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	31	16	51.6	30	16	53.3
EOS	33	15	45.5	31	14	45.2

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CIs were not applied to this smaller group of patients; that is in the patients requiring ventilatory support. However, trovafoxacin appeared numerically comparable to ciprofloxacin in both of these more severely ill subgroups. Once again, these results were consistent with those of the sponsor at the EOS (EOS: 50% versus 46.7% per arm respectively). Additionally, these results were consistent with those of the sponsor in study 154-113 (EOS: 15/31 (48.3%) trovafoxacin versus 18/33 (54.6%) ciprofloxacin).

As noted previously, in the sponsor's analysis, the overall success rate was higher in the less severely ill population. (sponsor EOS: 84.6%) trovafoxacin versus 70.7%). The results between the arms were comparable in both the MO's and the sponsor's analyses and indicate at least a 20 percentage point difference in success rates depending on disease severity and ventilatory status.

Table 137.21

Clinical Response at EOS for Clinically and Bacteriologically Evaluable Patients (as per MO):

Timepoint	Alatrofloxacin/Trovafoxacin			Ceftazidime/Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
EOT	37	21	56.8	50	30	60
EOS	39	21	53.8	58	26	51

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As noted from the above the treatment arms appeared relatively equal at the EOS with a slight numerical superiority of trovafoxacin. Additionally, these results differed moderately from those of the sponsor, where the alatrofloxacin/trovafoxacin arm was superior to the ceftazidime/ciprofloxacin arm at both the EOT and EOS (EOT: 68% versus 62% and EOS: 56% and 48% per arm respectively), whereas in the MO's analysis ciprofloxacin evidenced a moderate numerical superiority at the EOT and a moderate numerical inferiority at the EOS.

Clinical Response by Baseline Pathogen:

The MO elected to present clinical response by baseline pathogen as well as pathogen eradication rates for the EOS only. As stated in the introduction, the determination of bacteriologic outcome was based on either culture results or in the absence of a culture, the outcome was extrapolated from the clinical outcome. Neither variable was an individual, by-patient variable because there were patients who had more than 1 organism isolated from predominantly bronchoscopy samples.

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Table 137.20
Clinical Response by Baseline Pathogen at the EOS (as per MO)

Pathogen	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	5	4	80	6	4	66.7
<i>Moraxella catarrhalis</i>	-	-	-	2	1	50
<i>Streptococcus pneumoniae</i>	3	2	66.7	3	0	0
<i>Stenotrophomonas maltophilia</i>	1	0	0	-	-	-
<i>Haemophilus parainfluenzae</i>	1	0	0	3	2	66.7
<i>Klebsiella pneumoniae</i>	4	2	50	3	1	33.3
<i>Pseudomonas aeruginosa</i>	5	1	20	14	5	35.7
<i>Klebsiella oxytoca</i>	-	-	-	1	1	100
<i>Escherichia coli</i>	6	5	83.3	12	5	41.7
<i>Proteus mirabilis</i>	1	0	0	-	-	-
<i>Morganella morganii</i>	1	1	100	-	-	-
<i>Acinetobacter baumannii</i>	4	1	25	1	1	100
<i>Staphylococcus aureus</i>	11	8	72.7	15	6	40
<i>Serratia marcescens</i>	2	1	50	3	1	33.3
<i>Enterococcus faecalis</i>	1	0	0	2	1	50
<i>Enterobacter cloacae</i>	4	1	25	6	3	50
<i>Enterobacter aerogenes</i>	1	0	0	3	0	0
<i>Neisseria meningitidis</i>	2	2	100	-	-	-
<i>Bacteroides melaninogenicus</i>	1	1	100	-	-	-
<i>Acinetobacter calcoaceticus</i>	-	-	-	1	0	0
<i>Citrobacter diversus</i>	-	-	-	1	0	0
<i>Citrobacter freundii</i>	-	-	-	2	1	50
<i>Proteus vulgaris</i>	-	-	-	2	1	50
<i>Legionella pneumophila</i>	3	2	66.7	2	2	100
<i>Streptococcus mitis</i>	1	1	100	-	-	-
<i>Streptococcus agalactiae</i>	1	1	100	-	-	-
<i>Hafnia alvei</i>	1	1	100	-	-	-
<i>Pseudomonas fluorescens</i>	-	-	-	1	0	0
Total	55	34	61.8	75	33	44

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The MO's results differed from those of the sponsor (EOS: alatrofloxacin/trovafloxacin 80.3% versus ceftazidime/ciprofloxacin: 47.9%) although proportionately the clinical response rates were similar. In study 154-113, the clinical response rates for this subgroup were: EOS 59.4% trovafloxacin versus 54.8% ciprofloxacin. There was a much higher rate of clinical failure in patients with *Staphylococcus aureus* as the baseline pathogen on the ciprofloxacin arm. A CI was not applied as this was not an individual variable.

Below, in MO table 137.21 is clinical response by baseline pathogen only for the requested pathogens:

Table 137.21
Clinical Response by Baseline Pathogen at the EOS (Clinically evaluable Population/Requested Pathogens Only: as per MO)

Pathogen	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
	N	No. Cured	%	N	No. Cured	%
<i>Haemophilus influenzae</i>	5	4	80	6	4	66.7
<i>Escherichia coli</i>	6	5	83.3	12	5	41.7
<i>Klebsiella pneumoniae</i>	4	2	50	3	1	33.3
<i>Staphylococcus aureus</i>	11	8	72.7	15	6	40
<i>Pseudomonas aeruginosa</i>	5	1	20	14	5	35.7
Total	31	20	64.5	50	21	42

Thus indicating that when only the requested pathogens were evaluated, the clinical response of the alatrofloxacin/trovafloxacin-treated patients was superior to that of the ceftazidime/ciprofloxacin-treated

patients. This result was similar to that seen in the sponsor's analysis and once again appears to be in part due to the numerically inferior activity of ceftazidime/ciprofloxacin versus *Staphylococcus aureus*.

Mortality:

The MO found that there were 11 deaths on the trovafloxacin arm (11/85 {12.9%}) as compared to 10 on the ciprofloxacin arm (10/89 {11.22%}). These were deaths that occurred within 45 days of the study. As stated previously, the MO elected to evaluate these patients in the safety portion of this review. The number of deaths was comparable between the 2 studies.

Bacteriologic Response:

Table 137.22
Pathogen Eradication Rates at the EOS (Bacteriologically evaluable Population, as per MO)

Pathogen	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
	N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	5	4	80	6	5	83.3
<i>Moraxella catarrhalis</i>	-	-	-	2	1	50
<i>Streptococcus pneumoniae</i>	3	3	100	2	0	0
<i>Stenotrophomonas maltophilia</i>	1	0	0	-	-	-
<i>Haemophilus parainfluenzae</i>	1	1	100	3	3	100
<i>Klebsiella pneumoniae</i>	4	2	50	2	1	50
<i>Pseudomonas aeruginosa</i>	5	1	20	13	7	53.8
<i>Klebsiella oxytoca</i>	-	-	-	1	1	100
<i>Escherichia coli</i>	6	6	100	10	9	90
<i>Proteus mirabilis</i>	1	0	0	-	-	-
<i>Morganella morganii</i>	1	1	100	-	-	-
<i>Acinetobacter baumannii</i>	4	2	50	1	1	100
<i>Staphylococcus aureus</i>	10	9	90	12	6	50
<i>Serratia marcescens</i>	2	2	100	3	2	66.7
<i>Enterococcus faecalis</i>	1	0	0	2	1	50
<i>Enterobacter cloacae</i>	4	2	50	5	5	100
<i>Enterobacter aerogenes</i>	1	0	0	2	0	0
<i>Neisseria meningitidis</i>	2	2	100	-	-	-
<i>Bacteroides melaninogenicus</i>	1	1	100	-	-	-
<i>Acinetobacter calcoaceticus</i>	-	-	-	1	0	0
<i>Citrobacter diversus</i>	-	-	-	1	1	100
<i>Citrobacter freundii</i>	-	-	-	2	1	50
<i>Proteus vulgaris</i>	-	-	-	2	1	50
<i>Legionella pneumophila</i>	3	2	66.7	2	2	100
<i>Streptococcus mitis</i>	1	1	100	-	-	-
<i>Streptococcus agalactiae</i>	-	-	-	1	0	0
<i>Hafnia alvei</i>	1	1	100	-	-	-
<i>Pseudomonas fluorescens</i>	-	-	-	1	0	0
Total	51	36	70.5	68	47	69.1

Based on the MO's analysis, the overall pathogen eradication rate of alatrofloxacin/trovafloxacin was marginally numerically superior to that of ceftazidime/ciprofloxacin at the EOS. As stated above, the MO's outcome assessment was based either on repeat culture data or, in the absence of a culture, outcome was extrapolated from the EOT data as well as the clinical status of the individual patient.

The MO noted however, that the results of this analysis were similar to those of the sponsor (EOS: alatrofloxacin/trovafloxacin: 72.4% versus ceftazidime/ciprofloxacin: 64.7%). These rates were comparable to the sponsor's EOS pathogen eradication rates in study 154-113 (EOS: trovafloxacin 44/61 (72.1%) as compared to ciprofloxacin 34/52 (55.3%).

Although the MO determined that not all the organisms found in table 137.22 were pathogens, for example, *Neisseria meningitidis*, the exclusion of a small number of organisms from each arm, would not ensure a major difference in outcome

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The lower eradication rate of ciprofloxacin appeared to be attributable to the lower eradication rate of *Staphylococcus aureus*.

Pathogen eradication rates for the requested pathogens only, can be seen below in table 137.23:

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Table 137.23
Pathogen Eradication Rates at the EOS (Bacteriologically Evaluable Population/Requested Pathogens Only: as per MO)

Pathogen	Alatrofloxacin/Trovafloxacin			Ceftazidime/Ciprofloxacin		
	N	No. Erad.	%	N	No. Erad.	%
<i>Haemophilus influenzae</i>	5	4	80	6	5	83.3
<i>Escherichia coli</i>	6	6	100	10	9	90
<i>Klebsiella pneumoniae</i>	4	2	50	2	1	50
<i>Staphylococcus aureus</i>	10	9	90	(14)	6	(42.8)
<i>Pseudomonas aeruginosa</i>	5	1	20	13	7	53.8
Total	30	22	73.3	43	28	65.1

The MO's results are the similar as the sponsor's (EOS: alatrofloxacin/trovafloxacin: 75% versus ceftazidime/ciprofloxacin: 66.6%).

Overall, the 2 agents appeared numerically comparable in the eradication of *Haemophilus influenzae*, *Escherichia coli*, and *Klebsiella pneumoniae*. The activity of alatrofloxacin/trovafloxacin versus *Staphylococcus aureus* was much higher than that of ceftazidime/ciprofloxacin. Additionally and as in the sponsor's analysis the activity of alatrofloxacin/trovafloxacin versus *Pseudomonas aeruginosa* was very poor as compared to that of ceftazidime/ciprofloxacin which was 50%.

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Bacteriologic Response in Subjects with *Pseudomonas aeruginosa* at baseline:

There were 5 alatrofloxacin/trovafloxacin and 13 ceftazidime/ciprofloxacin subjects in the MO evaluable population that had *Pseudomonas aeruginosa* as the baseline pathogen.

4/5 trovafloxacin patients received concurrent anti-pseudomonal coverage (3 gentamicin and 1 amikacin) and 3 were clinical failures with persistence of the baseline pathogen. Only one of the 4 (25%) was a clinical cure with eradication. The 1 patient who received no concurrent aminoglycoside was also a failure with persistence. In study 154-113, 5 of the 6 patients on the trovafloxacin arm, who received additional anti-pseudomonal coverage, had eradication of the baseline isolate (83.3%). In that study, 3/7 (43%) patients who received monotherapy had persistence.

The total trovafloxacin versus *Pseudomonas aeruginosa* eradication rate for the 2 studies combined is $10/13 + 1/5 = 11/18$ (61.1%). Concurrent anti-pseudomonal therapy was utilized in 6 of these cases with resultant eradication (33.3%), although 3 of these cases were clinical failures. Therefore, in 3 of 18 (16.6%) clinically evaluable patients with baseline *Pseudomonas aeruginosa*, in whom additional coverage was used, both a clinical cure and pathogen eradication were obtained. The numbers between these 2 studies were too small and too inconsistent in order to be able to either verify or refute that sponsor's claim that additional anti-pseudomonal coverage may be helpful in the eradication of *Pseudomonas aeruginosa* in this population.

On the ceftazidime/ciprofloxacin arm of this study, 9/13 clinically evaluable patients with baseline *Pseudomonas aeruginosa*, received concurrent anti-pseudomonal coverage (6 gentamicin and 3 amikacin) and 6 were clinical failures with persistence of the baseline pathogen (66.6%). The remaining 3 patients were clinical cures with eradication (33.3%). Of the 4 patients who received no concurrent therapy, 2 were clinical cures with eradication, and 2 were clinical failures, one with eradication, and 1 with persistence. In study 154-113, 4/7 patients received additional anti-pseudomonal coverage, and persistence was seen in 3 of these cases, although clinical cure was seen in 4. The remaining 3 patients were failures with persistence (100%).

The total ciprofloxacin versus *Pseudomonas aeruginosa* eradication rate for the 2 studies combined is 7/13 + 1/7 = 8/20 (40%). Concurrent anti-pseudomonal therapy was utilized in 13 of these cases with resultant eradication in 4 cases (30.7%) although 9/13 of these cases were clinical failures. Therefore, in 4 of 13 clinically evaluable patients with baseline *Pseudomonas aeruginosa*, in whom additional coverage was used, both a clinical cure and pathogen eradication were obtained.

There is no doubt that the overall activity of trovafloxacin versus *Pseudomonas aeruginosa* appeared superior to that of ciprofloxacin, and that this result stemmed primarily from the controlled US study as opposed to this open study. Additionally, there were enough isolates from study 154-113, to meet the divisional requirements for approval by the "rule of 10".

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Bacteriologic Response in Subjects with *Staphylococcus aureus* at baseline:

10 MO evaluable alatrofloxacin/trovafloxacin subjects and 15 evaluable ceftazidime/ciprofloxacin subjects had *Staphylococcus aureus* isolated at baseline. On the alatrofloxacin/trovafloxacin arm, eradication was seen in 9/10 cases. 2 of these 9 were clinical failures. Additionally, there was one patient who was a clinical failure with persistence.

The MO elected to list the patients with the specimen source and other isolates from the same specimen below:

- # 54140269: TTA: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus parainfluenzae*, and *Serratia marcescens*. Failure with eradication of all isolates.
- #58710440: Lung biopsy: *Staphylococcus aureus* and *Klebsiella pneumoniae*. Failure with eradication of both isolates.
- #59260010: Sputum: *Staphylococcus aureus* only. Failure with persistence.
- #59480125: Sputum: *Staphylococcus aureus* and *Haemophilus influenzae*. Cure with eradication of both isolates.
- #59530216: Bronchial lavage: *Staphylococcus aureus* and *Hafnia alvei*. Cure with eradication of both isolates.
- #59530252: Bronchial lavage: *Staphylococcus aureus* and *Haemophilus influenzae*. Cure with eradication of both isolates.
- #59550221: Bronchial lavage: *Staphylococcus aureus*, *Haemophilus influenzae*, and *Bacteroides melaninogenicus*. Cure with eradication of all isolates.
- #59550267: Bronchial lavage: *Staphylococcus aureus*. Cure with eradication.
- #59550268: Bronchial lavage: *Staphylococcus aureus* and *Morganella morganii*. Cure with eradication of both isolates.
- #59660341: Orotracheal aspirate: *Staphylococcus aureus*, *Escherichia coli*, and *Acinetobacter baumannii*. Cure with eradication of all isolates.

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Notable from this list is that *Staphylococcus aureus* was the sole isolate in 2 cases only. There was no discernible pattern from this listing as to the necessity of this isolate being the sole pathogen in order to be considered a true pathogen.

A similar listing follows for the ceftazidime/ciprofloxacin arm:

- #54140297: Bronchial lavage: *Staphylococcus aureus*. Failure with persistence.
- #54370329: Sputum: *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*. Failure with persistence of all isolates.
- #58710427: Lung biopsy: *Staphylococcus aureus*. Failure with persistence
- #58710439: Blood: *Staphylococcus aureus* and sputum: *Enterobacter aerogenes* and *Pseudomonas aeruginosa*. Failure with persistence of the blood isolate.
- #59260011: Sputum: *Staphylococcus aureus*: Failure with persistence.
- #59260060: Sputum: *Staphylococcus aureus*: cure with eradication.
- #59260066: Sputum: *Staphylococcus aureus* and *Haemophilus influenzae*. Cure with eradication of both isolates.
- #59450134: Sputum: *Staphylococcus aureus*: Failure with persistence.
- #59480126: Sputum: *Staphylococcus aureus* and *Klebsiella pneumoniae*. Cure with eradication of both isolates.
- #59520094: Orotracheal aspirate: *Staphylococcus aureus* and *Escherichia coli*: Failure with persistence of both isolates.
- #59530251: Bronchial lavage: *Staphylococcus aureus* and *Pseudomonas aeruginosa*: Cure with eradication of both isolates.
- #59550247: Bronchial lavage: *Staphylococcus aureus* and *Moraxella catarrhalis*: Failure with persistence of both isolates.
- #59720325: TTA: *Staphylococcus aureus* (persistent), and *Citrobacter freundii* (eradicated): failure.
- #59750404: Sputum: *Staphylococcus aureus*: Cure with eradication.
- #59780367: Bronchial lavage: *Staphylococcus aureus*: Cure with eradication.

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On this arm of the 15 evaluable isolates, 14 had the organism isolated from the respiratory tree. Not all isolates had an EOS outcome, as 2 were EOT failures with persistence. *Staphylococcus aureus* was the sole baseline isolate in 7 of the cases and was isolated from the sputum in 4 of these (2 cures/eradication and 2 failures/persistence). If these patients were eliminated from the analysis, the eradication rate would change to 5/11 (45.4%). If the same was done for the trovafloxacin arm (eliminate 1 failure with persistence), the eradication rate would be 9/9 (100%). Alternatively, if only those specimens where *Staphylococcus aureus* was the sole pathogen were considered evaluable, independent of the source, the eradication rates would be trovafloxacin 1/2 (50%) versus ciprofloxacin 3/7 (42.8%).

In study 154-113, 8 MO evaluable trovafloxacin subjects and 6 evaluable ciprofloxacin subjects had *Staphylococcus aureus* at baseline.

Failure with persistence was seen in 4/8 (50%) of the trovafloxacin patients. Additionally, 1/4 (25%) of the clinical cures was associated with persistence. Thus 5/8 (62.5%) of isolates were associated with persistence. Therefore the cumulative eradication rate for all isolates would be $4/8 + 9/10 = 13/18$ (72.2%).

On the ciprofloxacin arm, 4/6 subjects were clinical cures with eradication (100%). The cumulative eradication rate was $4/6 + 6/12 = 10/18$ (57.8%). Or 6/14 (42.8%) if persistences carried forward from EOT = 10/20 (50%).

There appeared to be a good clinical correlation between eradication rates and clinical outcome in this subgroup of patients. The MO determined that trovafloxacin's activity against this isolate was better than that of the comparator. This is a requirement for approval, as the comparator is not approved for this isolate.

In terms of approval, if all specimens where *Staphylococcus aureus* as the sole isolate only were accepted, independent of source and in correlation with the Gram stain and clinical picture, then the cumulative eradication rate would be: $\frac{1}{2} + 0/3 = 1/5$ (20%), as only 3 sputum specimens met these parameters in 113 and all were failures with persistence.

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Cross-Tabulation of Clinical Response and Pathogen Outcome at the EOS:

There were 25 instances of incompatibility between clinical response and pathogen outcome in this trial. Specifically, there were 15 cases of clinical failure with bacteriologic eradication on the ceftazidime/ciprofloxacin arm and 9 cases on the alatrofloxacin/trovafloxacin arm. There were no cases of success with persistence on the ceftazidime/ciprofloxacin arm and 1 case on the alatrofloxacin/trovafloxacin arm.

On the ceftazidime/ciprofloxacin arm, the 15 failures were associated with *Citrobacter diversus* (1), *Enterobacter cloacae* (2), *Escherichia coli* (4), *Haemophilus influenzae* (1), *Haemophilus parainfluenzae* (1), *Klebsiella oxytoca* (1), *Pseudomonas aeruginosa* (2), and *Serratia marsecens* (1).

On the alatrofloxacin/trovafloxacin arm, the 9 failures were associated with *Acinetobacter baumannii* (1), *Enterobacter cloacae* (1), *Haemophilus parainfluenzae* (1), *Escherichia coli* (1), *Klebsiella pneumoniae* (1), *Serratia marsecens* (1), *staphylococcus aureus* (1), and *Streptococcus pneumoniae* (1). The 1 success was associated with *Klebsiella pneumoniae*.

No meaningful conclusions could be drawn from this data with regards to trovafloxacin. It appeared as if ceftazidime/ciprofloxacin was associated with more inconsistencies in cases where *Enterobacteriaceae* were considered pathogens.

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Safety Review:

88/135 (65%: 176 events) alatrofloxacin/trovafloxacin-treated subjects and 79/140 (56%: 167 events) ceftazidime/ciprofloxacin-treated subjects had at least one AE, (all causality). In this study, which included the intravenous administration of study drug for at least 3 days, there did not appear to be a large number of events associated with the intravenous insertion site (2/135(1%) versus 8/140 (6%) per arm respectively, as compared to study 154-113 where this type of event was seen in 29/127 (23%) of the trovafloxacin-treated subjects and 24/137 (18%) of the ciprofloxacin-treated subjects.

The percentage of subjects reporting at least 1 treatment-related adverse event was 12% (16/135: 19 events), on the alatrofloxacin/trovafloxacin arm, and 4% (5/140: 5 events), on the ceftazidime/ciprofloxacin arm.

The most commonly reported adverse event on the alatrofloxacin/trovafloxacin arm was related to the gastrointestinal system (vomiting).

On the ceftazidime/ciprofloxacin arm, no system was more affected.

Copied from the Esub and modified by the MO are the Sponsor's Tables 6.1 and 6.2, Summary of Adverse Events by Body System: All Causality and Table 6.3, Summary of Adverse Events by Body System, Treatment-Related.

Table 137.24
Adverse Events, All Treated Patients (Modified Sponsor Table 6.1)

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
Number of Subjects Treated	135 (100%)	140 (100%)
Subject-Days of Exposure	1304	1529
Subjects With At Least One Event	88 (65%)	79 (56%)
Number of Adverse Events	176	167
Subjects with Serious Adverse Events	37 (27%)	36 (26%)
Subjects with Severe Adverse Events	38 (28%)	33 (24%)
Subjects Discontinued Due to Adverse Events	16 (12%)	6 (4%)
Subjects with Dose Reductions or Temporary Discontinuations due to Adverse Events	0	0
Subjects Discontinued Due to Objective Test Findings	5 (4%)	4 (3%)
Subjects with Dose Reductions or Temporary Discontinuations due to Objective Test Findings	0	0

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Table 137.25
Adverse Events by Body System, All Causality (Modified Sponsor Table 6.2)

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	135 (100%)	140 (100%)
Subjects With At Least One Event	88 (65%)	79 (56%)
Subjects Discontinued due to Adverse Event	16 (12%)	6 (4%)
ADVERSE EVENTS BY BODY SYSTEM:		
Appl./Inj./Incision/Insertion Site	2 (1%)	8 (6%)
Autonomic Nervous	5 (4%)	0
Cardiovascular	23 (17%)	25 (18%)
Centr. & Periph. Nerv.	17 (13%)	9 (6%)
Endocrine	1 (<1%)	1 (<1%)
Gastrointestinal	24 (18%)	25 (18%)
General	30 (11%)	10 (7%)
Hematopoietic	6 (4%)	4 (2%)
Liver/Biliary	2 (1%)	3 (2%)
Metabolic/Nutritional	1 (<1%)	1 (<1%)
Musculoskeletal	2 (1%)	2 (1%)
Neoplasms	1 (<1%)	3 (2%)
Other Adverse Events	5 (4%)	7 (5%)
Psychiatric	5 (4%)	13 (9%)
Respiratory	25 (19%)	22 (16%)
Skin/Appendages	7 (5%)	6 (4%)
Special Senses	1 (<1%)	2 (1%)
Urinary System	9 (7%)	5 (6%)

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Table 137.26
Adverse Events by Body system: Treatment-Related (Modified Sponsor Table 6.3).

	Alatrofloxacin/Trovafloxacin	Ceftazidime/Ciprofloxacin
NUMBER OF SUBJECTS:		
Evaluable for Adverse Events	135 (100%)	140 (100%)
Subjects With At Least One Event	16 (12%)	5 (4%)
Subjects Discontinued due to Adverse Event	7 (5%)	1 (<1%)
ADVERSE EVENTS BY BODY SYSTEM:		
Autonomic Nervous	3 (2%)	0
Centr. & Periph. Nerv.	1 (<1%)	0
Gastrointestinal	10 (7%)	1 (<1%)
General	0	1 (<1%)
Psychiatric	1 (<1%)	1 (<1%)
Other Adverse Events	0	0
Skin/ Appendages	3 (2%)	1 (<1%)
Special Senses	0	1 (<1%)

Further breakdown of the treatment-related events, indicated that 3 (2%) of the events on the alatrofloxacin/trovafloxacin arm were severe in nature, as compared to 1 on the ceftazidime/ciprofloxacin arm. The 3 severe events on the alatrofloxacin/trovafloxacin arm, consisted of 2 episodes of skin rash and 1 episode of vomiting. The severe event on the ceftazidime/ciprofloxacin arm was multi-organ failure.

Table 137.27

Most Common AEs/Treatment-Related All Treated Patients (as per the MO)

# of subjects with at least 1 event	Alatrofloxacin/Trovafloxacin N = 135 16 (12%)		Ceftazidime/Ciprofloxacin N = 140 5 (4%)	
	Autonomic Nervous system	3	(2%)	0
Flushing	3	(2%)	0	-
GI System	10	(7%)	1	(<1%)
Vomiting	6	(4%)	0	(<1%)
Skin/Appendages	3	(2%)	1	-
Rash	3	(2%)	1	-

Deaths:

Overall (ITT population), there were 37 deaths on the alatrofloxacin/trovafloxacin arm and 30 on the ceftazidime/ciprofloxacin arm during the study. 9 deaths on the alatrofloxacin/trovafloxacin arm and 7 on the ceftazidime/ciprofloxacin arm occurred while receiving therapy and were considered unrelated to the study drug by the investigator. 23 deaths on the alatrofloxacin/trovafloxacin arm and 22 on the ceftazidime/ciprofloxacin arm occurred after therapy but during the study period and were also considered unrelated to the study drugs. An additional 6 subjects per arm respectively, died > 30 days after the last dose of the study drug and these deaths were also considered unrelated to the study drugs.

The subjects who died during the study are reviewed below:

Alatrofloxacin/Trovafloxacin (N = 37):

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- #58770418: 83 YO male died of worsening pneumonia during the post-treatment period, study day 7.
- #59260068: 68 YO died post-therapy of worsening pneumonia. Therapy was discontinued on study day 5.
- 359350142: 78 YO female died on study day 21 of worsening pneumonia. Study drugs stopped on study day 3.
- #59559224: 65 YO male died on study day 14 of a CVA.
- #59550274: 73 YO female died on study day 15 of a pulmonary embolism.
- #59550291: 49 YO male died on day 60 of progression of coma.
- #59550130: 75 YO female died on study day 10 of worsening COPD.
- #59560230: 94 YO female died on day 27 of multiorgan failure.
- #60730476: 84 YO male died on study day 10 of exacerbation of respiratory failure.
- #63570484: 67 YO female died unexpectedly on day 48.
- #54140271: 89 YO female died on study day 4 of worsening pneumonia.
- #54140293: 82 YO male died on study day 4 of septic shock and pneumonia.
- #54140298: 86 YO male died on study day of ARDS.
- #54390218: 60 YO female died on study day 13 of worsening underlying neurologic disease.
- #57950577: 72 YO female died on study day 2 of renal insufficiency.
- #58690025: 61 YO male died on study day 9 of septic shock and worsening pneumonia.
- #58710072: 40 YO male died on study day 4 of an acute MI.
- #58710422: 62 YO male died on study day 8 of a CVA.
- #58710423: 48 YO female died on study day 2 of a CVA.
- #58710426: 70 YO male died on study day 5 of cardiac arrest an head injury.
- #58710429: 76 YO male died on study day 9 of cardiac arrest, post-therapy.
- #59240537: 70 YO female died on study day 6 of multiorgan failure.
- #59260065: 67 YO female died on study day 51 of a CVA.
- #59260083: 74 YO female died on study day 3 of a recurrent subarachnoid hemorrhage.
- #59360111: 79 YO male died on study day 21 of a new aspiration pneumonia.
- #59400113: 54 YO female died on study day 2 of a subarachnoid hemorrhage.
- #59420146: 67 Yo male died on study day 4 of progression of cardiogenic shock.
- #59550227: 70 YO female died on study day 14 of worsening pneumonia.
- #59570282: 67 YO male died on study day 2 or worsening pancreatitis.
- #59640321: 71 YO female died on study day 10 of cardiac failure.
- #59660312: 78 YO male died on study day 15 of a brain tumor.
- #59720328: 74 YO male died on study day 11 of multiorgan failure.
- #59770378: 51 YO male died on study day 2 of progression of a CVA.
- #59780411: 70 YO male died on study day 13 of septic chock.
- #59780558: 58 YO female died on study day 9 of multiorgan failure.
- #60720441: 72 YO male died on study day 7 of ARDS.
- #60720443: 68 YO male died on study day 7 of intra-abdominal sepsis.
- #60730478: 85 YO male died on study day 4 of sepsis.

Ceftazidime/Ciprofloxacin (N = 30):

- #58690028: 76 YO male died on study day 7 of CHF.
- #58710424: 72 YO male died on study day 8 of an MI
- #58710431: 67 YO male died on study day 3 of an MI.
- #58710549: 55 YO male died on study day 6 of a CVA.
- #58770414: 85 YO female died on study day 5 of CHF.
- #59240146: 43 YO male died on study day 5 of multiorgan failure.
- #59240047: 72 YO male died on study 3 of CHF.
- #59300049: 73 YO male died on study day 7 of sepsis/gallbladder.
- #59450173: 88 YO male died on study day 3 of ventilatory failure.
- #59520094: 82 YO male died on study day 26 of an MI.

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- #59550215: 64 YO male died on study day 8 of worsening pneumonia.
- #59530249: 71 YO male died on study day 2 of septic shock.
- #59550273: 63 YO male died on study day 4 of septic shock.
- #59580238: 83 YO female died on study day 4 of cardiogenic shock,
- #50660309: 79 YO female died on study day 18 of pneumonia and multiorgan failure.
- #59720326: 51 YO female died on study day 12 of cardiac arrest.
- #60750457: 84 YO male died on study day 2 of respiratory failure.
- #63570481: 71 YO male died on study day 10 of cardiac arrest.
- #54140294: 85 YO male died on study day 22 of COPD.
- #54140295: 63 YO male died on study day 21 of CHF.
- #58710074: 63 YO female died on study day 30 of cardiac arrest.
- #58710079: 74 YO male died on study day 16 of a CVA.
- #58710425: 65 YO male died on study day 12 of a pulmonary embolism.
- #58770415: 73 YO male died on study day 13 of progressive prostatic cancer.
- #59260081: 74 YO female died on study day 23 of a progressive brain tumor.
- #59260084: 75 YO male died on study day 19 of ventricular fibrillation.
- #59550248: 75 YO male died on study day 16 of hypoxic encephalopathy.
- #59580239: 83 YO male died on study day 19 of melanoma.
- #59730318: 83 YO male died on study day 8 of renal disease.
- #60730473: 90 YO female died on study day 24 of cachexia.

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***Medical Officer's Comment:** The MO detected no clear pattern in the deaths above that could be attributed to the either regimen. Approximately 8 patients died of complications related to the disease under study, nosocomial pneumonia, and therefore could be classified as therapeutic failures on the alatrofloxacin/trovafloxacin arm as compared to 4 patients on the comparator arm. These numbers are not unexpected and compatible with those seen in study 154-113.*

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Other Serious Adverse Events Related to the Study Drug:

Other than the deaths which were considered serious, a total of 49 (36%) of the alatrofloxacin/trovafloxacin patients and 47 (34%) of the ceftazidime/ciprofloxacin patients had serious adverse events. All events on the alatrofloxacin/trovafloxacin arm were considered unrelated to the study drug as compared to 47 on the ceftazidime/ciprofloxacin arm.

The following patients from each treatment group had other serious adverse events which were related to the study drug and which the MO determined should be reviewed further:

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Alatrofloxacin/Trovafloxacin (N = 2):

- #59720327: 60 YO female permanently discontinued study drug on day 3 after the development of a maculopapular skin rash described as severe in nature. The rash cleared without therapy by study day 5.
- #59240014: 67 YO female developed a maculopapular rash on the abdomen and legs on study day 4. This event led to the permanent discontinuation of therapy and resolved without therapy by study day 9.

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Ceftazidime/Ciprofloxacin (N = 1)

- #60750458: elevated international normalized ratio and bruising related to study drug which resolved off therapy.

Rash (Not severe):APPEARS THIS WAY
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- #59480127: 34 YO female permanently discontinued alatrofloxacin on study day because of a maculopapular skin rash. This reaction was considered mild in nature and resolved off the study drug

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- #59300049: 63 YO male developed a maculopapular rash on the chest on study day 2. No action was taken and the rash was present at the EOT.

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ON ORIGINAL**Clinical Laboratory Abnormalities:**

5 patients on the alatrofloxacin/trovafloxacin arm and 2 patients on the ceftazidime/ciprofloxacin were discontinued from study drug due to laboratory abnormalities. In only one alatrofloxacin/trovafloxacin patient was the abnormality correlated with study drug by the investigator. A short narrative of this patient follows:

- #59550224: 65 YO male, history of cerebral hemorrhage, received intravenous alatrofloxacin for 7 days and oral trovafloxacin for 3 days. At baseline the patient had a normal alkaline phosphatase, which had increased to _____ on day 8. The level decreased to normal on study day 11. The investigator determined causality.

In addition however, to the above patient, the following patients were found to have clinical significant laboratory abnormalities:

Alatrofloxacin/Trovafloxacin (N = 10):APPEARS THIS WAY
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- #5871-0078: 67 YO male with normal SGOT, SGPT and Alkaline Phosphatase at the start of the study, developed increased LFTs to twice normal on study day 9 and _____ on study day 15. After a 12 day course of therapy. The LFTs decreased to normal approximately 3 weeks later.
- #58710428: 75 YO female received 11 days of therapy. Patient developed neutropenia day 5 which resolved post-therapy.
- #59240048: 63 YO with a history of colon cancer and partial hepatectomy. This patient was withdrawn from the trial on study day 3 because of increased bilirubin. The patient had received _____ blood post-operatively. Renal failure was also present. None of the above appeared related to the study drug.
- #59260059: 32 YO male with an extradural hematoma, received study drug for 10 days. Patient had abnormal LFTs (5-x normal) prior to therapy. After IV R/x the LFTs had decreased to 2 x normal but subsequently reincreased at the EOT visit to > 5 x normal. LFTs normalized 3 weeks later.
- #59360110: 50 YO male with extradural hematoma, received study drug for 5 days and was discontinued because of increased LFTs to 3 x normal. Levels decreased after 4 weeks.
- #59360110: 79 YO male with a CVA received 8 days of study drug and was discontinued because of increased LFT, predominantly Alkaline Phosphatase. Phosphatase which was 2 x normal. A later assessment revealed that the AE was not due to study drug but to an ischemic hepatic event.

- #59420146: 67 YO male, history of MI. Discontinued from therapy on study day 3 because of increased LFTs to This increase was attributed to cardiogenic shock and the patient died of this 5 days later.
- #59550274: 73 YO male with angina and CVA received 9 days of study drug and developed an alkaline phosphatase elevation on day 7. The investigator attributed the elevation which peaked at the EOT at to the study drug. Patient died of a pulmonary embolism and no follow-up was obtained.
- #59570278: 26 YO male post-traumatic NP, received study drug f10 days. The patient had increased LFTs on study day 3 which later resolved with no action taken. Causality was attributed to hepatic cytolysis and not to the study drug
- #59780558: 57 YO female post-surgery NP received study drug for 8 days and then Zosyn® and gentamicin for 7 days because of clinical failure. The patient had increased LFT's, and thrombocytopenia. This patient died of multiple organ failure and septic shock on day 12.

Ceftazidime/Ciprofloxacin (N=9):

- #541240272: 64 YO male received study drug for 10 days. Leukopenia developed. Outcome not known but causality not attributed to study drug.
- #5871-0424: 72 YO male, Parkinsonian and angina as well as renal impairment had evidence of increased LFTs on study day 6. The investigator attributed the increase to the ceftazidime component of the therapy. The patient died of an acute MI on day 8.
- #58710427: 22 YO male, head injury, developed increased LFTs on study day 6. No follow-up.
- #59260042: 66 YO male with a malignant brain tumor had increased LFTs on study day 3. No causality assessed.
- #59360109: 43 YO male post-surgery with abnormal LFTs on study day 4. Attributed to trauma history.
- #59520094: 81 YO male with a history of CHF had abnormal LFTs on study day 8. Patient died and no follow-up were obtained. Patient was also receiving clindamycin and amiodarone to which increases were attributed.
- #59550289: 78 YO developed increased LFTs on study day 10. These subsequently resolved and were attributed to the study drugs.
- #59790369: 52 YO with a history of intracerebral aneurysm and clipping developed severe anemia on study day 4, which resolved on therapy. Causality unknown.
- #60750458: 75 YO female developed an increased prothrombin time during therapy with ceftazidime. Causality was attributed to study drug and resolved with the discontinuation of coumadin therapy.

As per the sponsor, clinically significant SGOT abnormalities were seen in 8 (7%) of subjects and 13 (10%) of subjects per arm respectively. SGPT abnormalities were seen in 10 (8%) for the alatrofloxacin/trovafloxacin subjects and 14 (11%) of the ceftazidime/ciprofloxacin subjects.

7 (6%) of the alatrofloxacin/trovafloxacin patients and 10 (8%) of the ceftazidime/ciprofloxacin patients had elevated creatinine, none attributed to study drug, 9 (6%) alatrofloxacin/trovafloxacin and 8 (6%) ceftazidime/ciprofloxacin had increased bilirubin values.

Medical Officer's Comment: *The MO determined that all of the above abnormalities were most likely secondary to underlying disease processes.*

Conclusions:

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As per the Sponsor: (Copied from page 74 of the study report):

Alatrofloxacin (equivalent to 300 mg trovafloxacin once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for a total treatment duration of 10 to 14 days was statistically equivalent to intravenous ceftazidime (2000 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (750 mg twice daily) for a total treatment duration of 10 to 14 days for sponsor-defined clinical success rate at the end of treatment.

Sponsor-defined eradication rates were generally comparable at the end of study for most pathogens isolated. Higher eradication rates for the most frequently baseline pathogen, *Staphylococcus aureus*, were seen both at the end of treatment and end of study in the alatrofloxacin/trovafloxacin group compared to the ceftazidime/ciprofloxacin group.

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The pathogen eradication rate for *Pseudomonas aeruginosa* was higher in the ceftazidime/ciprofloxacin group, although the clinical success rate was similar between subjects in both treatment groups with this baseline pathogen. In subjects with *Pseudomonas* infection, gentamicin was used as adjunctive therapy in approximately 60% of the subjects in each treatment group. There was no evidence of emergence of resistance in *Pseudomonas aeruginosa* to trovafloxacin. There was no difference between subjects in the alatrofloxacin/trovafloxacin group who received monotherapy or dual therapy (optional gentamicin), however, due to the small number of subjects no definitive conclusions could be drawn.

Of note, all isolates of *Streptococcus pneumoniae*, including two penicillin-resistant isolates, were eradicated in the alatrofloxacin/trovafloxacin group whereas all isolates in the ceftazidime/ciprofloxacin group were persistent.

The percentage of subjects discontinued from treatment due to adverse events was 12% in the alatrofloxacin/trovafloxacin group and 4% in the ceftazidime/ciprofloxacin group. Seven (7) subjects in the alatrofloxacin/trovafloxacin group and one subject in the ceftazidime/ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all causality and treatment-related adverse events was 65% and 12%, respectively, for subjects in the alatrofloxacin/trovafloxacin group and 56% and 4%, respectively, for subjects in the ceftazidime/ciprofloxacin group. The most commonly reported treatment-related adverse event was vomiting in the alatrofloxacin/trovafloxacin group; all treatment-related adverse events in the ceftazidime/ciprofloxacin were reported by <1% of subjects.

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As per the Reviewer:

The MO's results were comparable to those of the sponsor, as were the clinically evaluable populations. The MO agreed with the sponsor's determinations of outcome, overall, in this trial, and thus accepted all of these determinations as well as those determinations applying to evaluability. The only differences were in the timing of the TOC, i.e. MO at EOS as opposed to sponsor TOC at the EOT (in accordance with evaluability guidelines, and in the MO's exclusion of "cures" who received less than 80% of the prescribed regimen. Additionally the MO changed the outcome in 1 patient on each arm of the study.

The MO's evaluable population consisted of 85 patients on the alatrofloxacin/trovafloxacin arm and 89 on the ceftazidime/ciprofloxacin arm. The demographic characteristics of the 2 populations were very similar in terms of age, weight, sex, and smoking status. There was a question of whether the patients on the comparator arm were more severely ill based on a higher baseline mean APACHE score, however, there was no statistical significance in the difference between mean APACHE scores.

At the EOS, the MO found a clinical success rate of 54/85 (63.5%) alatrofloxacin/trovafoxacin versus 51/89 (57.3%) ceftazidime/ciprofloxacin. These results revealed equivalence of the alatrofloxacin/trovafoxacin arm when a 95 % CI was applied.

The MO's TOC visit outcomes differed from those of the sponsor at the EOT (Sponsor: 74% trovafoxacin versus 70% ciprofloxacin; MO: 67.5% trovafoxacin versus 62.8% ciprofloxacin), in that the sponsor established equivalence at the EOT, whereas the MO did not, although the Δ was the same for both the MO and the applicant.

For all subgroups analyzed by the MO, including patients with mild/moderate disease (EOS: success rate alatrofloxacin/trovafoxacin 33/39 (84.6%) versus ceftazidime/ciprofloxacin 29/41 (70.7%), patients with severe disease (EOS: success rate alatrofloxacin/trovafoxacin 21/46 (45.7%) versus ceftazidime/ciprofloxacin 22/48 (45.8%), patients requiring mechanical ventilation (EOS: success rate alatrofloxacin/trovafoxacin 15/33 (45.5%) versus ceftazidime/ciprofloxacin 14/31 (45.2%), and patients who were both clinically and bacteriologically evaluable (EOS: success rate alatrofloxacin/trovafoxacin 21/39 (53.9%) versus ceftazidime/ciprofloxacin 26/58 (51%), the MO found results comparable with those found by the sponsor in similar analyses. The MO ascertained that the effectiveness of alatrofloxacin/trovafoxacin was numerically comparable to that of ceftazidime/ciprofloxacin in patients with mild/moderate disease and that it was numerically comparable if not equal for the other subgroups. As in the sponsor's analysis, the MO also found that those patients with mild/moderate disease had a higher clinical success rate by an almost 30 percentage point difference compared to severe disease.

Overall pathogen eradication rates were comparable between the 2 arms at 36/51 (70.5%) alatrofloxacin/trovafoxacin versus 47/68 (69.1%) ceftazidime/ciprofloxacin. This included all organisms designated as pathogens by the sponsor. Overall rates only for the requested pathogens were 22/30 (73.3%) alatrofloxacin/trovafoxacin versus 28/43 (65.1%) ceftazidime/ciprofloxacin. The MO determined that all of the above rates were comparable although, when an overall rate was utilized, it appeared that the MO's rate was more valid in terms of its being representative of true pathogens without any contaminants.

Pathogen eradication rates based on follow-up culture results, for the requested in the labeling pathogens were as follows:

Alatrofloxacin/Trovafoxacin:

Haemophilus influenzae: 4/5 (80%)
Escherichia coli: 6/6 (100%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 9/10 (90%)
Pseudomonas aeruginosa: 1/5 (20%)

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Ceftazidime/Ciprofloxacin:

Haemophilus influenzae: 5/6 (83.3%)
Escherichia coli: 9/10 (90%)
Klebsiella pneumoniae: 1/2 (50%)
Staphylococcus aureus: 8/15 (55%)
Pseudomonas aeruginosa: 3/7 (53.8%)

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The MO determined that the 2 agents were numerically comparable in their eradication of *Haemophilus influenzae* and that the numbers of evaluable *Escherichia coli* and *Klebsiella pneumoniae* isolates were too small to be able to draw any valid conclusions. Additionally, numerically, alatrofloxacin/trovafoxacin appeared superior to ceftazidime/ciprofloxacin in the eradication of *Staphylococcus aureus*.

The MO agreed with the sponsor's statement that "additional anti-pseudomonal coverage may be helpful in the eradication of *Pseudomonas aeruginosa* in this population." but determined that the wording of this

statement should be revised to reflect the need for additional ant-pseudomonal coverage both in presumptive as well as documented cases of NP due to *Pseudomonas aeruginosa*.

As the primary efficacy variable was clinical response at the EOS, the MO elected to utilize clinical response by pathogen as the primary determinant of microbiologic efficacy. It should be noted that bacterial eradication rates were often presumptively assigned according to the clinical picture and not a product of cultures. Below are the clinical response rates by pathogen, for those organisms requested by the sponsor:

Alatrofloxacin/Trovafloxacin:

Haemophilus influenzae: 4/5 (80%)
Escherichia coli: 5/6 (83.3%)
Klebsiella pneumoniae: 2/4 (50%)
Staphylococcus aureus: 8/11 (72.7%)
Pseudomonas aeruginosa: 1/5 (20%)

Ceftazidime/Ciprofloxacin:

Haemophilus influenzae: 4/6 (83.3%)
Escherichia coli: 5/12 (41.7%)
Klebsiella pneumoniae: 1/3 (33.3%)
Staphylococcus aureus: 5/14 (35.7%)
Pseudomonas aeruginosa: 5/14 (42%)

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As can be appreciated from the above, the clinical success rates for patients with *Staphylococcus aureus* and *Pseudomonas aeruginosa* were very low in this trial for patients on the ceftazidime/ciprofloxacin arm. Additionally, success rates were very low for those alatrofloxacin/trovafloxacin-treated patients with *Pseudomonas aeruginosa* as the baseline pathogen and quite high, as compared to study 154-113 in those patients with *Staphylococcus aureus*. The MO will address this issue in the MO's overall conclusion for the indication of nosocomial pneumonia.

From the safety review, the MO found that overall mortality was similar in both arms of the study and that causes of death were similar on both arms. There were rare episodes of dizziness or headache in this population of non-ambulatory patients as compared to the previously reviewed indications. Vomiting was the most common AE seen in the alatrofloxacin/trovafloxacin-treated patients as compared no specific AE in the ceftazidime/ciprofloxacin-treated patients.

There were a similar number of patients on each arm with LFT elevations and in only 1 patient on the alatrofloxacin/trovafloxacin arm where these were determined to be severe and related to the study drug.

The MO concluded that alatrofloxacin/trovafloxacin was numerically superior to ceftazidime/ciprofloxacin in the treatment of nosocomial pneumonia of mild/moderate severity (APACHE < 13), and further that no safety issues were identified in the review of this second pivotal study.

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Reviewer's Overall Conclusion with regards to Nosocomial Pneumonia:

The sponsor submitted 2 trials in support of this indication, 154-113, a US, double-blinded, comparative trial comparing the efficacy and safety of alatrofloxacin/trovafloxacin versus ciprofloxacin, and study 154-137, a multinational, non-US, open trial comparing the efficacy and safety of alatrofloxacin/trovafloxacin versus ceftazidime/ciprofloxacin for the indication of nosocomial pneumonia.

Although, the US study was blinded, and the European open, the overall trial design was very similar between the two. Additionally, data management was performed in a blinded fashion, by the sponsor's representatives in a uniform *post-hoc* fashion.

Please refer to the MORs of each study for details, however, in both studies, patients with well-documented NP, were randomized to receive between 10 -14 days of study drug. The initial phase in both studies was intravenous and subsequently (after day 3), the patients could have been converted to an oral regimen if stable. In both trials, vancomycin was allowed on either arm, if patients had documented MRSA. Clindamycin or metronidazole was allowed in both studies on the comparator arms only, if the investigator suspected an anaerobic component to the infectious process. More importantly, in study 154-113, patients on either arm were allowed to receive aztreonam for a documented NP due to *Pseudomonas aeruginosa*, and in study 154-137, intravenous gentamicin was allowed by-protocol only to the patients on the ceftazidime/ciprofloxacin arm who had a documented infection with *Pseudomonas aeruginosa*. Patients on both arms received adjunctive antipseudomonal therapy and prior to unblinding, the sponsor elected to allow the inclusion of the trovafloxacin patients who received adjunctive therapy into the evaluable population.

There was overall agreement between the MO and the sponsor in terms of evaluability and outcome assessments in both trials. The major difference between the analyses was the application of the TOC. The sponsor applied the TOC to the EOT as opposed to the MO, who applied it to the EOS.

The results of both trials are summarized below in MO table 1. At issue is the pooling of the data between the 2 trials, clinically and bacteriologically. The MO elected to provide clinical response by baseline pathogen in lieu of pathogen eradication rates. This decision was made in conjunction with the MTL, Brad Leissa MD, and is justified by the clinical nature of this indication and the lack of EOS cultures.

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MO Table 1
Clinical and Bacteriologic Efficacy of Studies 154-113 and 154-137/MO Evaluable Population

Study	154-113	154-137
Location	US	Multinational
Design	Randomized, Blinded	Randomized, Open
Comparator	Ciprofloxacin IV/PO	Ceftazidime IV/Ciprofloxacin PO
# MO Eval. Patients	147	174
#MO Eval. Trovafloxacin	70	85
#MO Eval. Comparator	77	89
#MO Bacteriologically Eval.	71 (37 trovafloxacin vs. 36 comparator)	97(39 trovafloxacin vs. 58 comparator)
Mean APACHE Score	13.1 trovafloxacin vs. 13.4 comparator	12.3 trovafloxacin vs. 13.6 comparator
Clinical Response EOS	48/70 (68.5%) trovafloxacin vs. 52/77 (67.5%)comparator	54/85 (63.5%) trovafloxacin vs. 51/89 (57.3%)comparator
Clinical Response Mild/Moderate Disease	38/50 (76%) trovafloxacin vs. 39/52 (75%) comparator	33/39 (84.6%) trovafloxacin vs. 29/41 (70.7%) comparator
Clinical Response Severe Disease	10/20 (50%) trovafloxacin vs. 13/25 (52%) comparator	21/46 (45.7%) trovafloxacin vs. 22/48 (45.8%) comparator
Clinical Response Mechanically Ventilated	10/18 (55.6%) trovafloxacin vs. 8/16 (50%) comparator	15/33 (45.5%) trovafloxacin vs. 14/31 (45.2%) comparator
Clinical Response Clinically and Bacteriologically Evaluable	24/37 (64.9%) trovafloxacin vs. 23/36 (63.9%) comparator	21/39 (53.8%) trovafloxacin vs. 26/58 (44.8%) comparator
Clinical Response by Pathogen (Requested in labeling only)	22/37 (59.5%) trovafloxacin vs. 16/30 (53.3%) comparator	20/31 (64.5%) trovafloxacin vs. 21/50 (42%) comparator
<i>Haemophilus influenzae</i>	5/6 (83%) trovafloxacin vs. 6/7 (86%) comparator	4/5 (80%) trovafloxacin vs. 4/6 (67%) comparator
<i>Escherichia coli</i>	3/6 (50%) trovafloxacin vs. 4/5 (80%) comparator	5/6 (83.3%) trovafloxacin vs. 5/12 (41.7%) comparator
<i>Klebsiella pneumoniae</i>	2/4 (50%) trovafloxacin vs. 1/5 (20%) comparator	2/4 (50%) trovafloxacin vs. 1/3 (33%) comparator
<i>Staphylococcus aureus</i>	4/8 (50%) trovafloxacin vs. 4/6 (67%) comparator	8/11 (73%) trovafloxacin vs. 6/15 (40%) comparator
<i>Pseudomonas aeruginosa</i>	8/13 (62%) trovafloxacin vs. 1/7 (14%) comparator	1/5 (20%) trovafloxacin vs. 5/14 (36%) comparator

Combined clinical response rates at the EOS were: 102/155 (65.8%) trovafloxacin versus 103/166 (62.4%) comparators, 95%CI with CCF: - 7.4%, 14.8% ($\Delta = 20$)

The MO determined that the clinical results of the two studies could be pooled. This decision was reached because of the similarities between the populations studied as well as the relative similarities between the clinical efficacy results. In both studies, overall clinical response rates at the EOS were > 60% for the trovafloxacin arms. However, in the open study, the rates were lower on both arms and numerically inferior (not significant), for the comparator. This decrease was surprising in light of the fact that study 154-137 was an open trial. The MO believed that these lower rates were due to the choice of the comparator and specifically, ceftazidime as the initial antimicrobial utilized, as well as to local effects such as different microbial flora, including a higher incidence of *Staphylococcus aureus*, as well as differences in the local practice of medicine. The MO determined that there were a larger number of failures during the initial phase of therapy, thus leading to an almost 10 percentage point drop in clinical response on the comparator arm in study 154-137 as compared to 154-113.

A review of previous submissions for this indication revealed the following:

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Zosyn® NDA 50-684/S-001: Zosyn® was approved for the indication of severe NP, based on the results of one clinical study where ceftazidime was utilized as the comparator agent. APACHE scores were not provided. The patients were determined to be moderately to severely ill based on clinical picture and need for ventilatory support by both the sponsor and the RMO. The study population consisted of patients with both CAP as well as NP and the 2 groups were analyzed separately. Tobramycin was allowed and was utilized in the predominant number of patients. Clinical response rates (EOS) were 47/63 (74%) Zosyn® versus 22/35 (53%) ceftazidime. Pathogen eradication rates (EOS) were as follows, per arm respectively: *Escherichia coli*: 4/6 (67%) vs. 3/6 (50%), *Haemophilus influenzae*: 19/20 (95%) vs. 5/12 (42%),

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Klebsiella pneumoniae 4/5 (80%) versus 3/5 (60%), *Pseudomonas aeruginosa* 6/11 (55%) versus 4/10 (40%), and *Staphylococcus aureus* 13/16 (81%) versus 7/16 (44%). Clinical response by pathogen was provided only for patients with *Pseudomonas aeruginosa* and was 4/10 (40%) versus 4/8 (50%) per arm respectively. Based on this submission, Zosyn® was approved for moderate to severe presumptive nosocomial pneumonia caused by beta-lactamase producing strains of *Staphylococcus aureus*. The label requires the addition of tobramycin when used empirically and until infection with *Pseudomonas aeruginosa* is ruled out.

NOTE: The clinical response rates of Zosyn® are comparable to those of trovafloxacin in the population of patients with mild/moderate disease, and were higher than those of the total population which included patients with severe disease. From a bacteriological standpoint, Zosyn® was numerically superior to trovafloxacin versus all the requested pathogens with the exception of *Pseudomonas aeruginosa*.

NOTE: There was no comparison between the submissions with regards to design. The bacteriology of the ofloxacin submission pointed to a population of patients with CAP.

Ciprofloxacin NDA 19-847/S-008 and NDA 19-857/S008: The applicant submitted a well-designed US trial (Study #089-053), for the indication of severe LRTI and pneumonia. Data from foreign trials was also submitted. At the time of this submission ciprofloxacin was already approved for the LRTI of mild/moderate severity and the applicant was requesting approval for the same indication in patients with severe disease at a higher dosage. The dose of ciprofloxacin utilized was high at 400 mg IV q8 (previously approved dose: 400 mg IV q12), and the comparator agent was imipenem (1000 mg q8 or 500 mg IV q6). APACHE scores were provided and the mean score on both arms was > 16, thus indicating a population at increased risk of death. Other factors that the RMO determined to further bolster the argument that a severely ill population was being studied were age >50 (mean age 59.9), the presence of several underlying conditions the use of ventilators, and the presence of the predominant number of patients in an ICU. In a review of this document, the MO found that there was no severity scoring system. Rather, analyses were performed on subpopulations with low and high APACHE scores as well as by ventilator status (58/71 evaluable ciprofloxacin patients were ventilated (81.6%) as compared to 66/81 (81.4%) of the imipenem patients). Clinical cure rates (pivotal study only), at the EOS (late follow-up), visit were 42/71 (59.2%) versus 32/81 (39.5%), thus indicating superiority of ciprofloxacin versus imipenem. Clinical response by APACHE scores were ciprofloxacin: APACHE low (10-14): 9/25 (36%) and high (-14-49): 23/56 (41%). The respective rates for the imipenem arm were 22/30 (73%) and 20/41 (49%). Clinical response rates by ventilator status were ciprofloxacin: ventilator: 34/58 (59%) and non-ventilated: 24/58 (41%). The respective rates for imipenem were 21/66 (32%) and 45/66 (68%) respectively.

From the above, the reviewing MO concluded that there appeared to be a difference in response rates when the ciprofloxacin patients were divided into those with an APACHE score < 15 and those with an APACHE score >15. It seemed that ciprofloxacin had greater efficacy in those patients with lower scores, as compared to the imipenem arm, where it made no difference. Clinical response rates by pathogen were as follows (ciprofloxacin only): *Haemophilus influenzae*: 14/19 (74%), *Klebsiella pneumoniae*: 8/9 (89%), *Pseudomonas aeruginosa*: 18/29 (62%) and *Staphylococcus aureus*: 8/14 (57%). The applicant received approval for the requested addition of severe disease at the requested dose caused for *Haemophilus influenzae* and *Klebsiella pneumoniae*. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were not

approved for severe NP, because a determination was made that although the numbers of patients with these pathogens were large, the cure rates (57% and 62% respectively), were too low.

NOTE: Of all the aforementioned NDA's, the trial design in the ciprofloxacin SNDA closely approximated that of the trovafloxacin NDA. The MO points out that the ciprofloxacin population studied was more severely ill than that reviewed in the current submission (see above percentages for comparisons). This statement is made (see table 113.16) because in the US study, only 18/70 (25.7%) of evaluable patients were on a ventilator as compared to 16/77 (20.7%) on the ciprofloxacin arm. 15/70 (21.4%) and 24/77 (31.1%) per arm respectively, had compromised respiration (as previously defined). 20/70 (28.5%) had severe disease on the trovafloxacin arm as compared to 35/77 (45.4%) on the ciprofloxacin arm. Approximately 25% of the sponsor's evaluable population had underlying COPD, CAD, asthma, or DM.

In the European study, 33/85(38.8%) of the trovafloxacin patients as compared to 31/89 (34.8%) of the ceftazidime/ciprofloxacin patients were ventilated and 40/85 (47%) of the trovafloxacin patients versus 43/89 (48.3%) of the ceftazidime/ciprofloxacin patients had compromised respiration.

Even if the patients of both studies were added up, the MO still determined that the overall percentage of severely ill patients in the current NDA was lower than that of the ciprofloxacin SNDA.

A review of the CRF of the current submission, revealed that there was no severity of illness scoring system. The investigators merely provided information with regards to underlying illnesses, ventilator status, smoking history and calculated APACHE II scores. In the signs and symptoms, the investigators were able to place a mark in a box numbered 0., 1, 2, and 3 indicating that the symptom was present and if so, was mild, moderate, or severe.

A comparison of the results of the ciprofloxacin SNDA and the current trovafloxacin NDA reveal that the efficacy rates in the populations termed severely ill were very similar (Ciprofloxacin NDA 34/58 (59.5%) as compared to trovafloxacin 10/18 (55.6%) US and 15/33 (45.5%) European but the proportion of the ciprofloxacin (SNDA) population was more severely ill. In other words, comparatively, trovafloxacin did as well in a population of less severely ill patients. The clinical response rates by pathogen were notable for the same rate versus *Pseudomonas aeruginosa*; however, ciprofloxacin was used as monotherapy (SNDA) in most patients (additional antipseudomonal therapy not allowed by-protocol) as compared to trovafloxacin (NDA) where aztreonam or gentamicin could have been used. Clinical response rates in patients with *Staphylococcus aureus* were similar in the SNDA US trial for ciprofloxacin compared to trovafloxacin. Nevertheless, ciprofloxacin did not receive approval for this pathogen. Clinical response rates in patients with *Klebsiella pneumoniae* were superior versus trovafloxacin and slightly lower for *Haemophilus influenzae*.

As per a literature review, (Antimicrobial Agents and Chemotherapy, Volume 38(3), 1984, 547-557: Ciprofloxacin versus Imipenem in severe Pneumonia; Fink et al), "Clinical studies to assess the efficacy of antibiotics for the treatment of pneumonia have been difficult to evaluate. Flaws have included lack of a double-blind design, exclusion of patients with underlying conditions associated with higher mortality, small sample sizes, and the absence of ITT analyses." In this double-blinded randomized comparative trial of high dose ciprofloxacin (400 mg IV TID), versus imipenem (1000 mg IV q6), as monotherapy in severely ill patients (APACHE 17.6), the clinical cure rates were ciprofloxacin 58/86 (67%) versus imipenem 44/83(53%). Pathogen eradication rates (EOS), included the following: *Staphylococcus aureus*: 13/20 (65%) ciprofloxacin versus 11/17 (65%) imipenem, *Escherichia coli*: 10/10 (100%) vs. 11/14 (79%), *Klebsiella* spp.: 10/11 (91%) vs. 12/18 (67%), and *Pseudomonas aeruginosa*: 11/33 (33%) vs. 11/27 (41%) respectively. As noted previously, this trial was performed in a more severely ill population and monotherapy was stipulated. The MO determined from this information that the presence of *Pseudomonas aeruginosa* as a respiratory pathogen is strongly associated with poor outcome and that even appropriate therapy with 2 anti-pseudomonal agents may not lead to a clinical cure.

The current literature overwhelmingly supports the MO's conclusion that NP is a difficult to treat clinical entity with a high mortality rate. Mortality rates are higher depending on the causative agent. In NP due to

Pseudomonas aeruginosa, mortality may approach 80% or higher (Foner et al: Bacterial pneumonia, pp 184 -7; Conn's Current Therapy 1995).

The treatment of NP is usually empirical and there is no consensus in the literature as to a gold standard or any one type of regimen that is associated with a high clinical response rate. Factors that influence the choice of an initial regimen are local experience and the severity of the NP as well as that of the underlying disease. The cornerstone of therapy remains combination therapy usually consisting of an aminoglycoside with a beta-lactam, thus providing for broad-spectrum coverage. A second or third generation cephalosporin is often used in combination with an aminoglycoside, and vancomycin is often also included in the regimen. As stated previously, anaerobic coverage may be added especially in ventilator-associated NP. Other than the ciprofloxacin versus imipenem study cited above, the MO also located the following information:

Hooper et al; NEJM 324:384 -394, 1991: IV ciprofloxacin versus ceftazidime: 15/17 (88%) ciprofloxacin-treated patients (with severe disease) had evidence of cure or improvement as compared to 13/15 (87%) ceftazidime-treated patients at the EOS. Failures on the ceftazidime arm were associated with Enterobacteriaceae or *Acinetobacter* spp. Failures on the ciprofloxacin arm were associated with *Staphylococcus aureus* or Streptococci.

Salta et al. Am J Med 1985; Suppl. 6A; 104 -109: Pneumonia treated with imipenem. Imipenem was effective versus *Pseudomonas aeruginosa*. An open trial of imipenem in bacterial pneumonia in 43 patients, 29 had NP (severity unknown). Clinical cure in 93% at the EOT.

Andrews et al: Clinical Therapeutics 16:236-52, 1994: Combined aztreonam/gentamicin for LRTIs: This study reported "excellent" efficacy for this combination even though only 47% of patients had a full response and an additional 37% had evidence of a partial response (severity unknown).

Mangi et al, AM J Med 84:68-74, 1988: Cefoperazone versus combination therapy of hospital-acquired pneumonia (severity unknown). Cefoperazone and ceftazidime were equally as effective in the treatment of NP. Specifically, clinical cure was seen in 45/62 (73%) of the cefoperazone patients as compared to 50/63 (79%) of the ceftazidime patients at the EOT.

Fernandez-Guerrero et al, Infection 19 (Suppl. 6):S320-5: Nosocomial pneumonia: Comparative multicenter trial between monotherapy with cefotaxime and treatment with antibiotic combinations (severity unknown).

The following cure rates have been obtained with various antibiotic regimens (unknown timepoint):

Cefotaxime: 79%

Cefotaxime and aminoglycoside: 77%

Cephalosporins with activity against Gram (-) organisms and aminoglycosides: 67%

Anti-pseudomonal cephalosporin and aminoglycoside: 76%

Clindamycin and aminoglycoside: 58%

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As stated above, the MO concluded from the literature review that NP is a difficult entity to treat. Mortality can be high especially when associated with *Pseudomonas aeruginosa*. Success rates usually range between 65 - 75% (EOS), depending on the causative pathogen, the patient's underlying condition, and the severity of the current episode. Optimal therapy provides broad-spectrum coverage. There is no consensus as to the usefulness of monotherapy versus combination but many ID specialists in the medical community believe that combination therapy with aztreonam or an aminoglycoside is useful. Vancomycin, clindamycin, and metronidazole are also utilized in the presence of the appropriate clinical setting or culture results.

From MO table 1, the MO determined that the overall clinical response rates in trial 154-113 (68.6% versus 67.5%) were within the expected range for a population of patients with mild to moderate disease. Additionally, the MO determined that the clinical response rates for the trovafloxacin-treated patients in

study 154-137 were within the expected range (63.5%) as compared to those on the comparator arm (57.3%). This lower clinical response rate may have been due to the inclusion of a more severely ill population on the comparator arm (difference in APACHE scores was not statistically significant, $p = 0.2147$), although this score is indicative of mortality and not severity of illness). Local factors such as hospital flora or differences in supportive measures may have also played a role. **The MO concluded that trovafloxacin is approvable for the indication of NP in patients with mild/moderate disease.**

Trovafloxacin is not approvable in patients who are severely ill or mechanically ventilated. Although the clinical response rates were numerically comparable not only between arms but between studies, the MO determined that clinical response rates in the 50% range were unacceptably low, especially in the face of potential monotherapy. More importantly, previously approved agents studied a higher proportion of severely ill patients (ciprofloxacin: 80%). This conclusion was not only based on a review of the literature (double-blinded randomized comparative trial of high dose ciprofloxacin versus imipenem as monotherapy in severely ill patients (APACHE 17.6): clinical cure rates: ciprofloxacin 58/86 (67%) versus imipenem 44/83(53%), but on previous regulatory history. Zosyn®, had an overall clinical response rate of 74% cured and improved versus the comparator (ceftazidime, which was 53%), in a population of severely ill patients. Additionally, the data from the ciprofloxacin NDA revealed a cure rate of 74% (or 59.5% in the mechanically ventilated) in a documented severely ill population with mean APACHE scores of 16 and of whom approximately 80% were on a ventilator. Furthermore, questions regarding the adequacy of the comparator regimen (ciprofloxacin 400 mgm bid as opposed to 400 mgm tid) preclude the granting of an approval for severe disease.

For the most frequently isolated baseline pathogens, and for which the sponsor is requesting approval, the MO determined that the sponsor met the divisional rule of "10" when the results of both studies were pooled. That is that "to include an organism in an indication, only those which are generally considered pathogenic and represent at least 10% of the evaluable cases OR 10 total (whichever is higher) AND the eradication rate must be clinically acceptable" can be considered. The only exception to the above was *Klebsiella pneumoniae* where the total number of evaluable patients with this isolate from both studies combined was 8 (as per the MO).

The MO determined that it was preferable to base the granting of organisms for this indication on the clinical response by pathogen rates as opposed to pathogen eradication rates.. The rationale for this decision was stated previously.

With regards to *Pseudomonas aeruginosa*, the results of study 154-113 indicated that trovafloxacin was effective versus this organism within the range that is currently clinically acceptable (8/13: 62%), in the case of monotherapy. The conflicting results of study 137 (1/5: 20%) were of concern, and therefore, although trovafloxacin is approvable for NP caused by *Pseudomonas aeruginosa* (total clinical response rate: 9/18 (50%)), the MO determined that the approval for this organism would be contingent upon the addition of a qualifying statement with regards to the addition of a second anti-pseudomonal agent, either aztreonam or an aminoglycoside. The above statement should be strongly worded because of the disparate results between the trials, questions regarding severity of illness, and the allowed use of combination therapy, and the sponsors inability to consistently show good evidence to support the use of trovafloxacin as effective monotherapy

The sponsor was requested to provide evidence of a lack of antagonism between trovafloxacin and other anti-pseudomonal agents. In response to this request, an abstract entitled "Synergistic Activity of Trovafloxacin with Other Agents (37th ICAAC, 1997) was submitted. The authors examined the synergistic activity of trovafloxacin with other agents via a checkerboard method. No antagonism was found with any combination. Synergy was seen for 10 strains of *Pseudomonas aeruginosa*: 4 with aztreonam, 3 with ticarcillin/clavulanate, 2 with ceftazidime, 1 with ceftriaxone, 1 with tobramycin, and 1 with cefoperazone. Additive or indifferent combinations included all those of trovafloxacin and imipenem, trovafloxacin and gentamicin, trovafloxacin and Zosyn®, and trovafloxacin and amikacin.

With regard to *Klebsiella pneumoniae*, the MO determined that both the sponsor's clinical response rates and the number of evaluable isolates in both studies were unacceptably low (2/4 (50%) both

studies separately or 4/8 (50%) combined), for a population of patients with mostly mild to moderate disease, and therefore trovafloxacin is not approvable for NP caused by this pathogen.

With regards to *Escherichia coli*, the MO determined that the additive results of both studies (5/6: 83.3% and 3/6 (50%) or total: 8/12: 67%), were adequate to support approval the approval for trovafloxacin in patients with NP caused by this pathogen.

With regards to *Haemophilus influenzae*, the MO found the clinical cure rate of 5/6 (83%) seen in study 154-113 was consistent with that of the supportive study 154-137 (4/5:80%). This rate was also consistent with that seen in the literature where it is pointed out that *Haemophilus influenzae* is one of the common pathogens associated with NP. However, it is usually seen in patients who aspirate early during the course of their hospitalization. In other words an "early" hospital-acquired infection. The MO determined that trovafloxacin was effective in patients with NP caused by *Haemophilus influenzae* and recommended unqualified approval.

With regards to *Staphylococcus aureus*, the MO determined that the clinical response rate of patients with this isolate was too low (study 154-113: 4/8 (50%), study 154-137:8/11 (72.7%) or TOTAL 12/19 (63.1%), in view of the higher cure rates that can be obtained in a more severely ill population. (Zosyn NDA: 81%) to support approval. Additionally, as per previous regulatory history, ciprofloxacin was NOT granted approval for this pathogen, despite its similar efficacy rate in a more severely ill population. Therefore, the MO could not recommend approval for this organism. It should be pointed out, that at this time, no fluoroquinolone is approved for this indication due to this organism. As *Staphylococcus aureus* is a common pathogen within this disease entity, the MO believes that the standard should be set at a higher level.

RECOMMENDED REGULATORY ACTION:

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The following statement can be added to the indications section of the labeling:

It is suggested that a clinical studies section be appended to the labeling with regards to this indication. This section should contain MO table 1.

The recommended dosage is alatrofloxacin 300 mg IV daily, which may be converted to trovafloxacin 200 mg PO daily for 10- 14 days.

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/S/
12 13 97
Regina Alivisatos, MD
Medical Officer, DSPIDPs

- Orig. NDA #20-759
- Orig. NDA #20-760
- HFD-590
- HFD-590/Div. Dir./MGoldberger */S/*
- HFD-590/Dep. Dir./RALbrecht
- HFD-590/MTL/BLeissa
- HFD-590/MO/RAlivisatos */S/ 12 13 97*
- HFD-590/CSO/PFogarty
- HFD-725/Biostat/Silliman
- HFD-344/Thomas

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Addendum to MOR of NDA 20 - 759/Nosocomial Pneumonia

In response to a request by the FDA, at the closure of a Telecon with Pfizer representatives on October 29, 1997, the sponsor submitted additional information to support their claim of efficacy of trovafloxacin in patients suffering from severe nosocomial pneumonia (Nov. 7, 1997). This information is reviewed below and consisted of extensive re-analyses of the data for efficacy utilizing ATS criteria as a determinant of severity of illness

At the conclusion of the review of the original submission, the MO determined that trovafloxacin was effective in the treatment of nosocomial pneumonia of mild to moderate severity, (APACHE scores not to exceed 13), caused by *Haemophilus influenzae*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

Approval was not recommended for the treatment of nosocomial pneumonia caused by *Klebsiella pneumoniae* and *Staphylococcus aureus*.

The MO agreed that the following statement should be added to the labeling:

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As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

Based on the data in the original submission, the MO found the following clinical efficacy rates:

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Table 1
Clinical Response Overall and by Disease Severity/FDA Evaluable Population (as per the MO)

Study	154-113	154-137
Location	US	Multinational
Design	Randomized, Blinded	Randomized, Open
Comparator	Ciprofloxacin IV/PO	Ceftazidime IV/Ciprofloxacin PO
Clinical Response EOS	48/70 (68.5%) trovafloxacin vs. 52/77 (67.5%) comparator	54/85 (63.5%) trovafloxacin vs. 51/89 (57.3%) comparator
Clinical Response Mild/Moderate Disease	38/50 (76%) trovafloxacin vs. 39/52 (75%) comparator	33/39 (84.6%) trovafloxacin vs. 29/41 (70.7%) comparator
Clinical Response Severe Disease	10/20 (50%) trovafloxacin vs. 13/25 (52%) comparator	21/46 (45.7%) trovafloxacin vs. 22/48 (45.8%) comparator
Clinical Response Mechanically Ventilated	10/18 (55.6%) trovafloxacin vs. 8/16 (50%) comparator	15/33 (45.5%) trovafloxacin vs. 14/31 (45.2%) comparator

Thus indicating that 18/70 (25.7%) of the FDA evaluable population from the US study, 154-113 were mechanically ventilated and therefore by definition, suffering from a severe NP as compared to 33/85 (39%) of the multinational population (study 154-137). The respective numbers for those patients suffering from "severe" disease, defined by the sponsor as patients requiring mechanical ventilation or supplemental oxygenation of > 35% in order to maintain an arterial oxygen saturation of 90%, were 20/70 (25.6%) and 46/85 (54.1%) per study respectively.

As noted in the MO's conclusion and repeated here, a comparison of trovafloxacin's data with those from previously reviewed antimicrobials that received an indication for severe disease revealed that:

Ciprofloxacin NDA 19-847/S-008 and NDA 19-857/S008: (See conclusion to MOR)

The dose of ciprofloxacin utilized was high at 400 mg IV q8 (previously approved dose: 400 mg IV q12), and the comparator agent was imipenem (1000 mg q8 or 500 mg IV q6). APACHE scores were provided and the mean score on both arms was > 16, thus indicating a severely ill population with an expected poor prognosis. Other factors that the reviewing MO determined to further bolster the argument that a severely ill population was being studied were age >50 (mean age 59.9), the presence of several underlying conditions, the use of ventilators, and the presence of the predominant number of patients in an ICU. In a review of this document, the MO found that there was no severity scoring system. Rather, analyses were performed on subpopulations with low and high APACHE scores as well as by ventilator status (58/71 evaluable ciprofloxacin patients were ventilated (81.6%) as compared to 66/81 (81.4%) of the imipenem

patients. Clinical cure rates (pivotal study only), at the EOS (late follow-up), visit were 42/71 (59.2%) versus 32/81 (39.5%), thus indicating superiority of ciprofloxacin versus imipenem. Clinical response by APACHE scores were ciprofloxacin: APACHE low (10-14): 9/25 (36%) and high (-14-49): 23/56 (41%). The respective rates for the imipenem arm were 22/30 (73%) and 20/41 (49%). Clinical response rates by ventilator status were ciprofloxacin: ventilator: 34/58 (59%) and non-ventilated: 24/58 (41%). The respective rates for imipenem were 21/66 (32%) and 45/66 (68%) respectively.

Therefore, in the ciprofloxacin SNDA, the applicant provided a more detailed analysis of the severely ill population including breakdown by age, ventilatory status, comorbid conditions, ICU admission status, and APACHE II scores. In that submission, 80% of patients per arm were severely ill and ventilated. The results from that trial can be seen above, however, the MO points out that in a truly severely ill population, ciprofloxacin efficacy was approximately 59%. Additionally, ciprofloxacin was utilized at a higher dose; thus causing the MO concern over the applicability of comparing trovafloxacin to an inadequate dose in a severely ill population as was done in this trial. (Adequacy of comparator regimen).

The MOR of the NDA of the only other antimicrobial approved for "severe" NP, Zosyn®, did not contain adequate information for the current MO to be able to make a judgement on the true severity of the disease process in the population studied. Clinical response rates (EOS) were 47/63 (74%) Zosyn® versus 22/35 (53%) ceftazidime (comparator).

With regard to the adequacy of the comparator, ceftazidime as monotherapy (the comparator agent utilized for the intravenous portion of the treatment regimen in study 154-137), this agent is approved for LRTI of mild to moderate severity. Approval was granted prior to the agency differentiating types of LRTI labeling. The labeling however does include a statement reflecting that this agent can be used in "severe" infections. No mention is made of the adequacy of this agent as monotherapy. The MO agrees however, that this agent is an adequate comparator when the use of other antimicrobials is allowed for as in this submission (aztreonam, gentamicin, vancomycin, clindamycin, and metronidazole).

The MO briefly reviews the demographics of the sponsor's evaluable population at this point as all further references will be made to the sponsor's and not the MO's evaluable population. This was done because the additional data submitted did not refer to the MO evaluable population and, as stated, in the MORs of studies 154-113 and 154-137, the MO mostly agreed with the sponsor's determinations of evaluability and outcome.

In study 154-113, of the clinically evaluable subjects, 29/88 (33%) of the alatrofloxacin/trovafloxacin subjects and 35/103 (34%) of the ciprofloxacin subjects required respiratory supportive therapy at baseline. This support was in the form of supplemental oxygen therapy or mechanical ventilation. 24/88 (27%) of the alatrofloxacin/trovafloxacin subjects and 22/103 (21%) of the ciprofloxacin subjects required mechanical ventilation.

The mean APACHE score at baseline for both treatment groups was 13.09.

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In addition, among clinically evaluable subjects, 33/88 (38%) on the alatrofloxacin/trovafloxacin arm and 49/103 (48%) on the ciprofloxacin arm had bilateral pneumonia at baseline. 15/88 (17%) on the alatrofloxacin/trovafloxacin arm and 20/103 (19%) on the ciprofloxacin arm had abnormalities in ≥ 3 lobes at baseline.

In study 154-137, of the clinically evaluable subjects 56/103 (54%) alatrofloxacin/trovafloxacin-treated subjects and 60/109 (55%) of the ceftazidime/ciprofloxacin treated subjects had severe disease. 48/103 (47%) and 54/109 (50%) respectively, had compromised respiratory function (included all subjects who were mechanically ventilated or required a fractional oxygen concentration of ≥ 0.35 to maintain an arterial oxygen tension of ≥ 60 mm Hg.).

41/103 (40%) of the alatrofloxacin/trovafloxacin-treated subjects and 37/109 (34%) of the ceftazidime/ciprofloxacin-treated subjects required mechanical ventilation.

The mean APACHE score at baseline for the alatrofloxacin/trovafloxacin-treated patients was 12.66 at baseline as compared to 13.59 for the ceftazidime/ciprofloxacin-treated group.

Thus, as per the MO's calculations, if both studies were combined, 85/191 (44.5%) of the clinically evaluable trovafloxacin subjects had severe disease as compared to 95/212 (44.8%) of the clinically evaluable comparator subjects (ciprofloxacin (113) and ceftazidime/ciprofloxacin (137), when the parameters of ventilatory support and/the need for high supplemental oxygen concentrations were utilized as determinants of disease severity.

The results from the original analyses are provided below:

Table 2

Sponsor-Defined Clinical Response/Clinically Evaluable Populations (as per the sponsor) at EOS:

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Success (Cure + Improvement)	Trovafloxacin	Ciprofloxacin	Ciprofloxacin /Ceftazidime	Comparators
Study 154-113/Overall	50/72 (69%)	54/79 (68%)		
Study 154-113/Severe	11/21 (52%)	14/26 (54%)		
Study 154-113/Mechanically Vent.	10/18(56%)	8/16 (50%)		
Study 154-113/Mild/Moderate	39/51 (76%)	40/53 (75%)		
Study 154-137/Overall	56/85 (66%)		52/89 (58%)	
Study 154-137/Severe	22/56 (49%)		22/60 (47%)	
Study 154-137/Mechanically Vent.	16/32 (50%)		14/30 (47%)	
Study 154-137/Mild/Moderate	34/40 (85%)		30/42 (71%)	
Total/Overall	106/157 (68%)			106/168 (63.1%)
Total/Severe	33/66 (50%)			36/86 (42%)
Total/Mechanically Vent.	26/50 (52%)			22/46 (48%)
Total/Mild/Moderate	73/91 (80%)			70/95 (74%)

Overall clinical response (success) rates at the EOS in study 154-113, (as per the sponsor), were: 50/72 (69%) versus 54/79 (68%) and in study 154-137 56/85 (66%) versus comparator 52/89 (58%). In study 154-113 equivalence but not superiority was demonstrated based on a 95% CI with CCF of -13.7%, 15.9% ($\Delta = 20$). In study 154-137, numerical superiority was demonstrated at the EOS with a 95% CI (with CCF) of -8.1%, 23% ($\Delta = 20$) but statistical significance was not achieved (as per FDA statistician, Dr. Nancy Silliman). Overall EOS clinical success rates for NP (combined results) were 106/157 (67.5%) and 106/168 (63.1%) comparators 95% CI: - 6.5%, 15.4% ($\Delta = 20$). Overall EOS clinical success rates for sponsor evaluable patients with severe disease were 33/66 (50%) versus comparators 36/73 (49.3%), 95% CI: - 17.4%, 18.7% ($\Delta = 20$). Mortality was as expected (ITT: 113:27% trovafloxacin versus 28% ciprofloxacin and ITT: 137: 27% trovafloxacin versus 21% ceftazidime/ciprofloxacin).

The MO concluded from the above that trovafloxacin was equally efficacious to both comparator regimens in the clinically evaluable severely ill population (as defined by the sponsor). Additionally, the MO had no objections to the pooling of the populations although, the MO did not determine that this lack of objection obviated the inadequacy of the comparator regimens utilized.

Therefore the MO determined that the sponsor's supplemental data could be utilized in lieu of requesting reanalyses on the MO's population not only because of general agreement with regard to evaluability and outcome issues but because the MO was convinced that the ATS scoring system was a more accurate indicator of severe disease.

The current submission consisted of a Word document as well as additional tables illustrating the sponsor's reanalyses by a variety of severity factors.

The sponsor initially provided the ATS criteria for severe nosocomial pneumonia. These are generally accepted criteria and are the same for both CAP and NP. These criteria were copied below:

Severity factors in pneumonia:

Severe pneumonia may be defined as the presence of one of the following factors:

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- Admission to the intensive care unit (NOS)
- Respiratory failure defined as the need for mechanical ventilation (NOS and CAP) or the need for >35% oxygen to maintain arterial oxygen saturation >90%(NOS), severe respiratory failure defined by a PaO₂/FIO₂ ratio <250 mm Hg (CAP)
- Respiratory frequency > 30 breaths per minute at admission (CAP)
- Multilobar pneumonia (NOS, CAP), rapid radiographic progression (NOS, CAP), bilateral involvement(CAP) or cavitation of a lung infiltrate(NOS)
- Evidence of severe sepsis with hypotension and/or end-organ dysfunction: (NOS and CAP)
- Shock (systolic blood pressure <90 mm Hg, or diastolic blood pressure <60 mm)
- Requirement for vasopressors for more than 4 hours
- Urine output <20 mL/h or total urine output < 80 mL in 4 hours (unless another explanation is available)
- Acute renal failure requiring dialysis

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CAP - ATS Guideline on Community-acquired Pneumonia (Niederman, 1993)
NOS - ATS Guideline on Nosocomial Pneumonia (Campbell, 1996)

Medical Officer's Comment: *The MO agreed with the general acceptability of these criteria.*

The sponsor also stated that other measuring systems such as the Fine score and the APACHE score are not severity measurements as such but rather predictive in nature to assess potential for good versus poor outcomes (independent of infection and anti-infective therapy).

Medical Officer's Comment: *The MO agreed with this determination.*

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The sponsor stated that (11/7/97):

"Two studies were presented in support of the indication of nosocomial pneumonia. These studies included 533 patients in the ITT analysis with an approximately 25% mortality. The comparative agents selected were those recommended in the ATS Consensus Statement (Campbell, 1996). It is important to note that no single agent is available that is always suitable for use in all nosocomial pneumonias, particularly with respect to infection due to *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Indeed, ethical conduct of the clinical study requires that appropriate therapy be used and consequently additional agents are necessary where certain organisms are identified. In any event, that the use of concomitant study antibiotics was greater in the comparator groups than in the trovafloxacin treated group implies potential superiority of trovafloxacin. One of the studies was double-blind, while the other was a randomized, open comparative design. However, an open design was not *a priori* inadequate. In the absence of evidence of unequal randomization in the groups and when the results of such a study are consistent with other blinded data, such data are fully acceptable and are considered appropriate

to pool to facilitate assessment of appropriate sub-groups. It should be noted that all sponsor assessments were done blinded to treatment group and in most cases were applied by computer algorithms. Since outcomes such as clinical success with no need for further antibiotic therapy and mortality are "hard" endpoints, the sponsor felt this open study is justified for inclusion."

The two study groups were comparable at baseline for a number of factors associated with increased risk or directly with the severity of the pneumonia. The original analysis presented by the sponsor for the overall nosocomial pneumonia groups demonstrated therapeutic equivalence. The original protocol specified analysis of severe patients (those on mechanical ventilation or high fractional oxygen) also showed comparable results. As mentioned above, a new analysis based on the ATS criteria for severe hospital-acquired pneumonia was performed. For the purpose of selecting patients for this subgroup analysis the following specific criteria were collected in the case report forms and applied: admission to intensive care; need for mechanical ventilation; need for oxygen therapy (>35% oxygen to maintain arterial oxygen saturation >90%); respiratory rate >30; multilobar pneumonia; systolic blood pressure <90 mm Hg; diastolic blood pressure <60 mm Hg. Efficacy in patients meeting the ATS criteria for severe nosocomial pneumonia is shown below.**

*The following tables were modified by the MO to reflect only clinically evaluable patients at the EOS.

Table 3
Clinical Outcome in Patients with Severe Nosocomial Pneumonia
(Pooled data 154-137 and 154-113/ ATS definition/As per the sponsor)

Total Assessed EOS Evaluable (n =)	Clinical Success (%)	CI
Ala > Trovafloxacin (n = 117)	59%	- 11.7, 13.3
Comparators (n = 122)	58.2%	

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Medical Officer's Comment: Thus the trovafloxacin group outcome was equivalent to the comparator outcomes when the ATS severity of illness scoring system was utilized. The 95% CI applied above is as per the sponsor and without continuity correction factor. Below is clinical outcome without ATS criteria as per the sponsor.

Table 4
Clinical Outcome in Nosocomial Pneumonia
(Pooled analysis - 154-113, 154-137/As per the sponsor)

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Clinical Success	Alatrofloxacin/ Trovafloxacin	Comparators	95%CI
Overall (EOS Eval)	106/157 (68%)	106/168 (63%)	-5.9, 14.8
Severe (vent or high O2)/EOS	33/66 (50%)	36/73 (49%)	-16.0, 17.3
Mechanical Ventilation/EOS	26/50 (52%)	22/46 (48%)	-15.8, 24.2
APACHE score > 16	22/39 (56%)	25/49 (51%)	-15.5, 26.3

Medical Officer's Comment: The sponsor provided additional analyses for other specific subgroups associated with increased severity or poor outcome (advanced age, multilobar infiltration, or comorbidity), and found equivalence between the treatment arms for all variables.

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Table 5
Patients with the Severity Factor at Baseline (As per the sponsor)

	Evaluable				ITT			
	Tro. N=	Comp. N=	Tro. %	Comp. %	Tro. N=	Comp. N=	Tro. %	Comp. %
Total Eval	191	212			259	274		
Mean age	63.6	66.7			64.8	67.2		
Age $\geq$ 65	103	54	133	63	147	57	180	66
Age $\geq$ 75	66	35	87	41	94	36	112	41
AT least one comorb	98	51	113	53	137	53	159	58
AT least two comorb	41	21	57	27	64	25	83	30
Original severe (Hi O ₂ +MV)	85	45	95	45	126	49	133	49
RR>30	26	14	20	9	37	14	29	11
SysBP<90	4	2	3	1	8	3	5	2
DiBP<60	38	20	39	18	54	21	57	21
Multilobar	78	41	89	42	111	43	121	44
ICU	77	40	91	43	113	44	127	46
High fractional O ₂	71	37	85	40	105	41	115	42
Mechanical Ventilation	65	34	59	28	98	38	89	32
At least one ATS severe	145	76	153	72	203	78	209	76
Pseudomonas	23	12	28	13	30	12	32	12
Apache $\geq$ 16	47	25	57	27	80	31	82	30

Table 6
Clinical Success at End of Study by Severity Factor/Group (As per the sponsor)

	Evaluable					ITT				
	Tro. N=	Comp. N=	Tro. %	Comp. %	CI	Tro. N=	Comp. N=	Tro. %	Comp. %	CI
Total Eval	157	68	168	63	-5.9,14.8	259	61	274	64	-11.5,5.0
Age $\geq$ 65	87	67	103	63	-12.3,9.9	147	57	180	63	-16.8,4.5
AT least one comorb	79	66	91	62	-10.2,18.8	137	59	159	58	-10.0,12.5
AT least two comorb	33	67	48	56	-10.9,31.8	64	58	83	58	-16.1,16.1
Original severe (Hi O ₂ +MV)	66	73	50	49	-16.0,17.3	126	49	133	53	-16.3,8.0
Mechanical Ventilation	50	52	46	48	-15.8,24.2	98	51	89	51	-13.9,14.8
At least one ATS severe	117	59	122	58	-11.7,13.3	203	55	209	60	-14.6,4.4
Multilobar	61	56	69	61	-22.1,11.8	111	56	121	60	-17.2,8.2
Pseudomonas	18	50	22	32	ND	30	53	32	44	ND
Apache $\geq$ 16	39	56	49	51	-15.5,26.3	80	46	82	48	-16.7,14.1

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The sponsor's conclusion is attached below:

"It is remarkable that when the data on severe nosocomial pneumonia are examined, using internationally recognized definitions for severity, or other definitions, the results consistently demonstrate that trovafloxacin is equivalent to the alternative regimens. It is important to recall that in studies reviewed here, the trovafloxacin regimen was a monotherapy regimen (except for a few uncommon situations equally applicable to both study arms) while the comparator was frequently a multidrug regimen. Indeed, although the results are equivalent, adjunctive antibiotic therapy was utilized much more commonly on the alternative regimens, providing yet another indication of the efficacy of trovafloxacin. In severe nosocomial pneumonia, less induction of bacterial resistance in the sentinel organism *Pseudomonas aeruginosa* was noted. The new subgroup analysis comparing clinical outcomes in patients with defined severe nosocomial pneumonia confirms overall equivalent efficacy between the regimens. Additional comparisons using a variety of individual severity factors also demonstrate equivalence. Substantial numbers of patients with significant severity factors were treated. In fact over 200 patients in each group met ATS criteria for severe pneumonia. Consequently, the overall equivalence to the comparative agents observed in the individual studies and pooled analysis (in both the evaluable and ITT analyses) supports the use of alatrofloxacin/trovafloxacin in nosocomial pneumonia including patients with severe pneumonia."

Medical Officer's Comment: Based on the above, the sponsor claimed equivalence with the comparators when the populations studied were analyzed applying a number of variables and in accordance with ATS guidelines. The MO does not disagree with the sponsor's numerical claims. However, it is again pointed out that the MO determined that the comparator regimen utilized in the pivotal, double-blind, US trial is not approved for severe nosocomial pneumonia. Ciprofloxacin is approved at a higher dose (400 mg every 8 hours) than that used in these studies. An extrapolation of the known data suggests that if the clinical efficacy rate in the ciprofloxacin NDA was 59% overall in a population that was compromised of 80% severely ill patients, then the 49% efficacy with 43% of the population determined to have severe disease, attained in this trial is indicative of the inadequacy of the dosage utilized. Ultimately the sponsor's results cannot be construed as superior to either comparator regimen (superiority necessary versus low dose ciprofloxacin as it is not approved at the lower dose for the indication), and therefore, the MO continues to recommend a non-approval for severe nosocomial pneumonia. On Nov. 10, 1997, the sponsor was requested to provide additional information as to the reason that ciprofloxacin was utilized at a lower dose and to state the rationale that could be used to justify the adequacy of the comparator.

With regards to the sponsor's statement regarding the use of concomitant antimicrobials to a greater degree on the comparator arms, thus implying potential superiority of the trovafloxacin regimen, the MO reminds the reader that in study 154-113, aztreonam was allowed on both study arms in the face of a documented infection with *Pseudomonas aeruginosa*. Vancomycin was allowed on both treatment arms in the face of a NP caused by MRSA and clindamycin or metronidazole were allowed on the ciprofloxacin arm, at the investigators discretion.

In that study, aztreonam was utilized in 9 trovafloxacin subjects and 11 ciprofloxacin subjects (as per the sponsor). Vancomycin was utilized in 9 trovafloxacin and 7 ciprofloxacin subjects. Clindamycin was utilized in 14 ciprofloxacin subjects (11 trovafloxacin subjects received clindamycin placebo), and metronidazole was utilized in 2 ciprofloxacin subjects.

In study 154-137, adjunctive therapy use was similar to that seen in 154-113 with the exception that gentamicin was substituted for aztreonam. A priori, adjunctive therapy was allowed only on the comparator arm, however, because patients did receive adjunctive therapy against protocol, the sponsor made a post-hoc decision to include these patients in the analyses of efficacy. In that trial, 5 alatrofloxacin/trovafloxacin ITT subjects received gentamicin as compared to 17 ITT subjects on the ceftazidime/ciprofloxacin arm. 5 ITT alatrofloxacin and 17 ITT ceftazidime/ciprofloxacin subjects received vancomycin and only 1 ceftazidime/ciprofloxacin subject received adjunctive therapy with clindamycin.

The MO does not agree with the sponsor's statement with regards to the increased antimicrobial usage on the comparator arms with the exception of the use of clindamycin in study 154 -113. Additionally, the MO did not determine that clindamycin usage was not a major determinant in the establishment of efficacy.

On December 4, 1997, the sponsor faxed a response intended to address the FDA concern with regards to the adequacy of the comparator regimen in study 154 -113. The sponsor stated the following:

"Pfizer maintains that the ciprofloxacin dosing used in the #113 nosocomial pneumonia study was, for all practical purposes equivalent to that used by Bayer to obtain labeling for 'severe' nosocomial pneumonia. There is no evidence that the currently approved dose of ciprofloxacin for severe nosocomial pneumonia is superior to the previously approved dose, and there are theoretical reasons to question the benefits of the dosing method used for ciprofloxacin in the pivotal study. The primary rationale for the additional ciprofloxacin probably related to spectrum weaknesses and resistance issues that are irrelevant to the dosing used in the trovafloxacin studies. In any event, there are suggestions of superiority of trovafloxacin over ciprofloxacin in the data. Finally, Pfizer presented the dosing to FDA in good faith prior to study start and would have been subject to criticism had we used something other than the then approved dose.

Medical Officer's Comment: *The MO agrees with the sponsor's claim that the dosage selected was the approved dosage of ciprofloxacin at the time of study design. Additionally, the protocol was submitted to the FDA and no comment was issued with regards to the dosage.*

The ciprofloxacin dosing in study #113 was equivalent to that used by Bayer in the pivotal study it conducted to secure the severe nosocomial pneumonia claim

It appears that a single pivotal study provided the basis for the approval of ciprofloxacin at a dose of 400mg TID for 'severe nosocomial pneumonia' (1). In this study however, there were two significant deviations from the labeled dosing regimen. Firstly, the protocol allowed investigators, at their discretion, to reduce the dose from 400 mg TID to 400 mg BID if the patient had a 'sensitive organism'. The definition of such organisms is not provided in the literature report. However, 24% of ciprofloxacin patients received less than the TID regimen for parts or all of the dosing period. It can not be determined from the published report which patients received how much drug. Secondly, ciprofloxacin dosing was adjusted downward for reduced renal function. Although the frequency with which this happened can not be determined from the paper, it is stated that the mean baseline creatinine was slightly elevated at 1.28 mg/dL and that BUN elevations occurred in 24% of the ciprofloxacin patients during the study. The package insert for IV ciprofloxacin calls for dose reductions to 200-400 mg q18-24 hours with creatinine clearances below 30 mL/min. It is likely that a substantial number of the patients in this study had reductions in their doses.

Medical Officer's Comment: *The MO has no comment with regards to the rationale for the development of a higher dosage form for ciprofloxacin. The MO acknowledges however, that there was the ability to decrease the dosage of ciprofloxacin in the previously cited study. This decrease to 400 mg IV bid was investigator-driven as well as dependent upon susceptibility reporting.*

These factors are significant because they did not occur in the trovafloxacin #113 study, resulting in effectively higher doses of ciprofloxacin. There was no reduction of ciprofloxacin dose for 'sensitive' organisms. Also, because blinding in the trovafloxacin studies included the pharmacy so that there was no one at the study site who knew the drug allocation (unlike the ciprofloxacin study), it would have been extremely difficult to dose adjust ciprofloxacin for renal function and still maintain blinding, especially given the additional antibiotics that were used in the ciprofloxacin arm. The median baseline creatinine in study #113 for the ciprofloxacin patients was 1.1 mg/dL, meaning that a substantial number were above the upper limit of normal even at baseline, but did not have dose reductions. Thus, the 'effective' ciprofloxacin dose used in the #113 study was greater than initially apparent, and probably equivalent, over all, to the dose used in the pivotal ciprofloxacin study.

Medical Officer's Comment: As stated above, the investigators did have the choice of decreasing the dosage of ciprofloxacin when sensitivity results were available. A review of NDA 19-847/S-8 revealed the following with regards to dosing:

"Patients were dosed based upon their estimated creatinine clearance, and the antimicrobial susceptibility of the causative organism according to the following schedule":

CrCl	A (Fully susceptible)	B (Moderately susceptible)
> 70 mL/min	Ciprofloxacin 400 bid Imipenem 500 q6	Ciprofloxacin 400 tid Imipenem 1g q8
	Ciprofloxacin 400 bid Imipenem 500 q8	Ciprofloxacin 400 tid Imipenem 500 q6
	Ciprofloxacin 300 bid Imipenem 500 q12	Ciprofloxacin 400 q12 Imipenem 500 q8
	Ciprofloxacin 250 q12 Imipenem 250 q12	Ciprofloxacin 300 q12 Imipenem 500 q12

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All patients were started on schedule B or high dose and changes were made based on investigators clinical assessments. If renal insufficiency developed, an unblinded individual (research pharmacist) could have made dosage adjustments based on CrCl.

Although the protocol called for bacteriologic eradication at the early (3-5 day post-therapy) follow-up to be the primary efficacy variable, the RMO disagreed and utilized clinical response as the primary efficacy variable. The RMO provided this analysis at both the early and late follow-up visits.

As per the RMO "For patients in both groups, almost all of the treatment duration was on regimen B; the mean duration of regimen B was 9.5 days for the ciprofloxacin group and 8.8 days for the imipenem, group (total mean duration of therapy was 10.5 days). 2% of the ciprofloxacin patients received regimen A only and 18% received both A and B. On the imipenem arm, 82% of patients received regimen B only, 1% regimen A only and 17% both. 76% of the clinically evaluable ciprofloxacin patients and 72% of the clinically evaluable imipenem patients received only the B regimen.

Based on the above information, the MO disagrees with the sponsor's contention that a significant number of patients received the lower dose. Clinical response rates for this trial were noted previously. The RMO did not provide a separate analysis of response by regimen.

The MO agreed with Pfizer's determination that ciprofloxacin dosage was adjusted for renal function. It is correct that 24% of the ciprofloxacin-treated patients had elevations of BUN during the study. There is no information available from the ciprofloxacin MOR as to how often dosage adjustments were made.

The sponsor states that no adjustments were made on the ciprofloxacin arms of the trovafloxacin studies. This is correct. However, it is merely speculative to assume that since adjustments were not made, that patients with creatinine elevations had by default higher ciprofloxacin doses, approximating the 400 tid level.

There is no evidence that the currently approved dose of ciprofloxacin for severe nosocomial pneumonia is superior to the previously approved dose

There are no studies comparing the efficacy and safety of twice a day IV ciprofloxacin with three times a day ciprofloxacin. In the absence of such studies, it is impossible to claim that the TID dosing (even if it had been consistently used in the pivotal study) is more effective than the BID

dosing, which was extensively used to treat nosocomial pneumonia for years. In any event, it is unlikely that any reasonably sized clinical trial could ever show a meaningful difference between the twice daily and three times daily dosing of ciprofloxacin in severe nosocomial pneumonia. It is generally believed that the underlying clinical condition is the most important driver for clinical outcome in this entity. In a disease where mortality is generally 20-60%, it is likely that such a clinical trial would have to be enormous (and clinically undoable) to show a difference in the two regimens.

***Medical Officer's Comment:** Again the sponsor's response is speculative. Within the context of the ciprofloxacin SNDA there were 6 smaller studies (European), that indicated a clear increase in clinical success rates when progressively higher ciprofloxacin doses were utilized. These studies included many types of infections including NP. There are no large trials however that have compared the 2 regimens. Without a doubt however, ciprofloxacin 400 mg tid was studied in a well-designed trial within the context of the SNDA and was shown to be superior to a good comparator regimen.*

There are theoretical reasons to question the benefits of the dosing method used for ciprofloxacin in the pivotal study

Beyond a certain minimum level, there is no evidence in either ciprofloxacin studies or in the literature to show that progressively greater amounts of antibiotic result in progressively greater efficacy. Although it may be commonly believed (or at least practiced, even among some Infectious Disease specialists) that 'if some works, more is better', there is no evidence, for example, that antibiotic levels 20 times the MIC for an organism are more clinically efficacious than 10 times. Ciprofloxacin, like all quinolones concentrates 5-15 fold over serum levels in lung tissue, already giving levels at twice daily dosing that are substantially above those needed to kill most organisms.

If one were concerned about inadequate dosing, three times a day ciprofloxacin might not be any more effective than twice a day dosing. The three times daily dosing with 400mg does not result in substantially higher peak levels of antibiotic. Many people believe that with quinolones it is the peak level that is important for organism killing. From this viewpoint, to improve efficacy it would have made more sense to use a larger dose (i.e. 600mg individual dose, or more) rather than simply adding a dose. However, Bayer may have been concerned about the toleration profile, which appears to have been a concern with the original IV ciprofloxacin development and approval. In any event, there are no clinical data to show that three doses a day are more effective than two.

***Medical Officer's Comment:** The MO is unaware of the argument of "more is better". The motivation behind the design of the ciprofloxacin SNDA is not in question at this time. As stated above, the regimen was efficacious. Any other conclusions drawn about the effectiveness of the higher dose regimen as opposed to the lower dose are merely speculative given the absence of additional clinical data.*

The primary rationale for the use of additional ciprofloxacin in the single pivotal study to support the 'severe nosocomial pneumonia' claim probably related to spectrum weaknesses and resistance issues that are irrelevant to the dosing used in the trovafloxacin study

It was, and remains a common belief in the medical community that a ciprofloxacin dose of 400mg BID is not adequate to treat *Streptococcus pneumoniae* infections, which was also the subject of an FDA advisory committee meeting. Indeed, under the 'lower respiratory tract infection' indication, the current package insert states that ciprofloxacin is not considered first line therapy for presumed or confirmed infections due to *Streptococcus pneumoniae*. We believe one of the primary reasons for the TID dosing in the pivotal study that Bayer used to claim severe nosocomial pneumonia was that they studied severe pneumonia, not exclusively nosocomial pneumonia, and included a large number of patients with community acquired pneumonia and potential *Streptococcus pneumoniae* infections. It is likely that investigators were very

uncomfortable with the prospect of treating patients with severe community acquired pneumococcal pneumonia with BID dosing.

There has also been concern over development of resistance during therapy with ciprofloxacin in nosocomial pneumonia, particularly with infections due to *Pseudomonas aeruginosa*. One thought has been that more antibiotic might reduce the incidence of resistance, apart from any effect on clinical efficacy. This was generally known to be a problem with ciprofloxacin dosed at 400mg twice daily, and it is likely that Bayer preferred that a higher dose of ciprofloxacin be used as monotherapy, rather than that a second (non-Bayer) antibiotic be added in an attempt to answer this criticism. Indeed, Bayer's interest in monotherapy with ciprofloxacin rather than combined therapy was the key design feature of the pivotal study. As this seems to be one of the few indications in infectious diseases where one can respectably advocate the use of more antibiotic rather than less, it is likely that Bayer was also quite comfortable with this approach. However, the primary use of monotherapy for pseudomonal pneumonia is in contrast to essentially all published recommendations for how severe nosocomial pneumonia should be treated, including those of the American Thoracic Society (2).

These issues driving a higher ciprofloxacin dose are not relevant to the trovafloxacin study. Since community acquired pneumonia was not enrolled, the presence of *Streptococcus pneumoniae* was not an issue for the ciprofloxacin arm. Additionally, Pfizer agrees with ATS that at least for infections due to *Pseudomonas aeruginosa*, dual therapy should be used, as was done in the #113 study. Although evidence that dual therapy improves clinical outcome is hard to come by, there is general consensus that at least it is useful to reduce development of resistance (2).

Medical Officer's Comment: *Once again the sponsor's comments are speculative and refer to the motivation of ciprofloxacin's sponsor. The MO agrees that ciprofloxacin is not first line therapy for CAP associated with Streptococcus pneumoniae. The MO points out however, that although the ciprofloxacin SNDA was intended to evaluate both CAP and NP, only 44/205 ITT ciprofloxacin patients actually had CAP. Thus the study was compromised mostly of patients with NP.*

The MO is unable to comment on Bayer's motivation to pursue the TID dosing. The MO disagrees with Pfizer's statement with regards to how NP should be treated. There is no clear documentation in the literature at this time with regards to the number of anti-microbials necessary to treat NP. Most commonly in clinical practice, more than one agent is utilized. This decision is clearly practitioner driven and based on a variety of factors such as severity of disease as well as local susceptibility and infection control issues.

There are other issues in the study that supported the use of ciprofloxacin in severe nosocomial pneumonia that detract from its strength:

- The study excluded patients with 'resistant' organisms, while the trovafloxacin studies did not.
- The primary endpoint was bacterial eradication and not clinical outcome.
- In the published report, it is very difficult to actually understand the analysis. For example, the intent to treat group excluded 25% of randomized patients for reasons that are not well explained.
- As noted above, there was considerable downward dose adjustment of ciprofloxacin that took place in the study, so that the significance of the higher dose is not clear.
- One of the stated rationales for the higher dose was the presence of resistant organisms (such as *Pseudomonas aeruginosa*) but one of the conclusions of the study was that dual therapy was needed for pseudomonal infections, thus drawing into question the reason for the higher dose.
- In spite of the above, the manuscript concluded that monotherapy was adequate, however the monotherapy hypothesis was not tested in the study, since both treatment arms were monotherapy regimens.

Medical Officer's Comment:

- *Patients in the ciprofloxacin SNDA could have been excluded if a resistant pathogen was isolated. This did not occur in the trovafloxacin trials. MO agrees with Pfizer.*

- *The primary endpoint as per protocol was bacteriologic efficacy and not clinical response. However, the RMO utilized clinical response at the EOS as the primary efficacy variable and the approval for ciprofloxacin in severe NP was based on these analyses.*
- *Approximately 25% of the randomized patients were excluded from the clinical trial for well-documented reasons. Specifically, of the 402 randomized patients, 229 were unevaluable for long term efficacy. The primary reasons for being unevaluable in the ciprofloxacin group were "no causative organisms" (30), "inadequate sputum specimens" (18), "resistant pre-therapy organisms" (20), and "no EOS visit" (12).*
- *Pfizer's conclusion that there was considerable downward dose adjustment of ciprofloxacin is merely speculative.*
- *The sponsor's determination of the rationale of the study is also speculative. The conclusion in the ciprofloxacin SNDA was that ciprofloxacin was superior to the comparator in the treatment of severe NP, however, the subset of patients with Pseudomonas aeruginosa had lower eradication and clinical response rates. 33% of the isolates developed resistance on the ciprofloxacin arm as compared to 53% on the imipenem arm. The conclusion in the ciprofloxacin SNDA was that neither ciprofloxacin nor imipenem could be recommended as monotherapy for patients with Pseudomonas aeruginosa at least in the initial phase of treatment.*
- *The conclusion was that ciprofloxacin was effective as monotherapy with the exception of the aforementioned cases. It should be noted that the addition of IV vancomycin and metronidazole was allowed by-protocol and other antimicrobial usage was prohibited. This was generally adhered to.*

As true monotherapy, trovafloxacin may be superior to ciprofloxacin.

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Because of the lack of anaerobic activity, additional blinded antibiotics (metronidazole or clindamycin) had to be added to the ciprofloxacin arm. Overall, in the two trovafloxacin studies of nosocomial pneumonia, 22% of patients on comparative agents received additional study antibiotics (aztreonam, vancomycin, clindamycin, metronidazole), while only 11% of trovafloxacin patients required additional antibiotics ($p < 0.001$) (table 3.2 in study reports for #113 and #137). Additionally, there is a trend to less development of resistance by Pseudomonas aeruginosa in trovafloxacin recipients (see prior response regarding severe nosocomial pneumonia).

***Medical Officer's Comment:** These data were presented previously. Certainly and as allowed by protocol, more patients received additional anaerobic coverage on the comparator arms. The MO does not disagree with the sponsor's statements although the conclusion that trovafloxacin is more effective as true monotherapy has not been adequately shown to the reviewer's satisfaction. The premise of monotherapy is to do away with the need for additional anaerobic and aerobic coverage.*

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Conclusions

Ciprofloxacin was in fact previously approved for use in nosocomial pneumonia under the broader terminology of 'lower respiratory tract infections'. The original ciprofloxacin application contained pneumonia data drawn largely from nosocomial pneumonia patients, many of whom were severely ill by any criteria. Ciprofloxacin was broadly used to treat nosocomial pneumonia under the original indication and dosing. There is no evidence that the new dosing scheme has led to any clinical benefits.

As already noted, at the time that the trovafloxacin Phase 3 studies were designed and begun, neither ciprofloxacin, nor any other agent, were approved for nosocomial pneumonia, as such. Ciprofloxacin was clearly one of the most commonly used agents for treatment of nosocomial pneumonia, and after discussion with FDA, Pfizer elected to use it as a comparative agent at the dose then approved for treatment of "lower respiratory tract infection", which was a commonly

used dose for treatment of nosocomial pneumonia. Pfizer could not predict what approvals might occur in the future, and could have been criticized for using a larger than approved dose as an attempt to bias adverse event results or other factors such as convenience or cost in favor of trovafloxacin, as now the study is criticized for potential efficacy bias in favor of trovafloxacin for having used the approved and commonly used dose of the comparator. In spite of this, the data clearly show that trovafloxacin is effective in the treatment of severe nosocomial pneumonia, and may effect other advantages, such as simpler treatment regimens, less development of resistance, and reduced risk of drug interactions.

1. Fink MP, Snyderman DR, Niederman MS, et. Al. Treatment of Severe Pneumonia in Hospitalized Patients: Results of a Multicenter, Randomized, Double-Blind Trial Comparing Intravenous Ciprofloxacin with Imipenem-Cilastatin. *Antimicrob. Agents Chemo.*, Mar. 1994, Vol. 38, no. 3, p. 547-557.
2. Hospital-acquired Pneumonia in Adults: Diagnosis, Assessment of Severity, Initial Antimicrobial Therapy, and Preventative Strategies; A Consensus Statement. American Thoracic Society, Medical Section of the American Lung Association. *Am. J. Respir. Crit. Care Med.*, 1995, vol. 153, p. 1711-1725.

Medical Officer's Conclusion: *The sponsor adequately demonstrated comparable efficacy with ciprofloxacin in a population of patients with severe NP as defined by ATS criteria.*

The issue of the adequacy of the comparator regimen and specifically the use of a lower dose of ciprofloxacin (400 bid) as opposed to the approved 400 mg tid was also addressed. The MO determined that the sponsor's response was primarily speculative with regards to ciprofloxacin's sponsor's motivation as well as with regards to the analyses of the results. The MO does not disagree with the sponsor that the dosage of ciprofloxacin utilized in the current trials was that which was approved at the time, however the higher dosage was that which received approval for the indication. This approval was granted while the trovafloxacin trials were ongoing.

The MO believes that an approval for severe NP should be issued only if trovafloxacin was found to be superior to the ciprofloxacin regimen. This however, was not the case. In the pivotal, blinded study, trovafloxacin was equivalent to ciprofloxacin but not superior. In study 154-137, trovafloxacin was numerically superior (statistical significance not achieved), to the ceftazidime/ciprofloxacin regimen however, that trial was an open study, and therefore the results may be biased. Equivalent efficacy in the severely ill subset was shown between trovafloxacin and the comparator regimens in both studies.

*In the absence of clear superiority, the MO continues to recommend that trovafloxacin be approved for mild to moderate NP caused by *Escherichia coli*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*.*

Pfizer's Recommendation for Nosocomial Pneumonia Indication Labeling for *Pseudomonas aeruginosa* Infections:

Pfizer believes the current statement in the proposed package insert regarding use of additional therapy in infections due to *Pseudomonas aeruginosa*, with minor modification, is the most appropriate approach and does not favor a statement that strongly directs a specific approach to medical therapy for several reasons:

There is little evidence in the literature and none in the trovafloxacin studies that dual therapy for nosocomial pneumonia due to *Pseudomonas aeruginosa* infections results in better clinical outcomes.

Indeed, in the trovafloxacin studies, the trend was in the opposite direction. To our knowledge, there is only a single report in the literature that shows dual therapy is clinically beneficial, and then only in bacteremic pseudomonal nosocomial pneumonia (1). Because there is no proof that additional therapy is beneficial in most cases of nosocomial pneumonia due to *Pseudomonas aeruginosa*, we do not believe a strongly directive statement is appropriate.

Medical Officer's Comment: *The MO agreed with the sponsor's statement regarding the dearth of evidence in the medical literature with regards to the requirement that dual therapy be utilized in patients with NP. The MO also agreed that in the trovafloxacin studies that no conclusions could be drawn as to*

the need for dual therapy in the subgroup of patients with NP caused by Pseudomonas aeruginosa. Clinical outcome was not affected either adversely or beneficially.

Package Inserts should reflect the data submitted that secured the approval:

Neither study #113 (trovafloxacin vs. ciprofloxacin) nor study #137 (trovafloxacin vs. ceftazidime) required additional antipseudomonal therapy at any time during the study. Indeed, protocol #113 prohibited additional therapy unless *Pseudomonas aeruginosa* was positively identified on a culture, and even in that case, it was left to the clinician's judgment as to whether additional therapy should or should not be added, depending upon all the factors present in these complex cases. Protocol #137 only allowed additional antipseudomonal therapy for identified cases in the comparative arm, although as noted in the study report, it was added in some cases to the trovafloxacin arm also. In fact, only about 50% of trovafloxacin patients who had *Pseudomonas aeruginosa* identified on a culture actually received additional antipseudomonal therapy in these studies. Those receiving the additional therapy did no better clinically than those who did not. Since the trovafloxacin studies did not require additional therapy, patients did not uniformly receive it, and patients did not demonstrably benefit when they did receive it, we do not believe a strongly directive statement is appropriate.

Medical Officer's Comment: *The MO reminds the reader that as per the study report of protocol 154 - 137 and the CRFs, 8 trovafloxacin-treated patients and 17 ceftazidime/ciprofloxacin-treated patients received adjunctive aminoglycosides when Pseudomonas aeruginosa was documented. 5/8 and 10/17 of these patients were clinically evaluable as per the sponsor. This is slightly more than 50% of the trovafloxacin patients. 4 of these cases were clinical failures.*

The MO agreed that patients with nosocomial pneumonia caused by Pseudomonas aeruginosa had conflicting results and that no definitive conclusions could be drawn.

There is no precedent in antibiotic package inserts for strongly directed practice recommendations unless they reflect actual study circumstances.

The only strongly directive package insert that we are aware of is for Zosyn, which states that "Initial presumptive treatment of patients with nosocomial pneumonia should start with Zosyn....PLUS AN AMINOGLYCOSIDE." It goes on to say that if *Pseudomonas aeruginosa* is not isolated, the additional therapy may be stopped. However, this statement simply reflects how the pivotal study was actually conducted. All patients received both Zosyn AND aminoglycoside from the initial dose, and it was a requirement that all patients with identified *Pseudomonas aeruginosa* continue the aminoglycoside (2). This approach seems to have been taken because an earlier study of Zosyn monotherapy failed, as mentioned in the package insert. This is quite different from the trovafloxacin studies. What is clear is that the original proposed statement for the trovafloxacin package insert is more specific and consistent with published guidelines (3) than that in any other package insert.

Medical Officer's Comment: *The MO agreed with the above with regards to the Zosyn® package insert.*

Package Inserts should not be used to direct medical practice in the absence of compelling medical evidence

The question of which medical practice is best for patients with nosocomial pneumonia, or a subset of these patients, is controversial, to say the least, and one best left to the larger medical community. It is in fact a controversial subject due to the lack of compelling data on which to base recommendations. Although the American Thoracic Society has published a consensus statement on this subject (3), the Infectious Disease Society of America has different views on a number of the issues, and is assembling another guideline (personal communication Lionell Mandell). We believe it would be a mistake to mandate a particular additional therapy, only to have that superseded by newer data or newer recommendations.

We believe that reminding physicians of the prerogative to use dual therapy in instances of nosocomial pneumonia due to *Pseudomonas aeruginosa* infection is useful and that this is appropriately accomplished with the original wording. However, we would have no objection to an added direct reference to the ATS Guidelines:

"NOSOCOMIAL PNEUMONIA caused by [organism list]. As with other antibiotics, treatment of nosocomial infections due to *Pseudomonas aeruginosa* may require combination therapy, as recommended in the American Thoracic Society consensus statement for treatment of hospital acquired pneumonia (3)."

1. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic Therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. *Am J Med* 1989, vol. 87, p. 540-546.

2. Zosyn Summary Basis of Approval.

3. Hospital-acquired Pneumonia in Adults: Diagnosis, Assessment of Severity, Initial Antimicrobial Therapy, and Preventative Strategies; A Consensus Statement. American Thoracic Society, Medical Section of the American Lung Association. *Am. J. Respir. Crit. Care Med.*, 1995, vol. 153, p. 1711-1725.

Medical Officer's Comment: *The MO agrees with the sponsor that the labeling should contain information reflecting actual antimicrobial study circumstances. The outcomes in both protocols were conflicting and the numbers too small to be able to draw definite conclusions. The MO cannot advocate or disagree with the addition of a second agent in patients with nosocomial pneumonia due to Pseudomonas aeruginosa. However, the MO points out that trovafloxacin will be used in the empirical treatment of patients before culture results are available.*

The following statement drafted by the MTL, "Nosocomial pneumonia (mild to moderate) caused by Escherichia coli, Pseudomonas aeruginosa, or Haemophilus influenzae. As with other antimicrobials, where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated." most accurately reflects study circumstances as well as current medical opinion and should be added to the labeling in both the I and U section as well as the D and A.

On 12/9/97, additional analyses for the NP indication were requested to address whether trovafloxacin was superior in severely ill patients vs. the comparator arms. Specifically, it was requested that Pfizer provide clinical efficacy tables (EOS = TOC) for both studies separately and combined (Pfizer clinically evaluable population, severe patients only as defined by mutually acceptable ATS criteria), for patients with and without concomitant antimicrobial therapy (all concomitant antimicrobial agents, including clindamycin, metronidazole, vancomycin, aztreonam and aminoglycosides). The question as expressed by this request: "Was trovafloxacin alone superior to ciprofloxacin/comparator alone or in combination with other agents in patients with severe disease only?"

This information was provided by the sponsor on 12/9/97 in the form of several tables sent by FAX. These tables were combined into the table below and revealed the following:

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Nosocomial Pneumonia Pfizer Clinically Evaluable Population at EOS Severe Disease ONLY by ATS Criteria							
		154 -113 (US) (vs. Ciprofloxacin IV 400 bid → PO Ciprofloxacin 750 bid)		154 - 137 (Europe) (vs. Ceftazidime 2 gm IV bid → PO Ciprofloxacin 750 bid)		Combined Studies	
		No. Cured/No. Eval	(%)	No. Cured/no. Eval	(%)	No. Cured/No. Eval	(%)
Trovan	Monotherapy	28/46	61	33/54	61	61/100	61
	Adjunctive	7/10	70	1/7	14	8/17	47
	Both	35/56	63	34/61	56	69/117	59
Comparator	Monotherapy	32/48	67	33/53	62	65/101	64
	Adjunctive	4/9	44	2/12	17	6/21	29
	Both	36/57	63	35/65	54	71/122	58

95% CI with CCF (d = 20)

Study 154 -113:

Trovan Monotherapy vs. Ciprofloxacin Monotherapy: - 27%, 15.7%

Trovan Both vs. Ciprofloxacin Both: - 20.2%, 19%

Study 154 - 137:

Trovan Monotherapy vs. Ceftazidime/Ciprofloxacin Monotherapy: - 21.4%, 19%

Trovan Both vs. Ceftazidime/Ciprofloxacin Both: - 17.1%, 21%

Combined:

Trovan Monotherapy vs. Comparators Monotherapy: - 18%, 11%

Trovan Both vs. Comparators Both: - 12.5%, 14%

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The MO requested that the sponsor provide line listings of the patients included in the adjunctive categories in the above table. These were faxed on December 11, 1997 and revealed the following:

In study 113: 7/10 (70%) trovafloxacin patients received aztreonam (2 failures, 5 cured or improved), 4/10 (40%) trovafloxacin patients received vancomycin (1 failure, 3 cured or improved), and none of the trovafloxacin patients received adjunctive anaerobic coverage. Only 1 of these patients received both vancomycin and aztreonam and that patient was improved at the EOS.

On the ciprofloxacin arm, only 1/9 (11%) patients received aztreonam and was a failure. This patient also received clindamycin. 2/9 (22%) patients received vancomycin and both were failures. One of these patients also received clindamycin. 6/9 (66%) patients received clindamycin and in addition to the 2 aforementioned failures, 2/6 were failures (or 4 total failures) and 2/6 (22%) were cured.

In study 137: 4/7 (57%) trovafloxacin patients received gentamicin (3 failures and 1 cured), 4/7 (57%) received vancomycin (all failed), and no patient received additional anaerobic coverage. Only one of these patients received both gentamicin and vancomycin and was a failure.

On the ceftazidime/ciprofloxacin arm, 8/12 (67%) patients received gentamicin (6 failures and 2 cured), 6/12 (50%) received vancomycin (5 failures and 1 cured), and none of the patients received additional anaerobic coverage. There were 2 patients who received both gentamicin and vancomycin (1 failure and 1 cured).

Medical Officer's Comment: Very similar numbers of patients from both studies combined received monotherapy versus concomitant therapy. Interestingly, only 1 (11%) patient on the ciprofloxacin arm of study 113 received additional antipseudomonal coverage as opposed to 7 or 70% of the trovafloxacin patients. The main difference in study 113 was the addition of anaerobic coverage in 67% of the ciprofloxacin patients and none of the trovafloxacin patients. However, in study 154 - 137, none of the

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severely ill patients on either arm received anaerobic coverage. Similar numbers of patients on both arms received gentamicin and vancomycin.

The 95% CI for the monotherapy patients in study 154 -113 with severe NP indicated that trovafloxacin was NOT equivalent to ciprofloxacin. Additionally, equivalence was not demonstrated when all severe trovafloxacin patients, any mode of therapy were compared to all severe ciprofloxacin patients, any mode of therapy. Equivalence was also not demonstrated for monotherapy in study 154 -137. In both studies combined, trovafloxacin monotherapy was equivalent to comparators monotherapy. Equivalence was also demonstrated in trovafloxacin patients with severe disease, combination therapy versus ceftazidime/ciprofloxacin combination therapy in study 154 -137, as well as in both studies combined.

Initially it appeared as if there was some superiority of trovafloxacin adjunctive therapy in both studies versus the adjunctive therapy comparators both studies, that is 47% versus 29%. However the numbers are too small 7/18 versus 6/21 to be able to detect any real difference.

From the above, the MO was unable to detect any superiority of trovafloxacin monotherapy versus comparators either as monotherapy or in conjunction with adjunctive antimicrobial therapy. Indeed, equivalence was not shown between trovafloxacin monotherapy and ciprofloxacin monotherapy in the pivotal US study or the open European study for severe NP. However, when the studies were combined, equivalence was demonstrated.

The above table was emailed to the sponsor on 12/10/97 for further comment with regards to trovafloxacin's claim of superiority as a monotherapeutic agent versus ciprofloxacin in the treatment of severe (as defined by ATS criteria) nosocomial pneumonia.

Medical Officer's Conclusion: The sponsor was unable to adequately demonstrate that trovafloxacin monotherapy was superior to ciprofloxacin monotherapy or combination therapy or both combined in the severely ill (as defined by ATS criteria) population. Trovafloxacin combination therapy was equivalent with the comparators combination therapy in study 154 - 137 and with all studies combined but not equivalent with ciprofloxacin combination in the pivotal US study.

The question of the adequacy of the comparator regimen becomes moot in the face of these analyses. If trovafloxacin was unable to meet the 95% CI at a lower than approved dose of ciprofloxacin for severe NP, then the issue of the use of the appropriate dose raises questions as to the efficacy of trovafloxacin for the indication itself.

Based on the above, the MO does not recommend approval for trovafloxacin in patients with severe nosocomial pneumonia.

On, December 12, 1997, the sponsor submitted a document entitled "Further Comments on Inclusion of *Staphylococcus aureus* and *Klebsiella pneumoniae* in Nosocomial Pneumonia and Community Acquired Pneumonia Indications" in which the sponsor presented further arguments as to why *Staphylococcus aureus* and *Klebsiella pneumoniae* are legitimate organisms for both of these indications and that sufficient data are available to include them. Portions of the sponsor's arguments are appended below:

Staphylococcus aureus:

-In Nosocomial pneumonia alone, there were 21 *Staphylococcus aureus* isolated and 14 successfully clinically treated at EOS (67%) in the two trovafloxacin protocols, results equal to the overall outcomes. The figures for the comparators are 10/21 (48%). The somewhat better efficacy with trovafloxacin is not surprising since trovafloxacin is at least an order of magnitude more active than ciprofloxacin or ceftazidime. In CAP, 18/18 were successfully treated in the trovafloxacin arms.

-*Staphylococcus aureus* was included in the levofloxacin CAP indication, apparently on the basis of successful outcomes in 15/17 cases, as reported in the clinical trials section of the package

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insert. As noted below however, the levofloxacin CAP studies were very weak in key design areas (one was unblinded and the other non-comparative).

--*Staphylococcus aureus* was included in the recent Zosyn® label for Nosocomial pneumonia apparently on the sole basis of organisms acquired in the single pivotal trial vs. ceftazidime in which 155 patients were randomized to Zosyn®. From the medical officer's review (p. 75), it is apparent that approval was gained on the basis of 13 successful courses out of 16 isolates.

--We regard this as a 'level playing field' issue. We believe we have studied adequate numbers that are at least equal to those studied in recent approvals. We do not believe the sponsors of levofloxacin and Zosyn® were required to specially 'prove the validity' of this particular isolate as Pfizer was, for an organism that is generally regarded as a pathogen in these infections.

Medical Officer's Comment: *The MO determined that the information presented above refers to 2 different indications, that is NP and CAP. With regards to NP, the MO found a combined clinical response rate of 12/19 (63%). The MO's rate is slightly lower than that of the sponsor, however, this rate is superior to that found in the ciprofloxacin NDA 19 - 847/S-3 for severe NP: 8/14 (57%). As noted previously, ciprofloxacin did not obtain an approval for this isolate in severe disease.*

With regards to the Zosyn® NDA 50 -684, the MO noted previously, that an approval was granted based on an eradication rate (EOS) of 13/16 (81%).

The MO determined that the levofloxacin data for the CAP indication are not pertinent to the current indication. A previous divisional decision stated that it would be inappropriate to extrapolate data from a more severe indication to a lesser severe.

Nevertheless, the MO agreed with the sponsor with regards to the adequacy of the data presented in the trovafloxacin submission. Certainly, this submission contained adequate information to grant an approval for this isolate in patients with mild to moderate NP only. The MO clarifies this issue because the data from the Zosyn® NDA, despite being obtained from a single clinical trial, were obtained from a severely ill population and the cure rate was higher than that of trovafloxacin. Additionally, as per the MO's data, the comparators in the ciprofloxacin NDA 19-847/S-3 had a combined clinical response rate of 10/15 (67%).

As per the sponsor:
Klebsiella pneumoniae

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--Across nosocomial pneumonia and CAP, 18/24 *Klebsiella pneumoniae* isolates were successfully treated. Eight were from Nosocomial pneumonia with 4 clinical successes, while 16 were from double blind, randomized, controlled trials in CAP, with 14/16 successfully treated (EOS). From p. 407 of the medical officer's review of levofloxacin, it appears that there were only 6 clinically evaluable subjects with this isolate, several of which appear to have originated in the non-comparative trial #M92-075. The medical officer did not recommend approval for this organism, however, there is a reference on p. 427 to additional data from supportive trials in an 'addendum', which is not available to Pfizer.

--The only other recent reference to *Klebsiella pneumoniae* is the levofloxacin package insert clinical trials section, where a figure of 10 isolates, all successfully treated, is cited.

--We regard this as a 'level playing field issue'. The primary source of the *Klebsiella pneumoniae* for the levofloxacin label was from an unblinded study (vs. ceftriaxone/cefuroxime) which was justly criticized by the medical officer because of this and other deficiencies. The only further data seem to have come from a non-comparative study, as reported in the clinical trials section. The trovafloxacin CAP data on *Klebsiella pneumoniae* are from much more robust double blind studies. More *Klebsiella pneumoniae* were studied in the trovafloxacin CAP program, by a considerable margin than in the levofloxacin program.

--The agency may fairly take the position that it has made an egregious error in the levofloxacin label and will not include organisms on such flimsy data in the future. However, the trovafloxacin data are much more robust and much greater in quantity. To not include *Klebsiella pneumoniae* would be unfair.

Medical Officer's Comment: *As per the MO and the sponsor the clinical response rate by pathogen for Klebsiella pneumoniae was 4/8 (50%). both studies combined in NP. The MO determined that this rate was very low compared with that of ciprofloxacin in NDA 19 - 847/S-3: 8/9 (89%). The MO as noted above, determined in conjunction with the Division, that it would be inappropriate to extrapolate data from a less severe indication (CAP), to a more severe (NP).*

Based on the above, the MO continues to recommend a non-approval for this organism in NP.

Medical Officer's Overall Conclusion:

**APPEARS THIS WAY
ON ORIGINAL**

Based on all the data reviewed and after labeling discussions with the sponsor on 12/18/97, the MO agreed to recommend approval for trovafloxacin in the treatment of NP without referring to severity. This decision was made because of the equivalent efficacy between trovafloxacin and the comparator agents in both clinical trials for the overall populations. The sponsor agreed to a Phase 4 commitment

RECOMMENDED REGULATORY ACTION:

**APPEARS THIS WAY
ON ORIGINAL**

The following statement should be added to the Indications and Usage section of the labeling:

Additionally, this statement should be added to the Dosage and Administration section. The approved dose is alatrofloxacin/trovafloxacin 300 mg IV to 200 mg PO daily for 10 -14 days.

A clinical studies section describing the results of the US trial is recommended.

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/S/ *12/19/97*
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Medical Officer, DSPIDPs

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- Orig. NDA #20-760
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- HFD-590/Div. Dir./MGoldberger
- HFD-590/Dep. Dir./RALbrecht
- HFD-590/MTL/BLeissa
- HFD-590/MO/RAlivisatos
- HFD-590/CSO/PFogarty
- HFD-725/Biostat/Silliman
- HFD-344/Thomas

/S/
/S/ 12/17/97

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Appendix I/NDA 20 - 759

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Study 154 –117/Complicated UTI:

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**Study 154 - 101 /Acute Exacerbation
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**Study 154 - 101 /Acute Exacerbation
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5056 Stuart Topkis, D.O.	Gilbert Weisman, D.O.	350 West Street Road Warminster, PA 18974
5057 Jack Tomlinson, M.D.	Barbara Gullatt, R.N. Millicent McDonald, R.N.	Grayline Clinical Drug Trials 706 Denver Street Wichita Falls, TX 76301
5058 Stephen Kreitzer, M.D.	Leonard Cosmo, M.D. David Goldstein, M.D.	Tampa Medical Research Associates 2919 Swann Avenue Suite 105 Tampa, FL 33609
	APPEARS THIS WAY ON ORIGINAL	Pulmonary Associates of Tampa 2919 Swann Avenue Suite 202 Tampa, FL 33609
5059 Narayan Krishnamurthy, M.D.	Scarlett West, R.N.	Alvin C York VA Medical Center 3400 Lebanon Road Murfreesboro, TN 37129
5060 Anjuli Nayak, M.D.	Janet Dunn Nicholas Nayak, M.D.	1300 Frankin Avenue Suite 355 & 180 Normal, IL 61761
5061 Michael Kalafer, M.D.	Charles Brown, M.D. Charles Landers, M.D. David Willms, M.D. Davies Wong, M.D.	Sharp Cabrillo Hospital 3475 Kenyon Street San Diego, CA 92110 Sharp Memorial Hospital 7901 Frost Street San Diego, CA 92123
5066 Robert Pieroni, M.D.	William DeBell, M.D. Cathy Gresham, M.D. Vijaya Sundar, M.D. John Wheat, M.D. William Winternitz, M.D.	Capstone Medical Center 700 University Boulevard East Tuscaloosa, AL 35401

**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5005 Willis Manfred Gooch, III, M.D.	Sylvia Corral, M.D. Nathan Dean, M.D. Nancy Henderson Sandra Knight Darla Longhurst James Pearl, M.D. Keith Pearson, M.D. Cheryl Ritchie George Thomsen, M.D.	Medical Research Associates of Utah 265 East 100 South Suite 255 Salt Lake City, UT 84111 Salt Lake Clinic 333 South 900 East Salt Lake City, UT 84102 Medical Research Associates of Utah Incorporated 324 East Tenth Avenue Salt Lake City, UT 84013
5011 Anthony Puopolo, M.D.	Aly El-Hag, M.D.	Umap Clinic 250 East 300 South Suite 200 Salt Lake City, UT 84111
5022 Lee Edward Payne, M.D.	James G. Adams, M.D. Jeffry Finklestein, M.D. Evan Guz, M.D. Edward Irick, M.D. Kevin Jordan, M.D. James King, M.D. Michael Magoon, M.D. Kelly P. O'Keefe, M.D. Rafael Pagan, M.D. David Porterfield, D.O. Mark Robbins, M.D. Tracy G. Sanson Gerald Schwartz, M.D. Randall Shuster, M.D. Anthony Steele, M.D. Christopher Steffy, M.D. Raymond Swienton, M.D. Maria Tiamson-Beato, M.D. Charles Wilson, M.D.	Fourth Street Clinic 404 South 400 West Salt Lake City, UT 84101 5 Water Street Milford, MA 01757 Division of Acute Care/PSA Wilford Hall Medical Center 2200 Bergquist Drive Suite 1 Lackland Airforce Base, TX 78236-5300
Diana Dark, M.D.		St. Lukes's Hospital 4400 Wornall Road Kansas City, MO 64111

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**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5041 Robert Fiddes, M.D.	Peter Arcan, M.D. Julian Fuentes, M.D.	Southern California Research Institute 12291 East Washington Blvd. Suite 204 Whittier, CA 90606
5042 J. Daniel Scott, M.D.	Alkesh Amin, M.D. Harvey Resnick, M.D. Irvin Sabrsula, M.D. Roberto Ticas, M.D.	R/D Clinical Research Inc. 135 Oyster Creek Drive Suite V Lake Jackson, TX 77566 Allergy and Immunology and Asthma Medical Group Inc. 4628 Georgetown Place Stockton, CA 95207
5072 George Bensch, M.D.	William Chapman, Jr. Jerold Yecies, M.D.	174 Edison Road Lake Hopatcong, NJ 07849
5073 Jean-Paul Bonnet, D.O.	Arthur Braunwell, Jr., D.O. John Daly, III, D.O. Christopher Damico, D.O. Stephen Gloria, D.O. Mary Magnusen, D.O. A. William Thomas, D.O.	California Research Foundation 2800 Third Avenue San Diego, CA 92103-6204
5074 Milan Brandon, M.D.	Donald Brandon, M.D. William Davis, M.D.	AAAA Medical Research Group 150 South 1000 East Salt Lake City, UT 84102
5075 Edwin Bronsky, M.D.	Joseph Anderson, Jr, M.D. Alan Bitner, M.D. Brent Burdett, M.D. Lorimer Christensen, M.D. David Goodman, M.D. David Gourley, M.D. Duane Harris, M.D. Anthony Henry, M.D. Vicki Lyons, M.D. Kay Walker, M.D. Henry Yeates, M.D.	Inland Empire Internal Medicine South 820 McClellan Suite 306 Spokane, WA 99204
5076 Timothy Bruya, M.D.	James Elmer, M.D. Jeffrey Elmer, M.D. Todd Green, M.D. Lawrence Klock, M.D. Richard Lambert, M.D. Donald Storey, M.D. Alan Whitehouse, M.D.	Associated Internists/ Pulmonary Group 104 West 5th 240-W Spokane, WA 99204

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**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5077 Jacques Caldwell, M.D.	Arthur Elkins Howard Offenberg, M.D.	Gainesville Clinical Research Center 7106 Northwest 11th Place Gainesville, FL 32605 and Wallis Medical Center Unit C-101 40 Southwest 12th Street Ocala, FL 32671
5078 C. Andrew Deabate, M.D.	J. Craig Cornett, M.D.	Medical Research Center 3600 Prytania Street Suite 100 New Orleans, LA 70115 Medical Research Center 3655 Veterans Memorial Blvd. Metairie, LA 70002
5079 W. Travis Ellison, M.D.	W. John Henry, III, M.D. John Milas, M.D. Douglas Owens, M.D.	Upstate Clinical Research Inc 555-A & 555-B Memorial Drive Extension Greer, SC 29651 108 West Church Street Greer, SC 29652
5080 Frank Garamy, Jr., M.D.	Philip Schworer, M.D.	747 Buttermilk Pike Crescent Springs, KY 41017
5081 James Garofalo, M.D.		602 Bloomfield Avenue West Caldwell, NJ 07006
5082 Mark Gotfried, M.D.	Bruce Bachus, M.D. David Baratz, M.D. Robert Comp, M.D. Bernard Levine J. Burr Ross, M.D. Ronald Servi, M.D. Robert Westfall, M.D.	Pulmonary Associates PA 9225 North 3rd Street Suite 200B Phoenix, AZ 85020 Pulmonary Associates PA 1112 East McDowell Road Phoenix, AZ 85006
5083 Robert Frost Jones, M.D.	Kraig Jacobson, M.D.	Allergy & Asthma Research Group 1488 Oak Street Eugene, OR 97401
5084 Craig LaForce, M.D.	Karen Dunn, M.D.	Carolina Clinical Research 4301 Lake Boone Trail Suite 309A Raleigh, NC 27607

**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5085 Thomas Littlejohn, III, M.D.	Thomas Cannon, M.D. David Collins, M.D. Kenneth Gallup, Jr., M.D. Thomas Hinson, Jr., M.D. Champ Jones, Jr., M.D. Robert Kelly, M.D. Irvin Perry, M.D. Gina Shar, M.D. Barry Sigal, M.D. Keith Van Zandt, M.D.	Piedmont Research Associates 1901 South Hawthorne Road Suite 306 Winston-Salem, NC 27103 Maplewood Family Practice 2805 Lyndhurst Avenue Winston-Salem, NC 27103 Salem Chest Specialist 3001 Lyndhurst Avenue Winston-Salem, NC 27103 610 Audubon Medical Plaza Louisville, KY 40217
5086 Michael Peveler, M.D.		
5087 Gary Post, M.D.	Lindy Gilchrist, M.D. Michael Piel, M.D. Terese Snowden, M.D.	Bellevue Family Practice 8200 East Bellevue Avenue Suite 280 Englewood, CO 80111
5088 Robert Rosen, M.D.	James Derrick Gale Harkness Donald Lendel, M.D. Gina Pasquale	Salem Research Group Inc. 3333 Brookview Hills Blvd. Suite 110 Winston-Salem, NC 27103 Pine Ridge Family Practice 7990 North Point Blvd. Winston-Salem, NC 27106
5089 David Stryker, M.D.	Quito Carr, M.D. Barbara McGuire, M.D. William Mitchell, M.D. Jeffrey Sollins, M.D.	New Mexico Medical Group PC 8324 Constitution Place NE Albuquerque, NM 87110 New Mexico Medical Group PC 717 Encino Place NE Suite 12 Albuquerque, NM 87102
5090 Alan Wanderer, M.D.	Julie Anderson Kennedy Lawrence Larsen, M.D. Paul Schkade, M.D.	Clinical Research Group of Colorado 3601 South Clarkson 220 Englewood, CO 80110
5091 W. Murray Yarbrough, M.D.	Richard Fuller, M.D.	Simon-Williamson Clinic PC 833 Princeton Avenue SW Birmingham, AL 35211
5092 William Ziering, M.D.	Loretta Hicks Siew Lin Wong	4747 North First Street Suite 177 Fresno, CA 93726

Study 154 –109: Acute Exacerbation of Chronic Bronchitis:

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5094 William McCall, Jr, M.D.	Wayne Beauford, M.D. Mark Doner, M.D.	Jordon Diagnostics and Research Inc. 300 Landsay Street Suite 200 High Point, NC 27262
APPEARS THIS WAY ON ORIGINAL		Bethany Medical Center 507 Landsay Street High Point, NC 27262 Forsyth Internal Medicine 1405 Plaza Drive Winston-Salem, NC 27103
5095 Robert Hippert, D.O.	Eugene Fellin, D.O. Robert Sellers, M.D.	Fleetwood Medical Associates 805 North Richmond Street P.O. Box 497 Fleetwood, PA 19522
5121 Marcus Zervos, M.D.	APPEARS THIS WAY ON ORIGINAL	William Beaumont Hospital 3601 West 13 Mile Road Royal Oak, MI 48073
5124 Kent Anthony, M.D.	Swapan Banerjee, M.D. Charles Couch, M.D. Leonard Kibert, M.D. Murali Kosuri, M.D.	R/D Clinical Research 2100 Space Park Drive Suite 230 Nassau Bay, TX 77058
APPEARS THIS WAY ON ORIGINAL		St. John Hospital 2050 Space Park Drive Nassau Bay, TX 77058
5125 Steven Bowman, M.D.	James Hampsey, M.D.	Tampa Bay Medical Research Inc. 3253 McMullen Booth Road Clearwater, FL 34621-2010
5127 Meera Dewan, M.D., P.C.	Raza Medhi, M.D.	11912 Elm Street Omaha, NE 68144
5129 Jeffrey Hartford, M.D.	Jonathan Bowman, M.D. Melody Dwyer, D.O. Grace Henry Robert Lebow, M.D. Craig Leymaster, M.D. Mary O'Malley Bryan Pogue, M.D. William Pogue, M.D. Richard Robinson, M.D. Delbert Scott, M.D. Monte Tolman, D.O. Amy Waselcuk	Advanced Clinical Research 10 South Cole Road Boise, ID 83709
		Fairview Medical Clinic 4809 Fairview Avenue Boise, ID 83706
		Terry Reilly Health Services 223 16th Avenue, North Nampa, ID 83687
		Boise Medical Center 425 West Bannock Street Boise, ID 83712

**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5130 Spencer Jones, M.D.	Daniel Davis, M.D. John Herrod, M.D. Werner Huck Kenneth Nielson, M.D. Mark Shephard, M.D. Rulon Simmons, M.D. Larry Staker, M.D.	Advanced Clinical Research 34 South 500 East 102 Salt Lake City, UT 84102 Bryner Clinic 745 East 300 South Salt Lake City, UT 84102
5132 Michael McAdoo, M.D.	Wade Reeves, M.D.	Milan Medical Center 6041 Telecom Drive Milan, TN 38358
5133 Dennis Mikolich, M.D.	Michael Baaklini, M.D.	Independent Research Nurses Incorporated Calart Tower 400 Reservoir Avenue Providence, RI 02907 Belltower Medical Offices 580 Metacom Avenue Unit #5 Bristol, RI 02809
5134 David Miller, D.O.	Martha Bacsik Ginger Brounce, R.N. Laura Lincoln, R.N. Anthony Mannino, M.D. Kathryn Martin	Bucks County Clinical Research 201 Woolston Drive Morrisville, PA 19067
5135 Michael Nelson, M.D.	Sean Barry, M.D. Lew Wesselius, M.D.	Veterans Administration Medical Center Dept. of Medicine 111 4801 Linwood Blvd. Kansas City, MO 64128
5136 David Schreck, M.D.	Frank Coppolino, M.D. Harold Cotler, D.O. Edward Gosselin, M.D. L. Scott Larsen, M.D. Alexandra Leschinsky, M.D. Frances Mifsud, M.D. Alan Miller, M.D. John Morlino, D.O. Alberto Rivera, M.D. Lanny Samson, M.D. Militza Suarez, M.D. Daniel Zacharias, M.D.	Muhlenberg Regional Medical Center Emergency Department Park & Randolph Roads Plainfield, NJ 07061 Emergency Medical Offices 369 Springfield Avenue Berkeley Heights, NJ 07922 2 Kings Highway & Route 35 Middletown, NJ 07748-2500

**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5137 Richard Sterling, M.D.	Franklin Coulter, M.D. Henry Marion, M.D.	511 Carolina Avenue Orangeburg, SC 29115
5138 Randall Stoltz, M.D.	Patrick Flamion, M.D. Bryan Laura, M.D. Richard Murray, M.D. Ward Neff, M.D. Raymond Newnum, M.D. John Polin, M.D. Jennifer Wahle, M.D.	GFI Pharmaceutical Services Inc. 800 St. Mary's Drive Evansville, IN 47714
5139 James Sullivan, M.D.	Gregory Flippo, M.D.	Parkway Medical 9228 Parkway East Birmingham, AL 35206
5140 John Upchurch, M.D.	Lyman Fritz, M.D.	St. Vincent Family Medical Center 9823 Parkway East Birmingham, AL 35215
5181 James Taylor, M.D.	Debbie Bergevin Kathleen Dorr Danita Erickson-Parkhurst Arthur Knodel, M.D. Clyde Koontz, M.D. John Rowlands, M.D. Barry Weled, M.D.	316 Martin Luther King Jr. Way Suite 401 Tacoma, WA 98405
5213 Jason Chu, M.D.	Carmen Agcaoili, M.D. Nelson Herlihy Edward Meyer, M.D. Stanley Newman, M.D. Marco Pavesi, M.D.	2557 Mowry Avenue Suite 12 Fremont, CA 94538
5215 George Knull, M.D.	George Hancock, M.D. Susan Marie Tiso Mark Wagner, M.D. Lisa Marie Wieler, M.D.	Harriman Jones Medical Group 2600 Redondo Avenue Long Beach, CA 90806
5250 Carlos Morales, M.D.	Theresa Bisnett, M.D.	Pulmonary Critical Care Dept (PSMP) 59th Medical Wing 2200 Bergquist Drive Suite 1 Lackland AFB, TX 78236-5300
Jan Westerman, M.D.	David Brickey, D.O. Stephen Derdak, D.O. Gina Dorlac, M.D. Lawrence Epstein, M.D. Peter Fort, M.D. James Henderson, M.D. Donald Howard, M.D. Wheeler Jarvis, M.D. Dennis Lawlor, M.D.	Wilford Hall Medical Center PS-IC Lackland AFB, TX 78236-5300

**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5499 Harvey Tilker, PhD. APPEARS THIS WAY ON ORIGINAL	Hollis Clark, M.D. Richard Crouch, M.D. Robert Korolevich, M.D. Janice Krizan, L.P.N. Jean Tilker, R.N.	Four Rivers Clinical Research 100 North Sixth Street Murray, KY 42071 Primary Care Medical Center Suite 480W 300 South Eighth Street Murray, KY 42071
5743 Boyde Harrison, M.D.	APPEARS THIS WAY ON ORIGINAL	Highway 195 East P.O. Box 655 Haleyville, AL 35565
5776 Daniel Krichbaum, PharmD.	Miles Andrew, M.D. David Baxter, D.O. William Bogan, M.D. Richard Buck, M.D. Shaukat Chaudhry, M.D. Alfred Cox, M.D. Steven Crowell, M.D. Lawrence Curry, D.O. James Harris, M.D. Anandkumar Koyani, M.D. Elizabeth Lauber, M.D. Charles Myers, M.D. Armando Perez-Soto, M.D. Thomas Seasley, M.D. Gary Sunada, M.D. Dwight Tapley, M.D.	Health Advance Institute 108 North Main Street Suite 707 South Bend, IN 46601 South Bend Clinic 211 North Eddy Street South Bend, IN 46634 303 South Main Street Mishawaka, IN 46544
APPEARS THIS WAY ON ORIGINAL	James Ausfahl, M.D. Daniel Brune, M.D. Jeffrey Morton, M.D. Edward Rufus, M.D.	524 East McKinley Avenue Mishawaka, IN 46545 Health Advance Institute One Illinois Drive P.O. Box 1466 Peoria, IL 61655-1466 Proctor First Care 4207 North Prospect Road Peoria Heights, IL 61614
5777 Alan Rosenthal, PharmD.	APPEARS THIS WAY ON ORIGINAL	Family and Sports Medicine Center 5401 North Knoxville Suite 48 Peoria, IL 61614 Creve Coeur Family Practice 120 Wagner Drive Creve Coeur, IL 61611

**Study 154 -109: Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5853 Chandra Khurana, M.D.	APPEARS THIS WAY ON ORIGINAL	Internal Medicine 304 South Western Avenue Peoria, IL 61605 Maya Family Medical Center 4527 North Pulaski Chicago, IL 60630
6248 Alan Storrow, M.D.	Jeffry Finklestein, M.D. Evan Guz, M.D. Edward Irick, M.D. Kevin Jordan, M.D. James King, M.D. Michael Magoon, M.D. Rafael Pagan, M.D. Mark Robbins, M.D. Gerald Schwartz, M.D. Randall Shuster, M.D. Anthony Steele, M.D. Christopher Steffy, M.D. Raymond Swienton, M.D. Maria Tiamson-Beato, M.D. Charles Wilson, M.D.	Division of Acute Care/PSA Wilford Hall Medical Center 2200 Bergquist Drive Suite 1 Lackland Airforce Base, TX 78236-5300

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**Study 154 -141 /Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5015 Sanford Chodosh, MD	Janice Tuck	Chief Of Pulmonary Medicine Veterans Affairs Outpatient Clinic Room 815 251 Causeway Street Boston, MA 02114
5017 John Gezon, MD	James Antinori, MD Kathy Atkinson, MD Daniel Duggleby, MD Robert Gannon, MD Lance Owens, MD Marcia Prather, MD Michael Romney, MD	Salt Lake Utah Research Project 1388 Arlington Drive Salt Lake City, UT 84103 Salt Lake Regional Medical Center 1050 East South Temple Salt Lake City, UT 84102
5034 Guillermo Rodriguez Gomez, MD	Celia Barrantes Howay, MD Katy Barrantes Jimenez, MD Andrea Bianchi Bruna, MD Eugenia Cuesta Jimenez, MD Sofia Gonzalez Ugalde, MD Jorge Mora Duarte, MD	3er Piso Biblioteca Medica Hospital Mexico San Jose, Costa Rica Hospital San Juan De Dios Apartado 10105 San Jose, Costa Rica
5078 C. Andrew Deabate, MD	Iris Perez Quiros, MD J. Craig Cornett, MD	Hospital Calderon Guardia Clinica De Pavas Apartado 10105 San Jose, Costa Rica Medical Research Center 3655 Veterans Boulevard Metairie, LA 70002 Medical Research Center 3600 Prytania Street, Suite 100 New Orleans, LA 70115

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**Study 154 -141 /Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5096 Jeffrey Adelglass, MD	David Harper, MD Jacqueline Kleven, DDS Jan Pickett, MD Julius Wolfram, MD	Dallas Clinical Research 9 Medical Parkway, Suite 202 Dallas, TX 75234 Trinity Professional 4333 North Josey Lane, Suite 101 Carrollton, TX 75010
5144 Kirk Jacobson, MD	Kathryn Gilliland, MD James Knackstedt, MD Donald Olson, MD David Strutin, MD Phillip Taggart, MD Peter Thompson, MD	Oregon Research Group 1200 Hilyard Street, Suite 200 Eugene, OR 97401 Oakway Medical Clinic 495 Oakway Road Eugene, OR 97401 Eugene Hospital And Clinic 1162 Willamette Street Eugene, OR 97401
5145 Stephen Kraus, MD	Edmond Griffin, MD D. Scott Karempelis, MD Bette Potter, MD	Georgia Clinical Research Center, Inc. 5671 Peachtree Dunwoody Road Suite 520 Atlanta Ga 30342 Atlanta Radiology Imaging Center 5671 Peachtree Dunwoody Road Suite 100 Atlanta, GA 30342
5147 Alex Pareigis, MD	Mark Blaser, MD Edward Ebert, DO William McCormick, MD James Moss, MD John Peterson, Ph.D, MD Richard Phillis, MD Randall Spaude, MD Mark Valiere, MD Bruce Vesole, MD	Medical Arts Associates, Ltd. 4600 3rd Street Moline, IL 61265
5148 Stan Parman, MD	Alexandra Leschinsky, MD John Morlino, DO Militza Suarez	Emergency Medical Offices Research 2 Kings Highway Middletown, NJ 07748

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of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5149 Gary Ruoff, MD	David Brown, Jr, DO Michael Dandois, DO Mark Deyoung, MD Earl Burhans, DO Catherine Harris, MD Ralph Hodges, MD Elaine Kountanis, MD Nayana Patel, MD Irina Targowski, MD Carol Voytas, MD Laurence Weber, MD William Woodhams, MD	Westside Family Medical Center 6565 West Main Street Kalamazoo, MI 49009
5150 Irwin Spirm, MD	Kathleen Goldstein, DO Albert Jurecic, MD	Delaware Valley Lung Center 1155 Markkress Road Cherry Hill, NJ 08003
5151 Keith Van Zandt, MD	Thomas Cannon, MD Michelle Combs Gina Shar Thomas Jolly, MD Champ Jones, MD Robert Kelly, MD Thomas Littlejohn, III, MD	Piedmont Research Associates 1901 South Hawthorne Road Suite 306 Winston-Salem, NC 27103 Maplewood Family Practice 2805 Lyndhurst Avenue Winston-Salem, NC 27103
5152 Lawrence Alwine, DO	APPEARS THIS WAY ON ORIGINAL	Primecare Family Med. 7811 North Point Boulevard Winston-Salem, NC 27105 Downingtown Family Medicine Downingtown Professional Plaza 797 East Lancaster Ave., Suite 2 Downingtown, PA 19335
5153 Spencer Coleman, MD	Jerry Bush, MD Julius Dunn, MD Bipin Kumar, MD	Wetumpka Clinic Pa 73970 Tallassee Highway Wetumpka, AL 36092 73996 Tallassee Highway Wetumpka, AL 36092
5154 John Estess, MD	Glenda Hamlin	244 Claud Road Eclectic, AL 36024 Hollandale Clinic Highway 12 And 61 Intersection P.O. Box 247 Hollandale, MS 38748

**Study 154 -141 /Acute Exacerbation
of Chronic Bronchitis:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5156 Andrew Hughes, MD	Patrick Bianchi, MD Thomas Bianchi, MD Keith Bufford, MD Jimmy Durden, MD Michael Peaden, MD Melvin Russell, MD	Community Medical Arts Center 875 Friendship Road Tallasse, AL 36078 Tallasse Family Care 115 Herren Hill Road Tallasse, AL 36078
5157 Mark Lamos, MD	Walter Hepner, MD Frank Sanzaro, MD Robert Wiedefeld, MD	3334 Papermill Road Phoenix, MD 21131 1122 Kenilworth Drive, Suite 200 Baltimore, MD 21204
5159 Onelio Perdomo, MD	Saket Prasad, MD	Family Medical Center Of Gadsden 206 Bay Street Gadsden, AL 35091
5160 Thomas Saddoris, II, MD	APPEARS THIS WAY ON ORIGINAL	Clackamas Medical Center 9123 Southeast Street Helens Road 150 Clackamas, OR 97015
5161 Sandra Willsie, DO	Amy Meoli, MD Dennis Pyszczynski, MD Anstella Robinson, MD Mark Yagan, MD	University Of Missouri At Kansas City School Of Medicine 2411 Holmes Kansas City, MO 64108 Truman Medical Center West 2301 Holmes Kansas City, MO 64108
5210 Thomas Nolen, MD	Harry Phillips, MD Joseph Story, MD	Columbiana Associates and Ami Columbiana Family Health Center 200 Mildred Street Columbiana, AL 35051
6579 - The site number was changed from 5155 to 6579. No subjects were William Gray, MD	Janet Robe	enrolled under either number. North 1414 Vercler Road Building 5 Spokane, WA. 99216

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**Study 154 -113 /Nosocomial
Pneumonia:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5106 Charles Ballow, PharmD	Sujata Bhavnani, PharmD James Lampasso, MD Mark Sands, MD	The Clinical Pharmacokinetics Laboratory Millard Fillmore Health System 3 Gates Circle Buffalo, NY 14209
5108 Edward Britt, MD	Jonathan Orens, MD	University of Maryland School of Medicine MSTF 800 10 South Pine Street Room 800 Baltimore, MD 21201-1192 University of Maryland Medical System 22 South Greene Street Baltimore, MD 21201-1595
5111 Daniel Herr, MS, MD	Raymond DiPhillips, MD	Washington Hospital Center Surgical Critical Care 110 Irving Street, Northwest Room 4B-46 Washington, DC 20010
5112 Timothy Kotschwar, PharmD	Sergio Cruz, MD Judy Dasovich, MD William Detton, DO John Duff, MD James Duff, MD Mary Jo Fisher, MD Wolfe Gerecht, MD Randy Halley, DO Larry Halverson, MD Dennis Hughes, DO Charles Marler, MD Steven Newbold, MD Richard Purcell, MD Carin Reust, MD Bill Rosen, MD Ralph Schmitz, MD Phillip Wittmer, DO	Cox Medical Center North 1423 North Jefferson Avenue Springfield, MO 65802 Cox Medical Center South 3801 South National Avenue Springfield, MO 65807 Cox Monette Hospital 801 North Lincoln Springfield, MO 65802 Monette Health 410 Cox Medical Center North 1423 North Jefferson Avenue Springfield, MO 65802 James River Care Center 3550 East Battlefield Road Springfield, MO 65807 Lacoba Homes Highway 60 East Monette, MO 65708
5115 Michael Niederman, MD	Carlos Ares, MD Arunabh, MD Avtar Bassin, MD Hugh Cassiere, MD Donald Chalfin, MD Frank Coletta, MD Alan Fein, MD Steven Feinsilver, MD	Winthrop University Hospital 259 First Street Mineola, NY 11501

**Study 154 -113 /Nosocomial
Pneumonia:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5117 Curtis Sessler, MD	Jonathan Ilowite, MD Stuart Lowenkron, MD Eric Makolo, MD John Rodrigues, MD Debra Schulman Jonathan Waxner, MD	APPEARS THIS WAY ON ORIGINAL Medical College of Virginia P.O. Box 980050 Richmond, VA 23298-0050 Medical College of Virginia 401 North 12th Street Richmond, VA 23298
5118 Claude Tellis, MD	Marsha Breeland Rita Gaupp Glenn Gomes, MD Mark Kantrow, MD Helen Penfield Richard Slataper, MD	Ochsner Clinic of Baton Rouge 16777 Medical Center Drive Baton Rouge, LA 70816 Medical Center of Baton Rouge 17000 Medical Center Drive Baton Rouge, LA 70816 Medical Center of Baton Rouge Skilled Nursing Facility 17000 Medical Center Drive Baton Rouge, LA 70816
5119 Scott Traub, PharmD	Judy Bennett David Bowe, RPH George Karras, MD Anne Marie Ranahan Paige Tourville	Mercy Hospital Director Clinical Pharmacology 271 Carew Street Springfield, MA 01102
5121 Marcus Zervos, MD	Judith Pypkowski	William Beaumont Hospital 3601 West 13 Mile Road Royal Oak, MI 48073
5123 Dennis Mikolich, MD	Lisa Crandall Willie Curioso, MD Lynne Haughey Johnna Pezzullo David Teixeira	Independent Research Nurses Inc. Calart Tower 400 Reservoir Avenue Providence, RI 02907 Department of Veterans Affairs Medical Center 830 Chalkstone Avenue Providence, RI 02908-4799 Omega Medical Research Calart Tower 400 Reservoir Avenue Providence, RI 02907

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**Study 154 -113 /Nosocomial
Pneumonia:**

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5126 Dennis Mikolich, MD	Lisa Crandall Lynne Haughey Joseph Meharg, MD Johnna Pezzullo	Independent Research Nurses Inc. Calart Tower 400 Reservoir Avenue Providence, RI 02907 Roger Williams Hospital 825 Chalkstone Avenue Providence, RI 02908-4735
5173 Selwyn Spangenthal, MD	Joseph Jemsek, MD Edward Landis, MD	Nalle Clinic 1918 Randolph Road Charlotte, NC 28207-2198 Nalle Clinic 1350 South Kings Drive Charlotte, NC 28207 Presbyterian Hospital 200 Hawthorne Lane Charlotte, NC 28204
5174 Faroque Khan, MB	Arsad Karcic, MD Ashok Karnik, MD Maryse Rousseau, RPh Ina Sim, RPH	Department of Medicine Nassau County Medical Center 2201 Hempstead Turnpike East Meadow, NY 11554 Meadowbrook Research and Education Foundation 2201 Hempstead Turnpike East Meadow, NY 11554
5175 Timothy Klein, MD	Linda Klein, MD Robin Odgen	Methodist Hospital of Memphis 7655 Poplar Avenue Suite 350 Germantown, TN 38138 Hillhaven Primacy Nursing Home 6025 Primacy Parkway Memphis, TN 38119 Beverly Rehabilitation and Care Center 6733 Quince Road Memphis, TN 38119 Nursing Home 3909 Covington Pike Memphis, TN 38135 American Transitional Hospital and Rehabilitation Center 6733 Quince Road Memphis, TN 38119
5181 James Taylor, MD	Arthur Knodel, MD Clyde Koontz, MD David Munoz, MD John Rowlands, MD Barry Weled, MD	Pulmonary Consultants 315 Martin Luther King Jr. Way 401 Tacoma, WA 98405 St. Joseph Hospital 1717 South J Street Tacoma, WA 98405

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
APPEARS THIS WAY ON ORIGINAL	APPEARS THIS WAY ON ORIGINAL	Tacoma General Hospital 315 Martin Luther King Jr. Way Tacoma, WA 98405 Allenmore Hospital South 19th and Union Streets Tacoma, WA 98405
5184 Paul Alessi, DO	Alex Makris, MD Sandra Paluzzi, DO Chester Smialowicz, MD J. Robert Williams, MD	103 East Gate Drive Cherry Hill, NJ 08034 Deborah Heart and Lung Center 200 Trenton Road Browns Mills, NJ 08015
5185 Matthew Brenner, MD	Darryl See, MD Lauri Thrupp, MD Gail Tominaga, MD	Pulmonary and Critical Care Medicine University of California Irvine Medical Center 101 City Drive South Orange, CA 92668
5188 Donald Fry, MD	Lisa Home-Lucero Loren Ketai, MD Kelly Knight-Bohnhoff David Pitcher, MD	University of New Mexico Department of Surgery 2211 Lomas Boulevard Northeast Albuquerque, NM 87131
5190 Stephen Green, MD	John Bryant, MD Richard Edwards, MD Douglas Kane, MD Hoskote Nagraj, MD Franklin Seney, MD James Spiller, DO	Hampton Roads Medical Specialists 2112 Executive Drive Hampton, VA 23666 Riverside Regional Medical Center 500 J. Clyde Morris Boulevard Newport News, VA 23601
5191 Paul Marik, MD	Michele Craft David Kaufman, MD Pam Sigel	St. Vincent Hospital 25 Winthrop Street Worcester, MA 01604
5193 Charles Schlepner, MD	Cynthia Anneski, MD Deborah Demicco, MD Thomas Evans, MD J. Boyd Francis, MD Dorothy Garner, MD Michael Judd, MD Katherine Minnick, MD	Veterans Affairs Medical Center Chief, Medical Service 1907 Boulevard Salem, VA 24153
5211 Andrew Quartin, MD	Gabriel Contreras, MD Daniel Kett, MD Donald Koggan, MD Douglas Onorato, MD Juan Torres, MD	Veterans Affairs Medical Center (111) 1201 Northwest 16th Street Miami, FL 33125

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5249 David Smith, MD	Barbara Lee, RN David McKinsey, MD Janet Rosasco, RN	Research Medical Center 2316 East Meyer Boulevard Kansas City, MO 64132 John Knox Village Care Center 600 Northwest Pryor Road Lee's Summit, KS 64081
5368 Jeffrey Timby, MD	James Ramage, Jr., MD Raymond Stanford, RN	Medical Associates of Savannah 310 Eisenhower Drive Savannah, GA 31406 Memorial Medical Center 4700 Waters Avenue Savannah, GA 31404
5384 Martin Tauber, MD	Henry Chambers, MD Young Kim, MD Belle Lee, PharmD	San Francisco General Hospital Building 30, Room 402 1001 Potrero Avenue San Francisco, CA 94110
5385 Maria Rodriguez-Barradas, MD	Richard Hamill, MD Daniel Musher, MD	Section of Infectious Diseases Veterans Affairs Medical Center Building 100, Rm 4B-378 2002 Holcombe Blvd. Houston, TX 77030
5386 Donald Graham, MD	Roger Harvey, DO Steven O'Marro, MD	Springfield Clinic 1025 South Seventh Street Springfield, IL 62703 St. Johns Hospital 800 East Carpenter Street Springfield, IL 62769 Memorial Medical Center 800 North Rutledge Street Springfield, IL 62781
5395 Dr. Ian Gould Dr. David Noble	Dr. G. Adey Dr. M. McNab Dr. R. Patey Dr. G. Smith N. Webster Dr. T. Weller	Aberdeen Royal Hospitals NHS Trust Aberdeen Royal Infirmary AB9 2ZB United Kingdom
5396 Dr. Ian Grant Dr. Robert Masterton	M. Garrioch A. Graham J. Laurenson Dr. S. Mckenzie S. Mclellan	Western General Hospitals NHS Trust Crewe Road Edinburgh EH4 2XU United Kingdom
5407 Dr. Peter Duncan	Dr. A. M. Bewley Dr. M. Jones Dr. M. Sabar	Royal Preston Hospital Sharoe Green lane Preston PR2 4HT United Kingdom

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5408 Dr. Robin Macmillan	Dr. E. Rhead Dr. Colin Smyth	Whiston Hospital Intensive Care Unit Warrington Road Whiston Prescot Merseyside L35 5DR United Kingdom
5409 Dr. Martin Street	Dr. Matthew Miller Dr. David Tayler	Royal Sussex County Hospital Eastern Road Brighton BN2 5BE United Kingdom
5410 Dr. Graham Sunderland	Dr. S. Allam Dr. W. Anderson Dominic Byrne Dr. Sant Chawla J. C. Ferguson Dr. Ghazanigar Dr. J. Khalid Dr. D. Kippen Dr. A. Lee C. C. Macbain Dr. J. Robinson Dr. A. Steven Dr. Vikram	Southern General Hospital 1345 Govan Road Glasgow G51 4TF Scotland
5423 Michael Alexander, MD	Yun Kai Chan, MD	Niagara Falls Medical Center 302-6453 Morrison Street Niagara Falls, Ontario L2E 7H1 Canada
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5441 Dr. Rene Pariente	Dr. Gilles Jebrak Dr. Marie Pichot	Hopital Beaujon 100 Boulevard De Gal Leclerc 92118 Clinchy Cedex France
5467 Michael Gelfand, MD	Jeffrey Campbell, PharmD Kerry Cleveland, MD Bryan Simmons, MD Deborah Winters	188 Sotu Bellevue Room 419 Memphis, TN 38104
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5483 Ronald Wainz, MD	George Haig, RPH Frank Horton, MD Daniel Pipoly, MD	The Toledo Hospital 2142 North Cove Boulevard Toledo, OH 43606

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5508 Dr. Yann Curran	Dr. Eric Goarant	Service Pneumologie Chr De St. Malo Rue De La marne St. Malo, France
5510 Dr. Vincent D'Orio	Dr. D. Franchimont Dr. B. Lambermont	Chu Du Sart Tilman Universite De Leige Services Des urgences Bat B35 4000 Liege 1 Belgium
5511 Dr. Fabrice Pierre Brunet	Dr. F. Bellenfant Dr. J. Dhainaut Dr. L. M. Joly Dr. M. Monchi Dr. B. Renaud Dr. C. Vezinet	University of Paris V Cochin Port Royal University Hospital Medical Intensive Care Unit 27 Rue Du Faubourg St. Jacques 75674 Paris Cecex 14 France
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5514 Dr. Wilfried Bohning	Dr. W. Gams Dr. M. Torregroza	Karl-Hansen-Klinik Antoniusstr 19 33175 Bad Lippspringe Germany
5515 Dr. Franz Daschner	Dr. Uwe Frank Dr. Dennis Mlangeni	Institut Fur Umweltmedizin Und Krankenhaushygiene Universitatkllinikum Freiburg Hugstetter Street 55 79106 Freiburg Germany Klinikum Der Albert-Ludwigs-Universitat Im Gebaude Der Universitat Frauenklinik Hugstetter Street 55 79106 Freiburg Germany
5516 Dr. Rudolf Huber	Dr. Rainald Fischer	Pneumology Klinikum Innenstadt Medizinische Klinik Klinikum University of Munchen Ziemssenstrasse Number 1 80336 Munchen Germany

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5517 Dr. Christian Witt	Dr. S. Kausch	Pneumology Department Medical Klinik Charite Hospital Universitätsklinikum Charite Medizinische Fakultat Der Humboldt-Universitat Zu Berlin Klinik Fur Innere Medizin Theodore Brugach Abteilung Kardiologie Pulmonologie Angiologie and Pneumologie Station 28 10098 Berlin Germany
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5541 Roy Brower, MD Pamela Lipsett, MD	Michael Breslow, MD Jeffrey Dodd-O, MD Todd Dorman, MD Elizabeth Lins Hope Mazurek Brian Rosenfeld, MD Sandra Swoboda Kathleen Truelove, RPH	The Johns Hopkins University School of Medicine Division of Pulmonary and Critical Care 720 Rutland Avenue Ross 858 Baltimore, MD 21205 The Johns Hopkins Hospital 600 North Wolfe Street Baltimore, MD 21287-4605 The Johns Hopkins University School of Medicine Department of Surgery Blalock 605 600 North Wolfe Street Baltimore, MD 21287-4605
APPEARS THIS WAY ON ORIGINAL		
5543 Dr. Raul Marques	Dr. Carlos Alves Dr. Augusto Filipe Dr. Paula Pamplona	Hospital Pulido Valente Servico De Pneumologia 1 Lisbon, Portugal
5546 Howard Koffler, MD	Nocola Demarco Albert Driver, MD Robin Haff, RN Neil Labove, MD John Messina Patricia Mullan, RPH	920 Lawn Avenue Sellersville, PA 18960 Grandview Medical Research Incorporated 711 Lawn Avenue Building 1 Sellersville, PA 18960 Grandview Hospital 700 Lawn Avenue Sellersville, PA 18960
APPEARS THIS WAY ON ORIGINAL		
5600 Dr. Jorge Pimentel	Dr. Armindo Faria-Simoes Dr. Julio Goncalves-Souto Dr. Paulo Martins Dr. Armindo Mendes-Rebelo	Hospitais Da Universidade Coimbra Unidade De Cuidados Intensivos Polivalente Coimbra, Portugal
5623 Dr. Antoni Marti	Dr. Mustafa Alarcon Dr. Ramon Estruch Dr. Joaquin Fernandez	Hospital Clinico Y Provincial Servicio De Neumologia Villarrol 170 08036 Barcelona Spain

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5627 Dr. Jose Martin	Dr. Vicente Ferrer Jordi Madronal Adalberto Villalonga	C/Juan De Garay 19 3 1 08041 Barcelona Spain Hospital General Vall D'Hebron Paseo Vall De Hebron S/N 08035 Barcelona Spain
5628 Arthur Clinton White, MD	Robert Atmar, MD Thomas Cate, MD Stephen Greenberg, MD Rayhan Hashmey, MD Kurt Krause, MD Fehmida Visnegarwala, MD Joan Wilson	Baylor College of Medicine Department of Medicine One Baylor Plaza (Room 561E) Houston, TX 77030 Ben Taub General Hospital 1504 Taub Loop Houston, TX 77030
5760 Jeffery Silber, MD	John Baxter, MD Mark Dinubile, MD Lynn Jefferies Roseann Lorenick, MD Carl Norden, MD	Cooper Hospital University Medical Center Education and Research Building 401 Haddon Avenue (Room 276) Camden, NJ 08103 Cooper Hospital University Medical Center One Cooper Plaza Camden, NJ 08103
5778 John Black, MD	H. Reid Mattison, MD Susan Scott, RN Douglas Webb, MD Richard Yates, MD	Infectious Disease of Indianapolis 1633 North Capitol Avenue Suite 700 Indianapolis, IN 46202 Methodist Hospital of Indiana Incorporated 1701 North Senate Boulevard Indianapolis, IN 46202
5780 Dr. Werner Bachmann	Dr. Bolle	Innere Medizin Kreiskrankenhaus Friesenerstrasse 41 96317 Kronach Germany
5834 Dr. Jean Petermans	Dr. Sabine Almer	Hopital La Citadelle Service De Geriatrie Boulevard Du 12 Emé De Ligne 1 4000 Liege Belgium
5835 Dr. Joaquin Duran	Dr. Begona La Hidaiga Dr. Jose Luis Lobo Berissain Dr. Salvador Luzarraga Dr. Manuel Perez Marti	Hospital Txagorritxu Service De Neumologia Jose Atxotegui S/N 01009 Vitoria Spain

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5837 Burt Meyers, MD	Neonita Ballon-Shlasko Rodolfo Castilho-Ruiz R. Castillo, MD Alejandra Gurtman, MD Shalom Hirschman, MD Meryl Mendelson, MD Genovefa Papanicolaou, MD Muhammad Shaikh, MD Deborah Vitalis	Mount Sinai Medical Center Division of infectious Diseases One Gustane L. Levy Place Box 1090 New York, NY 10029 Mount Sinai School of Medicine Mount Sinai Medical Center One Gustave L. Levy Place New York, NY 10029
5850 Martin Teplel, MD	Anita Jain, MD Donna Jones John Peterson, MD	Infectious Disease Physicians PA 704 East Main Street Moorestown, NJ 08057 Memorial Hospital of Burlington County 175 Madison Avenue Mount Holly, NJ 08060-2038
5903 Dr. Walther Grau	Dr. P. Strauss	Innere Abteilung Klinikum St. Marien 92224 Amberg Germany
5970 Alan Sugar, MD	Kimberly Hawkins	Boston University Medical Center Hospital E336 88 East Newton Street Boston, MA 02118-2393 Boston City Hospital 818 Harrison Avenue Boston, MA 02118
5984 John Samies, MD	Mark Knouse, MD Barbara Leri, PharmD Minh Ly Nguyen, MD Luther Rhode, s III, MD	1210 South Cedar Crest Boulevard Suite 2700 Allentown, PA 18103 Lehigh Valley Hospital Center Cedar Crest Allentown, PA 18105 Lehigh Valley Hospital I-78, P.O. Box 689 Allentown, PA 18105-1556
5985 David McEniry, MD	Teri Christiansen Philip Craven, MD Thomas Mann, MD Peter Marsh, MD Vernon Nesson, MD Lawrence Schwartz, MD Alan Tice, MD Marvin Wheller	1624 South I Street #402 Tacoma, WA 98405 Bel-Air Health Care Center 630 South Pearl Tacona, WA 98465 Ranier Vista Care Center 920-12th Avenue Southeast Puyallup, WA 98372

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5986 Mark Miller, MD	Jack Mendelson, MD Gloria Pinkus Joseph Portnoy, MD	SMBD Jewish General Hospital 3755 Cote-Ste-Catherine Road Montreal, Quebec H3T LE2 Canada
5987 Lance Kirkegaard, MD	Gayle Goodin Shinobu Inoue Penny Miller	Future Healthcare Research Center 6210 75th Street West Suite A-200 Tacoma, WA 98467 St. Clare Hospital 11315 Bridgeport Way Southwest Tacoma, WA 98467
6111 Dr. H. Landgraf	Dr. Iiona Eisele Dr. Stefan Schroder	li Inneren Abteilung Wenckebach Krankenhaus Wenckebachstrasse 23 12099 Berlin Germany
6112 Dr. Peter-Henning Althoff	Dr. Berthold Michels	Innere Abteilung Burgerhospital Nibelungenalle 37-41 60318 Frankfurt Germany
6113 Dr. Gerhard Cieslinski	Dr. Hannes Heitmann	Innere Abteilung Krankenhaus nordwest Steinbacher Hohl 2-26 60488 Frankfurt Germany
6115 Dr. Shane O'Neill	Dr. R. Coakley Dr. L. Connolly Dr. D. Duffy Dr. P. Glynn Dr. N. Hogan Dr. Aran Maree Dr. Andrew Maree Dr. E. Molloy Dr. R. Murphy Dr. N. Murphy Dr. M. O'Brien Helen O'Dwyer Dr. S. O'Rourke Dr. S. Rea Dr. R. Sharkey	Beaumont Hospital Department of Respiratory Medicine Beaumont Road Dublin 9 Ireland
6127 John Flaherty, MD	Paul Arnow, MD	University of Chicago Hospital Section of Infectious Diseases MC 5065 5841 South Maryland Avenue Chicago, IL 60637

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6339 Dr. John Colvin	Dr. Susan Rae	Nine Wells Hospital Dundee DD1 9SY Dundee Scotland
6367 Del Dehart, MD	Suhasini Gudipati, MD	Saginaw Cooperative Hospitals Inc. Internal Medicine 1000 Houghton Avenue Saginaw, MI 48602 St. Mary's Medical Center 830 South Jefferson Avenue Saginaw, MI 48601 Saginaw General Hospital 1447 North Harrison Saginaw, MI 48602 Saint Lukes Hospital 700 Cooper Avenue Saginaw, MI 48602
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6376 E. Joe Schelbar, MD	Walter Boomer, MD Richard Bregman, MD Phillip Butler, MD Phyllis Cotham Jeanne Gaber Mark Grosserode, MD Mark Rowland, MD Stanley Schwartz, MD Vernon Smith, MD	Healthcare Research Consultants 4619 South Harvard Suite A Tulsa, OK 74135 St. Francis Hospital 6161 South Yale Tulsa, OK 74136
6404 Dr. Hans Schulz	Dr. T. Karl Dr. F. Petri	Klinik Fur Innere Medizin Oskar Ziethen Krankenhaus Fanningenstrabe 41 10365 Berlin Germany
6455 Byungse Suh, MD	Kwaku Amexo, MD Cecilia Fumberg, MD Steven Gelone, PharmD Jacqueline Messa, MD Scott Olewiler, MD	Temple University Hospital and School of Medicine Section of Infectious Diseases Broad and Tioga Streets Philadelphia, PA 19140
6477 Dr. Franz Hartmann	Dr. D. Borger Dr. R. Dorr Dr. M. Engelhardt Dr. H. Horatz Dr. B. Pfeiffer Dr. J. Wilke	Medizinische Klinik St. Marienkrankenhaus Richard -Wagnerstrasse 14 60318 Frankfurt Germany
6497 Jacques Ameille	Marie-Cecile Bayeux	Hopital Raymond Poincare Service De Pneumologie 104 Boulevard Raymond Poincare 92380 Garches France

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
6538 Eileen Hilton, MD	Rubin Cohen, MD Harly Greenberg, MD Alan Multz, MD Leonard Rossoff, MD Steven Scharf, MD Carol Singer, MD Miriam Smith, MD Harry Steinberg, MD	Long Island Jewish Medical Center The Long Island campus for the Albert Einstein College of Medicine 270-05 76th Avenue New Hyde Park, NY 11040
6543 Dr. Thomas Muller	Dr. J. Blau Dr. U. Fremder	Krankenhaus Hofheim Medizinische Klinik III 65702 Hofheim/Taunus Germany

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5170 Gerard Huchon, MD		Hopital Ambroise Pare Service De Pneumologie 9 Avenue Charles De Gaulle 92100 Boulogne France
5414 Jean-Francois Muir, MD	Benhamou, MD	Head of Department Pneumology Chu Bois Guillaume Avenue Mal Juin 76230 Bois Guillaume France
5439 J. Ducroix, MD		Hopitaux Nord D'Amiens Medecine Interne E 80054 Amiens Cedex 1 France
5450 James Catterall, MD	Katharine Bale	Consultant Chest Physician Department of Respiratory Medicine Bristol Royal Infirmary Marlborough Road Bristol BS2 8HW United Kingdom
5795 Doria Grimard		Laboratoire De Microbiologie Hopital De Chicoutimi Incorporated 305 St-Vallier Chicoutimi Quebec G7H 5H6 Canada
5800 Gordon Ford, MD	Karen Rimmer, MD Sidney Viner, MD	Calgary General Hospital C4-024 841 Centre Avenue East Calgary AB T2E 0A1 Canada
5869 Iain MacDonald McLaren, MD	M.R. Ferguson, MD M.L. Pepperman, MD W.C. Russell, MD A. Swan, MD D.A. Turner, MD	Consultant Anaesthetist Leicester Royal Infirmary Leicester LE1 5WW United Kingdom
5871 Harry Bassaris, MD	Athanasios Skoutelis, MD	Patras University Medical School University Hospital Department of Medicine Section of Infectious Diseases Box 1045 26110 Rio Patras Greece
5877 Wolfgang Rosch, MD	Stauch Thomas	Krankenhaus Nordwest Medizinische Klinik Steinbacher Hohl 2-26 60488 Frankfurt Am Main Germany

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5923 Jon Ayres, MD	T. Fletcher, MD W.S. Tunnicliffe, MD	Consultant Clinical Trials unit Chest Research Institute Birmingham Heartlands Hospital Brodlesley Green East Birmingham B9 5ST United Kingdom
5924 Mervyn Singer, MD	Steve Batson	Department of Medicine University College London Medical School Rayne Institute, University Street London WC1E 6JJ United Kingdom University College London Hospital Mortimer Street London W1 United Kingdom
5926 Christopher Andrews, MD	C. Dance, MD	Consultant Anaesthetist Derriford Hospital Derriford Road Plymouth Devon P16 8DH United Kingdom
5929 Bryce Randalls, MD	L. Hayek, MD	Department of Anaesthetics Torbay Hospital Lawes Bridge Torquay Devon TQ2 7AA United Kingdom
5930 Pushpinder Singh Mangat, MD	Dafydd Wyn Thomas, MD	Consultant in Anaesthesia & Intensive Care c/o Intensive Therapy Unit Morriston Hospital NHS Trust Morriston Swansea Wales SA6 2NL United Kingdom
5933 Dennis Shale, MD	Alina Ionescu, MD A. Quoraishi, MD	Professor of Respiratory and Communicable Diseases Respiratory Medicine Llandough Hospital Llandough Penarth Cardiff CF64 2XX United Kingdom
5935 Michael Whitby, MD	P. Lavercombe, MD	Department of Infectious Diseases Infection Control and Sexual Health Princess Alexandra Hospital Ipswich Road Woolloongabba Queensland 4102 Australia Mater Miscricordiae Adult Hospital Raymond Terrace & Mater Miscricordiae Private Hospital Vulture Street South Brisbane Queensland 4101 Australia

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5936 Brent Richards, MD	I. Feather, MD J. Renton, MD H. Stevens, MD	Intensive Care Unite Gold Coast Hospital Nerang Street Southport Queensland 4215 Australia
5937 Peter James McDonald, MD	H. Pruul, MD S. Wesselingh, MD	Department of Microbiology & Infectious Diseases Flinders Medical Centre Flinders Drive, Bedford Park South Australia 5042 Australia
5938 John Moran, MD	R. Ruffin, MD	Intensive Care Therapy Unit The Queen Elizabeth Hospital 28 Woodville Road Woodville South Australia 5011 Australia
5940 Anthony Bell, MD	M. Clarence, MD K. Ott, MD	Department of Critical Care Medicine Royal Hobart Hospital Liverpool Street Hobart Tasmania 7000 Australia
5941 Matthew Peters, MD	T. Gottlieb, MD	Department of Thoracic Medicine Repatriation General Hospital Concord Hospital Road Concord New South Wales 2139 Australia
5942 Simon Finfer, MD	R. Raper, MD	Intensive Therapy Unit Royal North Shore Hospital Pacific Highway St. Leonards New South Wales 2065 Australia
5944 Thomas Torda, MD	A. Belessis, MD P. Jones, MD Z. Nanavati, MD Y. Shehabi, MD	Prince Henry Hospital Anzac Parade Little Bay New South Wales 2036 Australia
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5946 Keryn Christiansen, MD	B. Ng, MD R. Tarola, MD R. Wilson, MD	Department of Microbiology Royal Perth Hospital Wellington Street Perth Western Australia 6000 Australia

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PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5948 John Wilson, MD	Xun Li, MD	Fifth Floor Alfred Hospital Commercial Road Prahran Victoria 3181 Australia
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5953 Kamran Samii-Esfahani, MD	Edouard, MD Mimoz, MD Moine, MD	Head of Departement Anaesthesia Intensive Care Hopital De Bicetre 78 Rue De General Leclerc 94275 Le Kremlin Bicetre France Hopital De Bicetre 78 Rue De General Leclerc 94320 Chatillon Paris France
5954 Benoit Eurin, MD	Boudaoud, MD Dalibon, MD Jacob, MD Marie, MD Masbahi, MD Villiers, MD	Head of Departement Medical ICU Hopital Saint Loius 1 Avenue Claude Vellefaux 75475 Paris Cedex 10 France
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5961 Jean Michel Coulaud, MD	Leresche, MD	Head of Department Medical ICU Centre Hospitalier Intercom Montfermeil 10 Rue Du General Leclerc 93370 Montermeil France
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5963 Pierre-Yves Lallement, MD	Delvoye, MD Nicholas, MD	Centre Hospitalier Curie 46 Avenue Du General De Gaulle 02200 Soissons France
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5973 Raymond Zakhia, MD	Berton, MD Marechal, MD	Hopital De Warquines Rue Des Chauffours 27 B-7300 Boussu Belgium
5975 Hendrik Dienemann, MD	Angelika Mewes, MD Ruckdeschel, MD	Ludwig-Maximilians-Universitat Klinikum Crobhadern Chirurgische Klinik and Poliklinik Marchioninstr 15 81366 Munchen Germany
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5978 Thomas Henneberg, MD	Mauch, MD	Intensivstation Behring Krankenhaus Zehlendorf Gimpelsteig 3-5 14165 Berlin Germany
5979 Claudia Spies, MD	Isabel Hab, MD Mauch, MD Walter Schaffartzik, MD	Universitätsklinikum Benjamin Franklin Klinik Fur Anesthesiologie Und Operative Intensivmedizin Hindenburgdamm 30 12200 Berlin Germany
5980 Lothar Mathea, MD	Frau Fahr, MD Mounzer, MD	Rotes Kreuz Krankenhaus Chirurgie E Konigswarter Street 16 60316 Frankfurt Germany
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**Study 154 -137/Nosocomial
Pneumonia:**

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**Medical Officer Review of
Community Acquired Pneumonia Indication**

JUL 15 1998

1. Overview of requested labeling and organisms.

Concerning study design, the IDSA states "Whenever possible, the study design should be randomized, prospective, and double-blinded." Recommended evaluation timepoints include a baseline assessment to determine study eligibility and enrollment; daily assessment while hospitalized; and an assessment within 5-7 days after completion of therapy (with a follow-up chest radiograph within 72 hours of completion of therapy, plus follow-up sputum cultures if clinical material is available).

The discussion of evaluability criteria in the IDSA Guidelines includes the following points:

- A. all patients who receive at least 5 days of therapy and at least 80% of the prescribed medication should have an assessment of clinical response
- B. an assessment of clinical *cure* requires *complete resolution* of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph.
- C. clinical failure is defined as any of the following:
 - I. persistence or progression of all signs and symptoms after 3-5 days of therapy;
 - II. development of new pulmonary or extrapulmonary clinical findings consistent with active infection;
 - III. persistence or progression of radiographic abnormalities;
 - IV. death due to pneumonia; or
 - V. inability to complete the study because of adverse effects.

3. Points To Consider document regarding Community Acquired Pneumonia (CAP).

The divisional Points To Consider (PTC) document contains the following discussion regarding community acquired pneumonia (CAP):

“One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product, and one open trial are suggested. The adequate and well-controlled trial should preferably be performed in the US... In this trial, the primary effectiveness endpoints should be clinical and radiographic endpoints; however, microbiologic evaluations should also be performed on each patient. Isolation of a pathogen from the baseline sputum culture should not be required for overall evaluability; however, rigid case definitions including specific entry sputum microscopy and radiographic findings... should be included in the trial design.

“Patients should be analyzed in two separate groups: those who were clinically evaluable (whether or not microbiologically evaluable) and those who were both clinically and microbiologically evaluable...

“Also suggested is a second study, which may be an open trial, involving at least 2 investigators in different geographic areas (no one center contribution more than 55% of the evaluable patients) in which 80 evaluable patients are studied. In this trial, the microbiologic etiology of the pneumonia should be confirmed for each patient.

“In situations where atypical microorganisms causing community-acquired pneumonia are evaluated or when different susceptibility patterns are expected for specific microorganisms in different populations, different comparative agents and/or different patient populations may be selected for the two trials that should corroborate one another in the establishment of effectiveness in treating this infection. In these circumstances, it should be appropriate to perform two studies that investigate outcomes in both the clinically evaluable patients and in the clinically and microbiologically (i.e., the pathogen is confirmed by an approved laboratory test methodology) evaluable subset of patients. Analyses of the data should confirm (by means of comparing the direction of the independent 95% confidence interval testing or by appropriate other analysis if the subgroups can be combined from the two separate studies) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients.”

4. Divisional evaluability criteria (proposed):

The criteria in this document are comparable to the IDSA guidelines stated above. There are some differences that are noteworthy; these are italicised below:

"Inclusion criteria should include *at least two* signs and/or symptoms of acute infectious pneumonia (cough, purulent sputum production, auscultatory findings, dyspnea, tachypnea, hypoxemia, or the isolation of an organism from blood culture that is consistent with a respiratory pathogen)

and at least one of the following

fever ($> 38^{\circ}\text{C}$ orally or $>39^{\circ}\text{C}$ rectally or $>38.5^{\circ}\text{C}$ tympanically)

or

elevated peripheral WBC count ($> 10,000/\text{mL}$ or $>15\%$ bands)

"Evaluation visits should include a pre-therapy (enrollment) assessment, an on-therapy assessment (the frequency of which depends on the severity of the pneumonia under study), an end-of-therapy evaluation (optional for evaluability purposes), and a test-of-cure evaluation that should be at least 7 days or 5 half-lives of the agent, whichever is the longer period, following completion of therapy."

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5. Structure of claim

The sponsor has submitted a total of five clinical studies in support of the CAP indication. The general characteristics of these studies are outlined in the following table.

Clinical studies submitted as 'pivotal' to the CAP indication

Study # location	154-102 USA/Costa Rica	154-110 USA/Canada / South Africa	154-111 USA/Europe / Australia	154-112 USA/Europe / South Africa	154-134 USA/Canada
Design	Rand., Double- -blinded, dose-ranging, comparative	Rand, DB, comparative IV → oral	Rand, DB, DD, comparative IV → oral	Rand, DB, DD, comparative	Rand, DB, DD, comparative
comparator	cefaclor	IV→PO cipro/ ampicillin	ceftriaxone→ ceftin (± erythro)	amoxicillin ± erythromycin	clarithromycin
Dates of conduct	12/93 → 11/94	1/95 → 1/96	2/95 → 3/96	12/94 → 6/96	11/94 → 11/95
N per arm at enrollment	Trova 200 = 50 Trova 300 = 52 Ceclor = 47	Trova = 196 Cipro = 200	Trova = 215 Ceftriaxone = 222	Trova = 150 Amox = 152	Trova = 178 Clarithromycin = 180

All of these studies (with the exception of study 102, which was conducted as a phase 2 study and had a dose-ranging component using a 300 mg qd dose of trovafloxacin as well as the standard 200 mg qu dose) utilized a 200 mg daily dose of trovafloxacin, in either the IV or oral mode of administration.

6. Medical officer comments:

In general, the above protocols comply with the IDSA Guidelines, as well as the Divisional Points To Consider and Evaluability Criteria documents. There is no shortage of studies, given that the PTC document calls for two studies in support of the indication.

It should be noted that although clarithromycin is indicated for the treatment of pneumonia, it is not labeled for the treatment of CAP per se, and is only labeled for pneumonia due to *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*. Clarithromycin does, however, have activity against other organisms that might be encountered in CAP (for example, it is labeled for the treatment of both acute sinusitis and AECB due to *Moraxella catarrhalis* and *Haemophilus influenzae*, as well as due to *Streptococcus pneumoniae*). The sponsor discussed the appropriateness of clarithromycin as a comparator agent during the End of Phase 2 meeting with the Agency (24 August 1994), prior to initiating study 134. The Agency agreed at that time that clarithromycin was an appropriate selection as a comparator agent for this CAP study.

The IV to oral studies both recruited patients who were felt to be 'sufficiently ill to require initial hospitalization', although the entry criteria for each study appeared to be the same in both the PO and IV/PO protocols. (For example, there were no specific criteria such as pulse oximetry, respiratory rate, multilobar involvement on CXR, etc. that would have standardized criteria for initial intravenous therapy across centers and across studies.) Nonetheless, as demonstrated in tables 5 and 9 of the Integrated Summary of Efficacy (section H.4, pages 840 and 851, volume 1.3 of NDA), there did appear to be approximately twice as many patients with co-morbid conditions

in the IV/PO studies as were enrolled in the PO studies. For example, 60% of trovafloxacin IV/PO subjects had at least one co-morbid condition listed vs. 35% of the PO subjects; 33% vs. 19% had COPD, 17% vs. 6% had CHF, and 17% vs. 8% had diabetes mellitus.

The requested organisms are also worthy of comment. Neither *Staphylococcus aureus* nor *Pseudomonas aeruginosa* are organisms usually considered to be etiologic agents in 'community acquired pneumonia'; to a somewhat lesser extent, neither is *Klebsiella pneumoniae*. The numbers subjects infected with each of these organisms will be closely reviewed; if adequate numbers of these agents are in fact present in these studies, it may indicate that a more severely ill patient population gained enrollment into these studies. Admittedly, the spectrum of illness between 'community acquired' and 'nosocomial' pneumonia is overlapping to a greater and greater extent as current trends in health care drive increasingly ill patients out of the hospital and into "the community", be it to home with in-house nursing assistance, or to an assisted living environment prior to actual return home. Thus it is not surprising to see that some organisms formerly associated exclusively with 'nosocomial' pneumonias may be showing up in protocols designed to study 'community acquired' pneumonia.

7. Review strategy

The following review strategy will be adopted: the five studies will be stratified according to the soundness of their design and the numbers of subjects enrolled. In this manner, when an adequate number of these studies have been reviewed and audited to justify the inclusion of this indication in the label, the review will be considered to be completed. Each of these studies will be sequentially audited to ascertain the validity of the data entered on the Patient Profiles; following this, and assuming that the sponsor's assertion of efficacy in this indication is felt to be justified, organism-specific investigations will be conducted to verify which requested organisms can be recommended for inclusion in the product labeling.

The five submitted studies will be reviewed in the following order: 134 (oral); 110 (IV→ oral); 111 (IV→ oral); 112 (oral); and finally, the phase 2 study 102 (oral, dose-ranging comparative). Of the submitted studies, 134 used the best single-agent comparator and thus could most successfully be conducted in the double blind, double-dummy manner in which it was designed. (In contrast, study 110 was also conducted in a DB, DD manner, but because of the design required subjects to ingest 12 tablets a day during the oral phase of the study. This raises concerns over compliance on the part of the subjects, many of whom would have just been discharged from hospital. Similarly, study 112 called for patients to take as many as 16 tablets and/or capsules daily.)

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Medical Officer review of study 154-134

1. Per applicant

The synopsis of the applicant's final study report for study 134 is presented below; this is taken from pages 8-12 of the report, found in section

PROTOCOL 154-134: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN (CP-99,219) WITH CLARITHROMYCIN FOR THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA.

Principal Investigators:

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Lee Payne, MD	Alex Pareigis, MD	John Pappas, MD
Alain Martel, MD	Stan Parman, MD	Jeffery Applestein, MD
Claude St-Pierre, MD	Gary Ruoff, MD	Maureen McCabe, MD
Diana Dark, MD	Lawrence Alwine, DO	Kathryn Budzak, MD
Charles Vanhook, MD	John Estess, MD	Johnny Belenchia, MD
Robin Miller, MD	William Gray, MD	Donald Bias, MD
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Kent Anthony, MD	Sandra Willsie, DO	Hari Malik, MD
Steven Bowman, MD	Melvin Russell, MD	Steve Sanders, DO
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Jeffrey Hartford, MD	John Herrod, MD	Philip Masters, MD
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Michael Nelson, MD	Colby Grossman, MD	Boyd Harrison, MD
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Richard Sterling, MD	Craig Schultz, DO	Thomas Decker, MD
Randall Stoltz, MD	Joseph Follett, MD	Mark Hackman, MD
James Sullivan, MD	Gregory Collins, MD	William Markel, MD
John Upchurch, MD	Walter Gaman, MD	Michel Bergeron, MD
Alan Storrow, MD		

Study Publication: Not Applicable

Study Dates: 28 November 1994 to 13 November 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin and clarithromycin in the treatment of subjects with community-acquired pneumonia appropriate for oral therapy.

Study Design: Study 154-134 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg once daily) versus clarithromycin (500 mg twice daily), administered orally for 7 or 10 days for the treatment of community-acquired pneumonia.

Evaluation Groups:

	Trovafloxacin (200 mg daily)		Clarithromycin (500 mg BID)	
Entered Study ^a	179		180	
All Treated	178	(>99%)	180	(100%)
Completed Treatment	147	(83%)	154	(86%)
Completed Study	157	(88%)	167	(93%)
Evaluated for Efficacy				
Clinical Intent-to-treat	163	(91%)	172	(96%)
Clinically Evaluable ^b	144	(80%)	156	(87%)
Bacteriologically Intent-to-Treat	64	(36%)	72	(40%)
Bacteriologically Evaluable ^b	59	(33%)	67	(37%)
Assessed for Safety				
Adverse Events	178	(100%)	180	(100%)
Laboratory Tests	173	(97%)	174	(97%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥16 years of age at the baseline assessment, with clinically and radiologically documented community-acquired pneumonia were eligible to participate in this study.

Drug Administration: Study drug was in the form of trovafloxacin tablets and clarithromycin blinded tablets and was packaged in blister cards, using a double-dummy technique to maintain blinding.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens and blood cultures at baseline).

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis) and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Treatment groups were compared using the confidence interval approach. Confidence intervals (95%) were produced for the difference in success rates between treatments using the normal approximation method. Additionally, a chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment was used to account for investigator differences. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

Efficacy Results: Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -3.3, 6.5 and -6.0, 7.4, respectively) and at the end of study (95% CI: -5.0, 10.5 and -6.0, 10.1, respectively).

Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects and pathogen eradication rates for bacteriologically evaluable and intent-to-treat subjects are presented in the following table.

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Summary of the Sponsor's Assessment of Clinical Response (Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=144)	Clarithromycin 500 mg BID (N=156)	Trovafloxacin 200 mg (N=135)	Clarithromycin 500 mg BID (N=144)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	143 (100%)	155 (100%)	135 (100%)	144 (100%)
Success (Cure + improvement)	137 (96%)	146 (94%)	120 (89%)	124 (86%)
Distribution of Clinical Response:				
Cure	56 (39%)	59 (38%)	108 (80%)	113 (78%)
Improvement	81 (57%)	87 (56%)	12 (9%)	11 (8%)
Failure	6 (4%)	9 (6%)	6 (4%)	9 (6%)
Relapse	NA	NA	9 (7%)	11 (8%)
Summary of Sponsor-Defined Pathogen Eradication Rates (Clinically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=163)	Clarithromycin 500 mg BID (N=172)	Trovafloxacin 200 mg (N=163)	Clarithromycin 500 mg BID (N=172)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	162 (100%)	170 (100%)	163 (100%)	172 (100%)
Success (Cure + improvement)	145 (90%)	151 (89%)	137 (84%)	141 (82%)
Distribution of Clinical Response:				
Cure	59 (36%)	62 (36%)	122 (75%)	127 (74%)
Improvement	86 (53%)	89 (52%)	15 (9%)	14 (8%)
Failure	17 (10%)	19 (11%)	17 (10%)	20 (12%)
Relapse	NA	NA	9 (6%)	11 (6%)
Summary of Sponsor-Defined Pathogen Eradication Rates (Bacteriologically Evaluable Subjects)				
	Trovafloxacin 200 mg (N=59)	Clarithromycin 500 mg BID (N=67)	Trovafloxacin 200 mg (N=56)	Clarithromycin 500 mg BID (N=59)
Number of Pathogens^a				
Pathogen	End of Treatment		End of Study	
<i>H. influenzae</i>	12/12	15/16 (94%)	10/10	13/16 (81%)
<i>S. pneumoniae</i>	10/11	14/15 (93%)	11/12	13/15 (87%)
<i>C. pneumoniae</i>	6/6	10/10	5/6	5/6
<i>M. pneumoniae</i>	17/18 (94%)	18/18 (100%)	16/17 (94%)	17/17 (100%)
Summary of Sponsor-Defined Pathogen Eradication Rates (Bacteriologically Intent-to-Treat Subjects)				
	Trovafloxacin 200 mg (N=64)	Clarithromycin 500 mg BID (N=72)	Trovafloxacin 200 mg (N=64)	Clarithromycin 500 mg BID (N=72)
Number of Pathogens^a				
Pathogen	End of Treatment		End of Study	
<i>H. influenzae</i>	14/15 (93%)	15/17 (88%)	12/13	13/17 (76%)
<i>S. pneumoniae</i>	12/13	16/18 (89%)	12/13	15/18 (83%)
<i>C. pneumoniae</i>	6/6	11/11	5/6	10/12
<i>M. pneumoniae</i>	17/18 (94%)	18/18 (100%)	17/18 (94%)	18/18 (100%)
a ≥10 isolates of a given pathogen at any evaluation period; percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline NA=Not applicable Ref: Tables 5.1.1, 5.1.2, 5.4.1, and 5.4.2				

NDA 20-759/760
trovafloxacin

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values	Trovafloxacin 200 mg		Clarithromycin 500 mg BID	
	Number and Percentage (%) of Subjects			
Adverse Events:	100/178	(56%)	120/180	(67%)
All Causalities	57/178	(32%)	71/180	(39%)
Treatment-Related Adverse Events	18/178	(10%)	12/180	(7%)
Discontinuations Due to an Adverse Event ^a	39/173	(23%)	48/174	(28%)
Clinically Significant Laboratory Values				

^a For two subjects in the clarithromycin group, the investigator indicated study drug discontinuation on the adverse event page of the CRF (Table 6.1); however, study drug discontinuation was not checked off on the subject summary page of the CRF (Table 4.1).
Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, and 7.1

Eleven subjects in the trovafloxacin group and 13 subjects in the clarithromycin group had serious adverse events. With the exception of the one subject in the clarithromycin group who had a serious adverse event that was considered to be related to study drug, all serious adverse events were attributed to other illnesses or to the disease under study. There were three deaths that occurred greater than 30 days after the last treatment dose; all deaths were unrelated to study drug.

Summary and Conclusion: Trovafloxacin 200 mg once daily for 7 or 10 days was statistically equivalent to clarithromycin 500 mg BID for 7 or 10 days for the treatment of community-acquired pneumonia. The percentage of subjects discontinued from treatment due to adverse events was 10% in the trovafloxacin group and 7% in the clarithromycin group. The overall percentage of adverse events was lower (56%) in the trovafloxacin group compared to the clarithromycin group (67%); treatment-related adverse events were reported in 32% and 39% of subjects, respectively. The most commonly reported treatment-related adverse events in the trovafloxacin group were nausea (12%) and dizziness (10%). The most commonly reported treatment-related adverse events in the clarithromycin group were taste perversion (19%), nausea (8%) and diarrhea (7%).

2. Per Medical Officer

The design of this study is in keeping with the parameters set forth in the IDSA Guidelines and the two Divisional documents (Points To Consider and the draft Evaluability Criteria). Since the five studies submitted in support of the CAP indication are very similar in their overall design (except for the comparators used and whether they are strictly PO studies vs. IV → PO), an overview of this design will be presented here so that it may be referred back to in subsequent reviews of the remaining studies under this indication.

The following text is excerpted from the sponsor's text of protocol 154-134:

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Numbers

Up to 320 subjects will be randomized into this study. Each study site should attempt to enroll at least 10 subjects.

Recruitment will cease when the appropriate number of subjects have been enrolled even if some centers have not reached their agreed recruitment targets.

Inclusion criteria

1. Subjects aged 16 years or more

Women of childbearing potential (i.e., not surgically sterile or less than one year post-menopausal) must have a negative gonadotrophin pregnancy test (urine or serum) immediately prior to entry in the study and must use adequate contraception (for women on oral contraceptives additional barrier contraception must be used) both during and for one month after the end of treatment.

2. Subjects with a medical history, and clinical and radiological findings consistent with an uncomplicated community acquired pneumonia and appropriate for oral therapy.

The following criteria must be met:

a. New infiltrate(s) on chest X-ray

AND

b. At least one of the following signs or symptoms:

- 1). Cough or increasing severity of coughing
- 2). Acute changes in the quality of sputum
- 3). Oral temperature $>38^{\circ}\text{C}$ (100.4°F) or $<36.1^{\circ}\text{C}$ (97°F) or documented fever or hypothermia within the last 24 hours.
- 4). Auscultatory findings such as rales or evidence of pulmonary consolidation.
- 5). Leukocytosis (blood leukocyte count $>10,000/\text{mm}^3$ or $>15\%$ bands)

3. Written informed consent from the patient and the patient's parent or legal guardian if less than 18 years old.

Exclusion criteria

1. Pregnant women, nursing mothers or women of childbearing potential not practicing adequate contraception.

2. Known or suspected hypersensitivity to any quinolone or macrolide.

3. Treatment with any systemic antibiotic for 24 hours or longer within 72 hours prior to the baseline visit

4. Subjects with any of the following conditions:

- a) Pneumonia whose severity is sufficient to warrant initial intravenous antibiotic therapy.

- b) Suspected pulmonary infection (such as abscesses or empyemas) that may require antibiotic treatment for a period greater than 10 days.
 - c) Known Acquired Immunodeficiency Syndrome (AIDS) or suspected *Pneumocystis carinii* pneumonia.
 - d) Neutropenia, defined as a total white blood cell count less than 2500 leukocytes/mm³ or absolute neutrophil count less than 1000/mm³.
 - e) Immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including treatment with greater than 10mg/day of systemic prednisone or equivalent).
 - f) Cavitory lung disease by chest X-ray, or known lung cancer, or aspiration pneumonia.
 - g) Cystic fibrosis
 - h) Significant gastrointestinal or other conditions which may affect study drug absorption.
 - i) A history of any form of epilepsy or seizure.
- 5. Treatment with another investigational drug within four weeks prior to the baseline visit.
 - 6. Prior enrollment in this protocol.
 - 7. Evidence of recent drug or alcohol abuse or dependence.

October 18, 1994 Amendment

- 8. *Subjects receiving treatment with terfenadine or who may require treatment during the duration of treatment.***

STUDY TREATMENTS

Allocation to study treatment

The investigator will be provided with a masked randomization schedule consisting of a list of numbers to which the study drugs have been randomly allocated. The investigator will assign study numbers sequentially to the subjects as they are determined to be eligible for treatment. The study number will be entered onto the patient's case report form and the patient should receive study medication assigned to the corresponding number.

Drug presentation

All oral medication has been blinded by double-dummy technique and will be provided in blister packs with matching placebos. Drug supplies and the patient randomization number will be provided as follows:

CP-99,219	200mg daily as a single dose for 7 or 10 days.
Clarithromycin	500mg two times daily for 7 or 10 days.

Blister pack contains blinded oral CP-99,219 or matching placebo and blinded oral clarithromycin and matching placebo. Subjects will take two 100mg tablets of CP-99,219 or its matching placebo once a day and one 500mg blinded tablet of clarithromycin or its matching placebo twice a day.

Blister packs will be labelled:

"morning" (am) dose containing:
2 tabs 100 mg CP-99,219 or matching placebo.

1 tab 500 mg clarithromycin or matching placebo

"evening" (pm) dose containing:

1 tab 500 mg clarithromycin or matching placebo

Drug administration

On the first day of therapy, subjects will be instructed to take three tablets from the blister pack ("morning" dose) regardless of the time of day; a further single tablet will be taken 12 hours later if appropriate to time of day ("evening" dose). If first ("morning") dose is late in the day, the "evening" dose may be skipped for Day 1. Day 2 will begin with the "morning" dose regardless of Day 1 dosing. This daily administration schedule will be repeated until the second visit (day 3 to 5). At this visit the investigator will decide whether the patient requires a total of 7 days or 10 days of therapy. This decision will be based on resolution of pyrexia, improving clinical symptomatology and the presence of other comorbid conditions. Subjects who are afebrile and clinically improving may only need 7 days of therapy.

After visit 2 subjects will be instructed to continue treatment as outlined above, such that the patient completes a total of 7 or 10 days of therapy.

Mineral supplements, calcium-, aluminium-, or magnesium-based antacids should not be taken within (before or after) two hours of dosing. All study medications may be taken without regard to food.

PATIENT evaluation VISITS

Visit 1 DAY 1 (Baseline)

The following procedure will be undertaken within 48 hours prior to the start of therapy.

Clinical

The baseline visit assessment includes collection of demographic information, concurrent disease, antibiotic therapy within the last seven days, concomitant medication use, targeted physical examination and vital signs (pulse, respiration, blood pressure and body temperature).

Clinical assessment of signs and symptoms of pneumonia will include sputum characteristics, cough, dyspnea, pleuritic chest pain, chills or rigors and lung sounds. In addition a blood and urine sample for laboratory safety testing (see Section 9.3) will be obtained and sent to the central laboratory for testing. Women of childbearing potential will also provide a urine or serum sample for pregnancy testing.

Chest X-ray

Chest X- rays, both PA and lateral will be obtained. An AP chest X-ray is acceptable if the subject's medical condition does not allow a PA and lateral to be obtained.

Bacteriology

Sputum

Freshly expectorated purulent sputum samples must be examined macroscopically for consistency and color and microscopically to determine the suitability for culture (presence of

>25 polymorphonuclear leukocytes and < 10 squamous cells per low power field of a Gram stained specimen defined as an "adequate sputum"). Suitable adequate specimens must be cultured at a local approved laboratory, preliminary sensitivities determined, and isolates sent to the central testing laboratory for final sensitivity determination.

If a satisfactory specimen of expectorated sputum cannot be obtained, the investigator may carry out induction of sputum with nebulized saline or physiotherapy. Should this technique also prove unsuccessful and, if medically indicated, the investigator may attempt to obtain other lower respiratory secretions such as transtracheal aspiration, bronchial brushings or biopsy material (obtained by bronchoscopy).

All sputum and other respiratory isolates will be sent to the central laboratory for testing.

Blood

Blood samples for culture must be obtained from all subjects. If the blood culture subsequently proves to be positive for a pathogen, therapy may be continued, at the discretion of the investigator, only if there is evidence of clinical improvement. If there is no such improvement study therapy must be discontinued and evaluated as a treatment failure. It is important that follow-up blood cultures be obtained. The procedure outlined in Section 9.4, must be followed for all discontinuations.

Isolates from blood must also be sent to the central laboratory for testing.

Susceptibility testing

Information on susceptibility testing with CP-99,219 is provided in Appendix D.

No baseline pathogen or resistant pathogen

Subjects need not be discontinued from the study drug if they do not have a pathogen isolated at baseline or because the pathogen is resistant to any of the study medications. If the patient needs to be discontinued because of failure to improve clinically, then the patient should be discontinued (see Section 9.4) and evaluated as a treatment failure and appropriate therapy instituted. The appropriate therapy should be recorded under the concomitant medication section of the CRF. The patient must however be followed up for safety assessment.

Serology

Serum will be obtained at the baseline visit for the determination of antibodies to *Mycoplasma pneumoniae*, *Legionella* spp., *Chlamydia pneumoniae* and *Chlamydia psittaci*, and sent to the central laboratory for testing. Urine for *Legionella* antigen will also be obtained and sent to the central laboratory.

Visit 2 Day 4 (day 3 to 5)

Clinical

All signs and symptoms identified at the baseline visit should be assessed. New signs or symptoms since the first assessment should also be reported.

Other procedures to be performed at visit 2 are recording of vital signs, concomitant medication, study drug dosing, and adverse events volunteered by the patient or observed by the investigator.

The battery of blood safety tests performed at baseline should be repeated.

Bacteriology

If possible an "adequate" sputum sample must be obtained and sent for culture as defined for visit 1. All sputum isolates will be sent to the central laboratory for testing.

The absence of an adequate sputum specimen and reason must be documented as inability to produce sputum will be considered equivalent to a negative culture providing the patient is clinically improved or cured.

Blood culture is to be repeated if the baseline culture was positive. Isolates from blood must also be sent to the central laboratory for testing.

Visit 3 Day 11 (day 9 to-14) - the end of study therapy period

At the end of study therapy or at the time of premature discontinuations due to lack of efficacy the patient's response to treatment must be assessed by performing the following procedures:

Clinical

All signs and symptoms identified at the first and second visit as well as new signs or symptoms since the second visit should be assessed.

Other procedures to be performed at visit 3 are recording of vital signs concomitant medication, study drug dosing, adverse events volunteered by the patient or observed by the investigator.

Blood and urine samples should be obtained and the battery of blood and urine safety tests performed at baseline should be repeated.

At this visit the investigator is to provide an evaluation of clinical response, as described in Section 8.1.

Chest X-ray

A repeat chest X-ray must be undertaken and reported.

For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and interpreted with respect to the baseline X-ray.

Bacteriology

If possible an "adequate" sputum sample must be obtained and sent for culture as defined for visit 1. All sputum isolates will be sent to the central laboratory for testing.

The absence of an adequate sputum specimen and reason must be documented as inability to produce sputum will be considered equivalent to a negative culture providing the patient is clinically improved or cured.

Blood culture is to be repeated if previous blood sample (visit 2) was positive. Isolates from blood must also be sent to the central laboratory for testing.

Visit 4 Day 30 (day 28 to 35) - the final assessment.

The final assessment of the patient's response to treatment must be assessed by performing the following procedures. If the patient was assessed as a failure at the previous visit and discontinued then the activities relating to the assessment of efficacy should not be undertaken but activities associated with safety (e.g., adverse events and safety bloods) must be undertaken.

Clinical

All signs and symptoms identified at all the previous visits as well as new signs or symptoms since the last visit should be assessed.

Other procedures to be performed at visit 4 are recording of vital signs, concomitant medication, adverse events volunteered by the patient or observed by the investigator.

The battery of blood and urine safety tests performed at baseline need to be repeated only if an abnormality was present at visit 3 (day 9 to 14), or if subject is experiencing a clinically significant adverse event.

At this visit the investigator is to provide a final evaluation of clinical response, as described in Section 8.1.

Chest X-ray

A final chest X-ray needs to be undertaken only if the visit 3 (day 11) radiograph had not cleared (i.e., signs of infiltration remained) or the patient's clinician condition has deteriorated. For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and interpreted with respect to the baseline X-ray.

Bacteriology

If clinically indicated an "adequate" sputum sample must be obtained and sent for culture as defined for visit 1. All sputum isolates will be sent to the central laboratory.

The absence of an adequate sputum specimen and reason must be documented as inability to produce sputum will be considered equivalent to a negative culture providing the patient is clinically improved or cured.

Serology

Serum will be obtained for the determination of antibodies to the pathogens mentioned in Section 7.1.4.

STUDY EVALUATIONS

Clinical

The overall clinical response will be determined by the investigator at the end of study treatment (visit 3, day 11) and at the last follow-up assessment (visit 4, day 30) or at the time of discontinuation.

Clinical response will be classified by the investigator as cure, improvement, failure as defined in Appendix C . Clinical evaluation of response will be based on the global assessment of the clinical presentation of the patient and compared to the baseline assessment. Clinical assessment will be based upon resolution or improvement of radiological, clinical signs of infection such as resolution of fever, disappearance or diminution in purulent sputum production, improvement or resolution of dyspnea, cough and leukocytosis, as well as improvement in general physical condition.

Bacteriological

The bacteriological response will be determined by the sponsor from the culture results of visit 2, (day 4), at the end of treatment (visit 3, day 11) and at the end of the study (day 30) or at the time of discontinuation due to lack of efficacy.

Bacteriological response will be classified by the sponsor as indicated in Appendix C . Repeat cultures of sputum, if obtainable, will be done at visits 2, 3 and 4. Only "adequate" sputum specimens determined by Gram stain should be sent for culture. The absence of adequate sputum specimens at follow-up assessments will be considered equivalent to a negative culture if the clinical response is improved or cure. However, the investigator must document the fact that there was an inadequate sputum production

Standardized susceptibility testing will be performed on all pathogens (see Section 7.1.3). Collection of specimens that require semi-invasive techniques (e.g., bronchoscopy) should only be repeated if there is a suboptimal clinical response.

Radiological assessment

Consecutive chest X rays will be evaluated and their evolution will be graded as:

Resolution: disappearance of all radiological signs of infection

Marked improvement: Significant improvement in the radiological signs of infection compared to baseline.

Radiological failure: no change or worsening in the radiological signs of infection compared to baseline.

Serological

Serological assessments will be undertaken at baseline and day 30.

SAFETY ASPECTS

Adverse events will be monitored up to visit 4 (day 30). Serious adverse events will be monitored throughout the study and for 30 days after the last dose of study drug.

Adverse events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study drug will be recorded on the Adverse Event page(s) of the case report form. Please note that adverse events are not limited to suspected adverse drug reactions but also include illnesses with onset during the study, or exacerbations of pre-existing illnesses which should therefore also be recorded.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a Serious Adverse Event requiring immediate notification to the Pfizer appointed monitor (see Section 9.2). Follow-up of the adverse event, even after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the Pfizer appointed monitor.

Serious Adverse Events

All Serious Adverse Events which occur during the study until the last follow-up visit required by the protocol and for 30 days after the last dose of study drug, whichever comes later, regardless of treatment group or suspected relationship to drug, must be reported immediately by telephone to the Pfizer appointed monitor.

Serious Adverse Events include those that suggest a significant hazard, such as events which:

- are fatal
- are life-threatening
- result in permanent disability
- require in-patient hospitalization or prolongation of a hospital stay
- involve cancer, a congenital anomaly or drug overdose

It should be emphasized that, regardless of the above criteria, any additional adverse experience which the investigator considers serious should be immediately reported.

Any serious adverse event occurring either during the clinical trial and for 30 days after the last dose of study drug must be reported immediately independent of the circumstances or suspected cause.

All deaths should be immediately reported, regardless of elapsed time between last dose in a clinical trial and the death, and thus extends beyond the 30 day post study limit.

For all serious adverse events, the investigator is obligated to pursue and provide information as requested by the Pfizer appointed monitor in addition to that on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Pfizer appointed monitor. The investigator should ensure that information on such cases is reported by telephone or other means and information entered in the case report form is accurate and consistent.

For Canadian studies, in order to conform with Canadian Regulatory requirements as well as U.S. Regulatory requirements, such reactions originating from investigational drug studies conducted in Canada must also be reported IMMEDIATELY to the Director of Drug Regulatory Affairs, Pfizer Canada, Montreal (514-695-0500).

Laboratory safety tests and abnormal laboratory results

October 18, 1994

Since clarithromycin may raise theophylline levels, all subjects on concomitant theophylline should have theophylline levels monitored periodically at the local laboratory.

The clinical laboratory tests, outlined below, will be performed at baseline (visit 1), during therapy (visit 2, day 4 - no urinalysis) and at the end of therapy (visit 3, day 11). Additional safety tests, i.e., at day 30 need only to be undertaken if clinically indicated (e.g., post therapy, clinically significant adverse event) or if a clinically significant abnormality was present at visit 3.

The laboratory safety tests will be conducted by a central laboratory appointed by Pfizer. Transfer of laboratory data from the central laboratory to the investigator and to Pfizer will be by hard copy and where possible by electronic means. The results of all known laboratory tests required by the protocol will be held/recorded in the patient's Case Report Forms (CRFs).

Hematology

Hemoglobin, hematocrit, red blood cells, white blood cells, differential count and platelets.

Biochemistry

AST, ALT, total bilirubin, LDH, alkaline phosphatase, urea, creatinine, total protein, albumin, sodium, potassium, bicarbonate, chloride and random blood glucose.

Urinalysis

Microscopy and urine chemistry (protein, glucose, ketones, bilirubin, pH, urobilinogen, blood and nitrate).

Clinically significant laboratory tests

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the Pfizer appointed monitor.

Further procedures for specific laboratory abnormalities are given in Appendix B.

Discontinuation from study (withdrawals from study)

The reason for a patient discontinuing from the clinical trial must be recorded in the case report form. A discontinuation occurs when an enrolled patient ceases participation in the clinical trial, regardless of the circumstances, prior to completion of the protocol. A discontinuation must be reported immediately to the Pfizer appointed monitor if it is due to a Serious Adverse Event. The investigator is encouraged to contact the Pfizer appointed monitor to discuss

any patient he is considering withdrawing from the trial. However, the final decision as to withdrawal rests with the investigator.

The final efficacy evaluation required by the protocol and microbiology (see Section 7.4.) will be performed at the time of study drug discontinuation. However, subjects must be followed for safety until visit 4. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the patient's condition. Any medication started after the discontinuation but before visit 4 must also be recorded on the concomitant medication section of the case record form.

Medical Officer comments:

In general, this study is a well designed, DB,DD trial against an appropriate comparator agent. The trial design basically follows the recommendations of the IDSA guidelines.

Although a total of 71 investigators (68 US and 3 Canadian) were listed as contributing to this study, only 51 of them (including 2 Canadian investigators who enrolled a total of 6 subjects) eventually contributed enrolled subjects. The following 9 of these investigators contributed at least 10 subjects to this study:

<u>Investigator</u>	<u>ID#</u>	<u>location</u>	<u>N</u>	<u>#subinvestigators</u>	<u>subjects per investigator</u>
Sullivan	5139	Alabama	44	1	22.0
Gezon	5017	Utah	32	7	4.0
Herrod	5209	Utah	28	26	1.1
Upchurch	5140	Oregon	20	1	10.0
Hartford	5129	Idaho	18	12	1.5
Miller	5051	Oregon	15	5	2.5
Follett	5252	Wyoming	14	5	2.3
Schultz	5251	Iowa	11	13	0.8
Pearl	5214	Utah	11	9	1.1

The number of subinvestigators and the ratio of enrolled subjects per investigator is listed to provide an index of the intensity of enrollment per listed investigator. Since the dates of this study are listed as November 1994 to November 1995, it can be seen that Dr. Sullivan and his co-investigator (Dr. Flippo), each saw 22 patients with CAP at a single practice site (Parkway Medical, Birmingham AL) over the course of one respiratory season in Alabama.

The geographic distribution of the largest recruiting centers in this study appears to be predominantly the western portion of the US, with the sole exception of Alabama. The states represented above are not among those with the highest degree of emerging penicillin resistance in pneumococci. Interestingly 71/358 enrolled subjects (20%) in this study ended up being from the state of Utah.

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Clarithromycin patients

PID	Investigator	Location	OK?	Comments
50170192	Gezon	UT	✓	
50240505	Martel	Canada	✓	
51290465	Hartford	ID	✓	
51390403	Sullivan	AL	✓	
51390416	"_"		✓	
51400020	Upchurch	AL	•	No CRFs in CANDA
51400104	"_"		✓	
51400387	"_"		✓	
51560125	Saddoris	OR	✓	Baseline radiologist interpretation negative
52090194	Herrod	UT	✓	
52520305	Follett	WY	✓	
52560235	Weerasinghe	NY	✓	
52580226	Applestein	CA	✓	
52620259	Bias	KY	✓	
52630276	Freiberg	MN	✓	
54620479	Weiss	FL	✓	Baseline CXR read as "no interval change; no acute pneumonia or CHF." Amended to read "possible lingular infiltrate"
58070449	Markel	CO	✓	
58070450	"_"		✓	

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[Faint, illegible text]

Trovafloxacin patients

PID	Investigator	Location	OK?	Comments
50170382	Gezon	UT	✓	WBC count 14.7 K (baseline) to 3.5 K (day 3)
50170384	"_"		✓	
50170486	"_"		✓	
50220481	Payne	TX	•	no CRFs found for this patient in CANDAs
50500313	VanHook	CO	✓	
51390177	Sullivan	AL	✓	<i>this patient was afebrile, had a normal WBC count, no purulent sputum, and a handwritten CXR interpretation of "possible abnormality of LLL". Symptoms listed were 2+ cough and 2+ increased sputum production, which was inadequate by Gram stain criteria and never cultured. It is this type of patient for whom a radiologist's report would be valuable to validate that, at a minimum, there was objective evidence of pneumonia.</i>
51400102	Upchurch	OR	✓	
51400197	"_"		•	no CRFs found in CANDAs
51490090	Ruoff	MI	✓	<i>CXR report included, documenting radiologist reading of "normal chest" and subsequent withdrawal of subject from study</i>
51520049	Alwine	PA	✓	<i>subject has duplicate inclusion/exclusion criteria sheets, in different handwriting but same date and PID number.</i>
51520118	"_"		•	CRF includes seven pages of 'data clarification' sheets, indicative of multiple corrections/changes to CRF forms.
51540065	Estess	MS	✓	
51600126	Saddoris	OR	✓	
52090399	Herrod	UT	✓	
52520307	Follett	WY	✓	
52580227	Applestein	CA	✓	WBC (b)(4)
52620258	Bias	KY	✓	
52660230	Sanders	OK	✓	

General comments:

- No radiologist reports were included in any of the CRFs, despite the protocol statement that:

"A repeat chest X-ray must be undertaken and reported.

For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and interpreted with respect to the baseline X-ray."

The sponsor was asked to present radiology reports on the audited subjects listed above. The following communication was transmitted to the sponsor on 9 October 1997 via electronic mail:

The CAP studies are designed in such a way that the only piece of objective clinical data that is required for entry is a CXR showing a 'new' infiltrate. (This of course implies the presence of a baseline

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radiograph, but that is a pre-enrollment requirement that is in my opinion overly restrictive. That is not the point of this communication.)

Four of the five CAP studies (102 is the only one that does not) specify that the interpretation of xrays will be done by a radiologist.

I was disappointed to find that these interpretations were not included in the primary dataset that is included in the case record forms for each enrolled subject.

(The sole exception appears to be study 112, which includes some radiology reports in the CRFs.)

As I mentioned, this is the only piece of objective clinical evidence that is required for study entry in these studies.

I do not want to request that all such documentation be provided at this point. However, I would like to review a sample of one study's radiology reports as a check on the correlation between the information provided in the CRF (which varies from an apparrent verbatim transcription of a radiology report, to nothing other than checking off the boxes on the CRF) and the official interpretation of the admission CXR.

Here is a 10% random sample of subjects enrolled in study 154-134. I have selected this study because it is (in my opinion) the best designed in terms of blinding and comparator, and is domestic. Please provide all radiologist reports on all entry radiographs taken on the following study subjects:

The sponsor's response:

2. None of the laboratory reports in the CRFs for this study reported a differential WBC count that included the number or percent immature forms (i.e., 'bands'). This is not of major concern, although this is a generally recognized parameter of acute infection that is helpful in making the diagnosis of an acute bacterial infectious process. It is also part of the entry criteria [page 8 of original protocol, item 5.2.b.5: "leukocytosis (blood leukocyte count > 10,000/mm³ or >15% bands)].
3. Of the CRFs examined, practically all of the treated subjects received 10 days of therapy. In the study report (table 3 in appendix), 16 subjects in the trovafloxacin arm and 16 in the clarithromycin arm received 7 days of therapy, compared to 129 and 133, respectively, who received 10 days. The proposed labeling requests a 7-14 day duration of therapy in the table presented in the DOSAGE AND ADMINISTRATION section. This study does not support a lower limit of 7 days of therapy for this indication.
4. The results of the CRF audit, in general, reveal no other inconsistencies of major concern. There were two CRFs in the trovafloxacin subjects and one clarithromycin subject for whom no CRFs were imaged in the "CRF Casebook" section of the CANDAs. Although not of major concern, this represents 3/36 or 8% of the audited CRFs.

Medical Officer conclusions regarding efficacy results, study 134:

1. This double-blinded study supports the clinical efficacy of trovafloxacin in the treatment of community-acquired pneumonia. The sponsor's evaluation using the clinically evaluable EOS endpoint demonstrates equivalence with the approved comparator, clarithromycin. The bacteriologically (and clinically) evaluable subset at EOS did not demonstrate any remarkable organism-specific differences in outcome between the two treatment arms.
2. The results of subjects who were considered failure or relapse did not reveal any discrepancies; both study arms had 11 culture negative failure/relapses. Of the remaining subjects who were culture positive at baseline, the clarithromycin failure/relapses had 3 *M. catarrhalis* and 3 *H. influenzae* failures, whereas there were none of either of these organisms listed as failure/relapses in the trovafloxacin arm (out of a total of 13 isolates for *H. influenzae*, and 4 for *M. catarrhalis*).

Medical officer review of CAP study 110

I. Per applicant

The synopsis of the applicant's final study report for study 110 is presented below; this is taken from the electronic submission, pages 9-15 of the Final Study Report (found in 8.G.1.A.1 of the NDA, under the 'Clinical Studies Relevant to the Claim Structure' section).

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN (CP-116,517) FOLLOWED BY ORAL TROVAFLOXACIN (CP-99,219) WITH INTRAVENOUS CIPROFLOXACIN AND AMPICILLIN FOLLOWED BY ORAL CIPROFLOXACIN AND AMOXICILLIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Principal Investigators:

Joseph Rosman, M.D.	Bruce Ribner, M.D.	Laurence Weiss, M.D.
Louis Roddy, M.D.	David Rodman, M.D.	J. Todd Bagwell, M.D.
Michaël Nelson, M.D.	Larry Rumans, M.D.	Lala Dunbar, M.D., Ph.D.
Spencer Coleman, M.D.	William Salzer, M.D.	Mark Dowell, M.D.
Ronald Geckler, M.D.	Kathryn Middleton, M.D.	Paul Gubbins, Pharm.D.
Ian Baird, M.D.	Michael Sherman, M.D.	Arthur Link, Jr., M.D.
Jeffrey Blumenthal, M.D.	Carol Terregino, M.D.	Robert Piasecki, M.D.
Marvin Bittner, M.D.	David Smith, M.D.	Maruicio Reinoso, M.D.
G. Douglas Campbell, M.D.	Jan Westerman, M.D.	Richard Greenberg, M.D.
Imad Farrukh, M.D.	Rodney Snow, M.D.	Richard Honsinger, M.D.
George Gass, M.D.	Christopher Brown, M.D.	James Felicetta, M.D.
Colby Grossman, M.D.	James Cuellar, M.D.	Richard Quintiliani, M.D.
Guillermo Gutierrez, M.D., Ph.D.	Patrick Flume, M.D.	Gary Garber, M.D.
Hoi Ho, M.D.	Robert Gammon, M.D.	David McCormack, M.D.
Fredric Jackson, M.D., PS	Nelson Gantz, M.D., FACP	Donna Occhipinti, Pharm.D.
Luis Jauregui, M.D.	Lionel Mandell, M.D.	Harvey Tilker, Ph.D.
Michael Kirkpatrick, M.D.	Miquel Mogyoros, M.D.	Justus Kilian, M.D.
Terrance Kurtz, D.O.	Julio Ramirez, M.D.	Gunter Klaus Schleicher, M.D.
Joseph Plouffe, M.D.	Sam Roberts, M.D.	Abel Jacobus Dekock, M.D.
Jeffrey Renston, M.D.	Lewis Winter, M.D.	Mark Beale, M.D.

Study Publication: Not Applicable

Study Dates: 19 January 1995 - 30 January 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ciprofloxacin and ampicillin followed by oral ciprofloxacin and amoxicillin in the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-110 was a randomized, multicenter, double-blind trial of alatrofloxacin (200 mg once daily) administered intravenously for 2-7 days followed by oral trovafloxacin (200 mg once a day) to complete 7-10 days of total treatment versus intravenous ciprofloxacin (400 mg twice daily) and ampicillin (500 mg every 6 hours) for 2-7 days followed by oral treatment with ciprofloxacin (500 mg twice daily) and amoxicillin (500 mg three times daily) to complete 7-10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia.

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	Evaluation Groups ^a :			
	Alatrofloxacin ↓ Trovafoxacin		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin	
Entered Study ^b	198		202	
All Treated	196	(100%)	200	(100%)
Completed Treatment	147	(75%)	168	(84%)
Completed Study	177	(90%)	180	(90%)
Evaluated for Efficacy			201	(>99%)
Clinical Intent-to-Treat	196	(99%)	181	(90%)
Clinically Evaluable	169	(85%)	94	(47%)
Bacteriological Intent-to-Treat	89	(45%)	88	(44%)
Bacteriologically Evaluable	76	(38%)		
Assessed for Safety	196	(100%)	200	(100%)
Adverse Events	192	(98%)	197	(99%)
Laboratory Tests				

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a The daily doses of alatrofloxacin and trovafloxacin were each 200 mg. The daily doses of intravenous and oral ciprofloxacin were 400 mg BID and 500 mg BID, respectively. The daily doses of ampicillin and amoxicillin were each 500 mg, administered every 6 hours (ampicillin) or TID (amoxicillin).

b Subjects who were randomized.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and initial intravenous therapy were eligible to participate in this study.

Drug Administration: Study drug was in the form of intravenous solution (alatrofloxacin, ciprofloxacin, and ampicillin); and trovafloxacin tablets and ciprofloxacin and amoxicillin capsules which were packaged in blister packs, using a double-dummy technique to maintain blinding.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Treatment groups were compared using the confidence interval approach. Confidence intervals (95%) were produced for the difference in success rates between treatments using the normal approximation method. Additionally, the Cochran-Mantel-Haenszel test controlling for centers was done. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

Efficacy: Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -8.3, 3.7 and -10.0, 4.0, respectively) and at the end of study (95% CI: -9.8, 5.5 and -8.8, 5.9, respectively). Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects and pathogen eradication rates for bacteriologically evaluable and intent-to-treat subjects are presented in the following tables.

Summary of the Sponsor's Assessment of Clinical Response (Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Alatrofloxacin ↓ Trovafoxacin (N=169)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=181)	Alatrofloxacin ↓ Trovafoxacin (N=140)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=165)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	168 (100%)	179 (100%)	140 (100%)	165 (100%)
Success (Cure + improvement)	151 (90%)	165 (92%)	120 (86%)	145 (88%)
Distribution of Clinical Response:				
Cure	75 (45%)	74 (41%)	106 (76%)	130 (79%)
Improvement	76 (45%)	91 (51%)	14 (10%)	15 (9%)
Failure	17 (10%)	14 (8%)	17 (12%)	14 (8%)
Relapse	NA	NA	3 (2%)	6 (4%)
(Clinical Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Alatrofloxacin ↓ Trovafoxacin (N=196)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=201)	Alatrofloxacin ↓ Trovafoxacin (N=196)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=201)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed ^a	192 (100%)	198 (100%)	196 (100%)	201 (100%)
Success (Cure + improvement)	161 (84%)	172 (87%)	162 (83%)	169 (84%)
Distribution of Clinical Response:				
Cure	81 (42%)	75 (38%)	136 (69%)	144 (72%)
Improvement	80 (42%)	97 (49%)	26 (13%)	25 (12%)
Failure	31 (16%)	26 (13%)	31 (16%)	26 (13%)
Relapse	NA	NA	3 (2%)	6 (3%)
NA = Not Applicable				
a Four subjects in the alatrofloxacin/trovafoxacin group and three subjects in the ciprofloxacin/ampicillin/amoxicillin group had missing assessments at the End of Treatment but were assessed at the End of Study.				
Ref.: Tables 5.1.1 and 5.1.2				

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Summary of Sponsor-Defined Pathogen Eradication Rates (Bacteriologically Evaluable Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=76)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=88)	Alatrofloxacin ↓ Trovafloxacin (N=64)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=75)
Number and Percentage (%) of Pathogens				
Pathogen ^a	End of Treatment		End of Study	
<i>S. pneumoniae</i>	35/39 (90%)	38/39 (97%)	30/33 (91%)	32/34 (94%)
<i>H. influenzae</i>	18/19 (95%)	20/21 (95%)	14/16 (88%)	20/21 (95%)
<i>S. aureus</i>	4/4	6/6	3/3	4/4
<i>K. pneumoniae</i>	1/1	7/7	1/1	6/6
<i>C. pneumoniae</i>	2/4	9/9	2/4	9/9
<i>L. pneumophila</i>	2/2	4/4	2/2	4/4
<i>M. pneumoniae</i>	8/8	8/9	8/8	7/8
(Bacteriological Intent-to-Treat Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=89)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=94)	Alatrofloxacin ↓ Trovafloxacin (N=89)	Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=94)
Number and Percentage (%) of Pathogens				
Pathogen ^a	End of Treatment		End of Study	
<i>S. pneumoniae</i>	39/46 (85%)	39/40 (98%)	36/41 (88%)	36/38 (95%)
<i>H. influenzae</i>	19/20 (95%)	22/23 (96%)	17/19 (89%)	21/22 (95%)
<i>S. aureus</i>	6/7	6/6	6/6	4/4
<i>K. pneumoniae</i>	1/2	7/7	1/1	6/6
<i>C. pneumoniae</i>	3/5	9/9	3/5	9/9
<i>L. pneumophila</i>	2/2	4/4	2/2	4/4
<i>M. pneumoniae</i>	8/8	8/9	8/8	8/9
NA=Not applicable				
a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (<i>C. pneumoniae</i> , <i>L. pneumophila</i> , and <i>M. pneumoniae</i>); percents displayed only when denominator is ≥15.				
A subject could have had more than one pathogen isolated at baseline				
Ref.: Tables 5.4.1 and 5.4.2				

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The subgroup of alatrofloxacin/trovafloxacin subjects with baseline *S. pneumoniae* had a greater proportion of subjects with baseline risk factors for poorer outcome (49% versus 33%) compared to the ciprofloxacin/ampicillin/amoxicillin subjects. Of the alatrofloxacin/trovafloxacin subjects with *S. pneumoniae*, 24% were ≥65 years, 27% were bacteremic, and 13% required high fractional oxygen or mechanical ventilation, versus 14%, 16%, and 5%, respectively, of subjects in the ciprofloxacin/ampicillin/amoxicillin group. This was associated with a numerically higher clinical failure rate (and associated microbiologic presumed persistence) in the alatrofloxacin/trovafloxacin subjects with baseline *S. pneumoniae*. Only a single subject with clinical *S. pneumoniae* failure had a repeat positive culture (with no change in MIC) and this was a subject with several high risk factors for poor outcome.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Alatrofloxacin ↓ Trovafoxacin		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	140/196	(71%)	133/200	(67%)
Treatment-Related Adverse Events	53/196	(27%)	47/200	(24%)
Discontinuations Due to an Adverse Event ^a	26/196	(13%)	19/200	(10%)
Clinically Significant Laboratory Values	101/192	(53%)	108/197	(55%)

a For five subjects in the alatrofloxacin/trovafoxacin group and four subjects in the ciprofloxacin/ampicillin/amoxicillin group, the investigator indicated the study drug discontinuation on the adverse event page on the CRF (Table 6.1; however, study drug discontinuation was not checked off on the subject summary page of the CRF (Table 4.1).
Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, and 7.1

Six (6) subjects in the alatrofloxacin/trovafoxacin group and 14 subjects in the ciprofloxacin/ampicillin/amoxicillin group died during this study, of which two in the alatrofloxacin/trovafoxacin group and 10 in the ciprofloxacin/ampicillin/amoxicillin group occurred in the first 35 days. All deaths were considered by the investigator to be unrelated to study drug. Thirty-six (36) subjects in the alatrofloxacin/trovafoxacin group and 29 subjects in the ciprofloxacin/ampicillin/amoxicillin group had serious adverse events. With the exception of one subject in the alatrofloxacin/trovafoxacin group who had serious adverse events (nausea/vomiting) that were considered by the investigator to be related to study drug, all serious adverse events were attributed to other events or illnesses or to the disease under study.

Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafoxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy were statistically equivalent for clinical success rate at the end of treatment and at the end of study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable for the most frequently isolated baseline pathogens (*S. pneumoniae* and *H. influenzae*) between the two treatment groups at the end of treatment and at the end of study.

The percentage of subjects discontinued from treatment due to adverse events was 13% in the alatrofloxacin/trovafoxacin group and 10% in the ciprofloxacin/ampicillin/amoxicillin group. The overall percentage of all and treatment-related adverse events for subjects in the alatrofloxacin/trovafoxacin group was comparable to that of subjects in the ciprofloxacin/ampicillin/amoxicillin group (71% and 27% versus 67% and 24%, respectively). The most commonly reported treatment-related adverse events were headache in the alatrofloxacin/trovafoxacin group and diarrhea and dyspepsia in the ciprofloxacin/ampicillin/amoxicillin group. Injection site reactions were comparable between the alatrofloxacin/trovafoxacin and ciprofloxacin/ampicillin/amoxicillin groups (6% and 8%, respectively). Mortality (Day 1 - 35) was lower in the alatrofloxacin/trovafoxacin group compared to the ciprofloxacin/ampicillin/amoxicillin group (1% and 5%, respectively).

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2. Per medical officer

A. Discussion of study design, execution, and analysis

This study was designed to comply with the IDSA Guidelines for the design and conduct of clinical trials which seek the CAP indication. In general, this study would appear to have been designed and conducted in such a manner. The inclusion and exclusion criteria for this study, as outlined by the sponsor, were as follows:

The following characteristics were to have been present:

a) New infiltrate(s) on chest x-ray;

and

b) At least one of the following

1. Cough or increasing severity of coughing
2. Acute changes in the quality of sputum
3. Oral temperature $>38^{\circ}\text{C}$ (100.4°F) or $<36.1^{\circ}\text{C}$ (97°F) or documented fever or hypothermia within the last 24 hours.
4. Auscultatory findings such as rales or evidence of pulmonary consolidation.
5. Leukocytes (blood leukocyte count $>10,000/\text{mm}^3$ or $>15\%$ bands).

Medical officer comments: the IDSA guidelines call for at least TWO of the listed clinical signs or symptoms to be present, along with the presence of a new infiltrate on Chest X-ray.

The statement 'NEW infiltrate' implies the presence of a baseline CXR for each patient entered into the study. Although this would be the optimal situation, I do not believe that subjects should be considered unvaluable if there were not such a baseline film available to the investigator.

Although there is no mention of this issue anywhere in the Final Study Report, the issue of who shall interpret the baseline and follow-up CXRs is clearly delineated in the original study protocol: (section 7.1.2, page 15) "[baseline] Chest X-rays, both PA and lateral, will be obtained and reported by a qualified radiologist"; (section 7.3.2, page 18): "For the assignment of outcomes, all X-rays from a given patient will be read by a qualified radiologist and interpreted with respect to the baseline X-ray." The CRF files that will be audited will be checked for the presence of a radiologist report, at the very least for the baseline CXR used for entry into the study.

It should be noted that the above criteria are identical to those used for the previously reviewed CAP studies, both of which were oral only and designed for the study of outpatients. Although the listed inclusion criteria in section 3.3.1 state "... requiring hospitalization and initial intravenous therapy", this protocol makes no attempt to prospectively objectify differences between the patients enrolled in this study, as compared to those enrolled in the oral only studies. The enrolling investigators presumably had to justify the patient's admission within the context of that hospital's criteria for hospitalization; however, these criteria might vary considerably from hospital to hospital, from locality to locality. In conclusion, it is not readily discernable from this protocol that the patients will be necessarily sicker than the oral only studies.

Sequence of study evaluations:

At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for clinical diagnosis of community acquired pneumonia, as defined above, gave informed consent and met all additional inclusion criteria (see Section 3.3.1), and none of the exclusion criteria (see Section 3.3.2), were eligible for randomization. Baseline visit assessments were to include collection of demographic information, medical history and physical examination, concomitant medication use, and vital signs (pulse, respiration, blood pressure, and body temperature). Clinical assessment of signs and symptoms of pneumonia were to include sputum characteristics, cough, dyspnea, chills/rigors, pleuritic chest pain, lung sounds, and chest x-ray (PA and lateral views). In addition, a standard panel of blood (including culture) and urine tests were to be performed. Initial serology testing for evidence of infection with *Legionella spp.*, *C. pneumoniae*, *M. pneumoniae*, and *Chlamydia psittaci* was to be performed. Macroscopic sputum examination (i.e., color, consistency, and volume) followed by Gram stain and microscopic examination (i.e., polymorphonuclear cells per low power field [LPF], squamous epithelial cells per LPF) of sputum were to be performed. If a satisfactory specimen could not be obtained the investigator could have induced sputum with nebulised saline solution or physiotherapy. If this technique was unsuccessful the investigator could have used such techniques as transtracheal aspiration, bronchial brushings or biopsy material obtained by bronchoscopy.

Susceptibility to the study drugs, trovafloxacin, ciprofloxacin and ampicillin, was to be determined for all potentially significant organisms isolated from sputum specimens, that were considered adequate. Randomization was permitted prior to the availability of the baseline culture and sensitivity report. If no pathogen was detected on baseline culture or if a pathogen was resistant to study medication, study therapy could continue, at the discretion of the investigator.

Medical officer comment: ciprofloxacin is approved for the treatment of Lower Respiratory Infections due to several Gram-negative organisms, as well as those due to Streptococcus pneumoniae. Because this agent is not considered optimal therapy for Gram positive and/or anaerobic respiratory pathogens, I agree with the decision to add ampicillin → amoxicillin to the comparator regimen. However, it should be noted that this regimen does not provide what would be considered optimal therapy for atypical pathogens, and ciprofloxacin is not labeled for treatment of such infections. For more aged subjects, particularly if the setting is nosocomial or nursing home-related pneumonia, atypical agents are low on the list of potential etiologies and a fluoroquinolone + ampicillin regimen is appropriate. However, since this protocol allows for entry of anyone age 18 or above, and with pneumonia originating in the 'community', I would have questioned the use of such a comparator regimen for this study had I been involved with this drug's early development program. It is acknowledged, however, that the sponsor asserts in Appendix 4 to the cover letter of NDA 20-759:

At Visit 2 (Day 4), a subject's need for continued intravenous therapy was to be assessed daily from Study Day 3 to 7. Subjects were to be switched to oral therapy if the following conditions applied:

- resolution of fever (based on daily maximum temperature);
- improvement of symptoms;
- no progression of x-ray changes.

At Visit 2 (Day 4) efficacy observations were to be performed including all clinical assessments of signs and symptoms of pneumonia to assess response to study therapy; bacteriologic response was to be assessed through sputum samples. Blood cultures were to be repeated only if they had been positive at the previous visit. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory (hematology and biochemistry) evaluations.

At Visit 3 (Day 11; end of treatment) efficacy observations were to be performed including all clinical assessments of signs and symptoms of pneumonia to assess response to study therapy; bacteriologic response was to be assessed through sputum samples. Blood cultures were to be repeated only if they had been positive at the previous visit; a chest x-ray was also to be performed. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, adverse events, and laboratory (hematology, biochemistry, and urinalysis) evaluations. The investigator was to provide an evaluation of clinical response.

At Visit 4 (Day 30; end of study), efficacy observations were to be performed including all clinical assessments of signs and symptoms of pneumonia to assess response to study therapy; bacteriologic response was to be assessed through sputum samples. Blood cultures were to be repeated only if they had been positive at the previous visit. If the Visit 3 chest x-ray had not resolved to the subject's baseline, a final x-ray was to be done at Visit 4. In addition to efficacy observations, safety was assessed through recording of concomitant medication, vital signs, study drug dosing, and adverse events. Laboratory evaluations were only to be performed if a clinically significant abnormality was present as Visit 3 (Day 11) or if the subject was experiencing a clinically significant adverse event. A final serology was to be performed and the investigator was to provide a final evaluation of clinical response.

This study was conducted in compliance with a local or central Institutional Review Board (IRB) and informed consent regulations.

Administration of study drug:

Study drug for intravenous administration was prepared using a double-dummy technique to maintain blinding. Intravenous alatrofloxacin or matching placebo for intravenous administration was provided in vials of 5 mg/mL (100 mg/20 mL) to be

diluted to 1 mg/mL with 5% dextrose (D5W). Intravenous ciprofloxacin or matching placebo was provided in vials of 10 mg/mL (200 mg/20 mL) to be diluted to 2 mg/mL (total 400 mg/200 mL) with D5W. Intravenous ampicillin was provided in vials of 500 mg ampicillin powder to be reconstituted in 50 mL of normal saline solution. Subjects assigned to alatrofloxacin/trovafloxacin group had a pharmacy blinded ampicillin placebo prepared containing 50 mL normal saline. Subjects received one of the following intravenous treatment regimens:

Alatrofloxacin 200 mg in 200 mL of D5W once daily (2 x 100 mg vials) and 50 mL normal saline every 6 hours (ampicillin placebo).

Ciprofloxacin 400 mg in 200 mL of D5W twice daily and ampicillin 500 mg in 50 mL normal saline solution every 6 hours.

Medical officer comment: During the conduct of this study, a total of 22 patients were treated with an inappropriately low dose of intravenous study drug. This situation is detailed in the following excerpt from the Final Study Report:

Study drug administration deviations included 22 subjects who received only one vial of IV quinolone (100 mg of alatrofloxacin or 200 mg of ciprofloxacin) instead of two vials as specified in the protocol; these subjects received the correct doses of study drug during the oral dosing period and the ciprofloxacin subjects received the correct dose of IV ampicillin. The sponsor did not exclude these subjects from the classification of clinical evaluability because of this deviation in study drug administration as almost all of these subjects had a successful clinical response; see Section 8.3.1 for further discussion.

The medical officer agrees that it is not necessary to exclude these subjects from analysis. This type of dosing error was not particular to a single study center, but was distributed over a number of sites. It would therefore appear to have been something other than a systematic error that would have argued more strongly for exclusion of the subjects enrolled from that center.

All subjects were to receive intravenous study medication every 6 hours in combinations of active drug and placebos for active drug.

When the investigator had determined a subject's resolution of fever with an improvement of symptoms and no new x-ray findings, the subject was switched from intravenous to oral therapy. Study drug for oral administration was in the form of tablets and capsules and was packaged in blister packs, using a double-dummy technique to maintain blinding. After 2 to 7 days of intravenous treatment with randomized study medication subjects received one of the following treatments orally:

Trovafloxacin 200 mg/day as a single active dose (2 x 100 mg tablet)

Ciprofloxacin 1000 mg/day in two equally divided doses (2 x 250 mg capsule per dose) and amoxicillin 1500 mg/day in three equally divided doses (3 x 250 mg capsule)

All subjects were to receive oral study medication in the morning, afternoon and evening in combinations of active drug and placebos for active drug.

Subjects with more severe pneumonias at baseline (respiratory compromise or bacteremia) may have received up to a total of 14 days of combined IV and oral therapy.

At intervals during treatment or at the time of premature discontinuation of study therapy, appropriate entries for tablets/capsules taken and returned were completed on the case report form (CRF) and the Pfizer Drug Inventory Record (PDIR). If doses were missed, the reason was to be recorded on the CRF.

Medical officer comment: during this oral therapy phase of the study, subjects were taking a total of 12 tablets/capsules per day. One can only speculate on whether this formidable number of pills might have had a negative impact on patient compliance.

Data analysis:

All Randomized Subjects

The all randomized subjects subset included all subjects who were randomized to a treatment group, regardless of whether or not a particular subject received any study medication.

All Treated Subjects

The all treated subjects subset included all subjects who received one or more doses of active double-blind study medication. This subset was used for all safety tables.

Clinical Intent-to-Treat Subjects

The clinical intent-to-treat subjects subset included those subjects in the all randomized subjects subset who had a baseline diagnosis of the disease or condition under investigation determined by protocol specific inclusion criteria (subject had a medical history and clinical radiological findings consistent with community-acquired bronchopneumonia or lobar pneumonia of severity that required hospitalization and initial intravenous therapy; including a new infiltrate on chest x-ray and at least one of the following signs or symptoms: cough or increasing severity of cough, acute changes in the quality of sputum, oral temperature $>38^{\circ}\text{C}$ [100.4°F] or $<36.1^{\circ}\text{C}$ [97°F] or documented fever or hypothermia within the last 24 hours, auscultatory findings such as rales or evidence of pulmonary consolidation, and/or leukocytosis [blood leukocyte count $>10,000/\text{mm}^3$ or $>15\%$ bands]). Some subjects in this subset may never have received any study medication. Subjects found to have tuberculosis or pneumocystis pneumonia were excluded from the clinical intent-to-treat subset.

Clinically Evaluable Subjects

The clinically evaluable subjects subset included all subjects in the clinical intent-to-treat subjects subset who received study medication, unless any one or more of the criteria for non-evaluability applied (See Section 4.2).

Bacteriological Intent-to-Treat Subjects

The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline. Some subjects in this subset may never have received any study medication.

Bacteriologically Evaluable Subjects

The bacteriologically evaluable subjects subset included all subjects in the clinically evaluable subjects subset with at least one pathogen identified at baseline by culture or appropriate serology, unless one or more of the criteria for non-evaluability applied (see Section 4.3).

Criteria for Clinical Evaluability

If any of the following were present, the subject was considered non-evaluable for clinical efficacy.

1. **Insufficient Therapy:** A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement (≥ 5 days) was not evaluable.

Medical officer comment: The IDSA guidelines for Infectious Pneumonia state that "inability to complete the study because of adverse effects" should be considered a reason for declaring a subject to be a clinical failure. This fundamental point is a major item of difference between the sponsor's analysis of the study results and those suggested by the IDSA guidelines.

2. **Prior Antibiotic Usage:** A subject was not evaluable if the subject had been treated with any systemic antibiotic for 24 hours or longer within 72 hours prior to enrollment without documented evidence of resistance or the subject was a clinical failure and had a culture positive baseline pathogen in the evaluable baseline window.

3. **Concomitant Antibiotics Given for Intercurrent Illness:** A subject who was prescribed a concomitant antibiotic (at any time before the End of Treatment assessment) that was potentially effective against the condition under study was not evaluable if the concomitant antibiotic was given for an adverse event or intercurrent illness. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the clinically evaluable subjects subset. For the purpose of subject evaluability, prior antibiotic use that ended on Day 1 was not considered to be concomitant.

Medical officer comment: this aspect of the study analysis is subject to considerable bias. How does one distinguish between an intercurrent infectious illness and study drug failure? Does it matter whether the 'intercurrent infection' is a process for which the sponsor also seeks approval in the trovafloxacin label? For example: subjects 5135-0172, 5224-0282, 5430-0371, and 5501-0236 were all placed on additional antimicrobials following completion of trovafloxacin therapy, all for reasons described as "exacerbation of chronic obstructive pulmonary disease" or "acute bronchitis". In a study of community acquired pneumonia, such 'intercurrent illnesses' are difficult to distinguish from a clinical failure of the study drug to successfully treat the originally diagnosed pneumonia. The rationale behind such subject outcomes will be carefully scrutinized.

4. **Intercurrent Illness:** A subject who developed an intercurrent illness whose clinical course confounded the clinical evaluation of the disease or condition under investigation was not evaluable. The Pfizer Clinical Group determined intercurrent illnesses that caused a subject to be not evaluable for this reason.
5. **No Post-Baseline Clinical Assessments:** A subject with no post-baseline investigator clinical assessments was not evaluable unless given an antibiotic for insufficient response any time during study, up to and including the last day of the End of Study analysis window.
6. **No Post-Baseline Assessment in the Evaluable Analysis Window:** In order to be evaluable a subject must have had an assessment in at least one evaluable timepoint window, unless
 - the investigator's clinical response was a failure before the beginning of the End of Treatment window (Days 5-20), or

- the subject was given an antibiotic for insufficient response at any time during study, up to and including the last day of the End of Study analysis window (Days 21-40).

A subject was included in the analysis at the End of Study assessment if either the subject was:

- clinically evaluable for the End of Treatment visit, and
- was not given any antibiotics for intercurrent illness before the assessment at the End of Study visit, and
- had a clinical assessment in the appropriate window or was given an antibiotic for insufficient response at any time during the study, up to and including the last day of the End of Study analysis window, or the subject was:
 - clinically evaluable for the End of Treatment visit, and
 - the sponsor-defined clinical response was failure or relapse (Section 4.5).

Criteria for Bacteriological Evaluability

If any of the following were present, the subject was considered non-evaluable for bacteriological efficacy.

1. **No Baseline Pathogen:** No baseline causative pathogen was isolated.
2. **Baseline Culture Outside Baseline Visit Window:** The baseline culture was done more than 2 calendar days before the first dose of double-blind study medication.
3. **No Post-Baseline Cultures:** Post-baseline cultures were not obtained, except in the instance of no suitable culture material due to clinical cure or improvement based on the investigator-defined clinical response, in either the evaluable End of Treatment or End of Study analysis windows unless:
 - subject was given an antibiotic for insufficient response, at any time up to and including the last day of the evaluable End of Study analysis window, or
 - the investigator's clinical response was failure, at any time up to and including the last day of the evaluable End of Study analysis window.

Subjects with a serologically defined baseline atypical pathogen were bacteriologically evaluable if they were clinically evaluable.

Bacteriologically evaluable subjects were excluded from the analysis at the End of Study visit if:

- they were excluded from the clinical analysis at the End of Study visit, or
- they did not have a culture result in the End of Study window, unless given an antibiotic for inadequate response or the investigator's clinical response was failure any time during study, up to and including the last day of the End of Study analysis window.

Subjects with a serologically defined baseline atypical pathogen were included in the bacteriological analysis at End of Study if they were included in the clinical analysis at End of Study.

Primary and Secondary Endpoints for Efficacy

Primary efficacy endpoints were:

- Sponsor-defined subject clinical response at the End of Treatment visit and;
- Pathogen eradication rates at the End of Treatment visit.

Secondary efficacy endpoints were:

- Pathogen eradication rates at the End of Study visit;
- Investigator-defined subject clinical response at the End of Treatment visit, and sponsor-defined and investigator-defined subject clinical response at the End of Study visit.

Medical officer comment: the end of study endpoint will be considered to be of primary importance. The Divisional Draft Evaluability Criteria state that "a test-of-cure evaluation... should be at least 7 days or 5 half-lives of the agent, whichever is the longer period, following completion of therapy." Admittedly, this document was not available to the sponsor at the time this protocol was submitted to the IND and, subsequently, implemented. It should nonetheless be intrinsically obvious that one cannot accurately assess the clinical and bacteriologic outcome of a course of therapy until all traces of the administered antimicrobial have been eliminated from the patient, and any residual infectious agent(s), if present, are permitted some time period to make their continued presence clinically manifest.

Sponsor-Defined Subject Clinical Response

For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the global evaluations made by the investigator at the End of Treatment and End of Study visits. The occurrence of any of the following conditions were to supersede the investigator's assessment.

1. Failure: If the investigator-defined subject clinical response was failure at any visit, then the sponsor-defined subject clinical response was failure at all subsequent visits.
2. Failure: If a subject was given a concomitant antibiotic for insufficient clinical response during double-blind therapy plus one day then the Sponsor Defined Subject Clinical Response was a failure at the End of Treatment and all subsequent assessments. If a subject was given a concomitant antibiotic for insufficient clinical response at any time before the assessment plus one day, the Sponsor Clinical Response was failure at that assessment and all subsequent assessments. If a subject did not have an assessment in a particular window and was given an antibiotic for insufficient response in that assessment window then the Sponsor Defined Clinical Response was a failure at that timepoint and all subsequent assessments.

3. Failure: If a subject had no post-baseline assessment, that subject was classified as a clinical failure at both the End of Treatment and End of Study visits (Intent-to-Treat Analysis only).
4. Relapse:
 - If a subject was a clinical cure or improvement at the End of Treatment visit and was assessed by the investigator to be a failure at a subsequent visit, then that subject was classified as a clinical relapse at the End of Study visit.
 - If a subject was a clinical cure or improvement at the End of Treatment visit, but required an additional antibiotic therapy for the primary disease before the End of Study visit, then the subject was classified as a clinical relapse at the End of Study visit.

For the analysis of the clinical intent-to-treat subject subset, a 'last observation carried forward' strategy was used for subjects who were lost to follow-up before the End of Study visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment was treated as missing data.

Confidence intervals (95%) for differences in clinical success (cure + improvement) between treatments were calculated as the primary means to compare treatment groups. The Cochran-Mantel-Haenszel test controlling for centers was also done. Centers with less than five observations in either or both treatment groups were pooled for the purposes of the analysis.

The definition of equivalence, as suggested by some regulatory agencies, is that the 95% confidence interval for the difference in response rates is within 10% when the true satisfactory response rate of the reference drug is 90% or better. Assuming the clinical response rate of the reference drug is 90%, the number of subjects for each treatment group required to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy does not exceed 10% is 142 subjects per treatment group.

Sponsor-Defined Pathogen Outcome

For both evaluable and intent-to-treat subjects, the sponsor classified each baseline organism as a pathogen or as a non-pathogen. Each baseline organism classified as a pathogen was assigned a sponsor-defined pathogen outcome. Multiple baseline pathogens identified in culture samples from the same subject were assigned separate outcomes. Baseline pathogens were assigned a separate outcome for the End of Treatment and End of Study visits.

If multiple visits occurred within the End of Treatment analysis window, the last outcome assigned to each baseline pathogen was used. If multiple visits occurred within the End of Study window, the worst case outcome was used. Selection of worst case outcome followed the order: Persistence or Relapse, Presumed Persistence, Presumptive Eradication, Eradication.

1. Eradication: Baseline pathogen was absent from a culture from the same site. If the subject was started on a concomitant antibiotic for insufficient response on

the same day or up to 3 days after this negative culture, the eradication was carried forward to all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up, the eradication was carried to subsequent implied visits.

2. Presumptive Eradication: No culture was obtained (either not done, or absence of adequate culturable material), and sponsor-defined subject clinical response was cured or improved.
3. Persistence: Baseline pathogen present in a culture sample from the same site (or any relevant site, including blood). If the subject was started on a concomitant antibiotic for insufficient response on the same day or up to 3 days after this positive culture, the persistence was carried forward to all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up, persistence was carried to subsequent implied visits.
4. Presumed Persistence:
 - Use of concomitant antibiotic therapy due to insufficient response, not starting on the same day as, or within 3 days after, a positive or negative culture, in the absence of prior microbiological data in the same evaluable analysis window resulted in a sponsor-defined pathogen outcome of presumed persistence at that visit and all subsequent visits, regardless of subsequent culture results. If the subject was lost to follow-up then the presumed persistence was carried to subsequent implied visits. Absence of microbiological data was defined as either no visit in the window or culture not done at all visits in the window.
 - No culture was obtained (either not done, or absence of adequate culturable material) and the sponsor-defined subject clinical response was failure.
 - The baseline pathogens of subjects who were lost to follow-up (i.e., no visit) at either the End of Treatment or End of Study visits were assigned the outcome presumed persistence if the organism was persistent at any previous visit.
5. Relapse: The original baseline pathogen was present at the End of Study visit in a culture from the same site after the End of Treatment culture was negative.

In addition, organisms not present at baseline were classified as follows:

1. Superinfection: A pathogen, other than one identified at baseline, that was identified at any post-baseline time in culture material obtained from the site of infection consistent with the disease under study and associated with emergence or worsening of clinical and laboratory evidence of infection necessitating antibiotic therapy.
2. Colonization: Any organism, other than one identified at baseline, that was identified at any post-baseline time in culture material obtained from the site of

infection consistent with the disease under study, and not associated with signs or symptoms of active infection necessitating antibiotic therapy.

Each atypical pathogen, identified by serology test, was assigned a sponsor-defined organism outcome, as follows:

- Presumed Persistence. A serologically defined atypical pathogen, and sponsor-defined subject clinical response was failure.
- Presumed Eradication. A serologically defined atypical pathogen (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella*), and the sponsor-defined subject clinical response was cure or improvement.

Confidence intervals (95%) for differences in pathogen eradication rates between treatments were calculated. The Cochran-Mantel-Haenszel test controlling for centers was also done.

B. Medical officer comments on sponsor's analysis of study, and random audit of CRFs

This study was conducted in three countries: US, Canada, and South Africa. The great majority of study sites enlisted were in the US (N=52) compared to Canada and South Africa (4 each). In terms of enrolling study sites, 36 were in the US, 2 in Canada, and 4 in South Africa. Randomized subjects were predominantly American: there were 338 Americans, 53 South Africans, and 9 Canadians randomized into this study.

The following table presents the names and locations of the ten leading centers that enrolled subjects into this study:

<u>Investigator</u>	<u>ID#</u>	<u>location</u>	<u>N</u>	<u># subinvestigators</u>	<u>subjects per investigator</u>
Dowell	5501	WY	39	1	19.5
Dekock	5992	S. Africa	28	4	5.6
Bittner	5224	NE	26	12	2.0
Grossman	5231	SC	25	2	8.3
Baird	5222	OH	23	0	23.0
Plouffe	5239	OH	18	0	18.0
Honsinger	5556	NM	16	3	4.0
Mandell	5430	Canada	14	1	7.0
Weiss	5462	FL	13	5	2.1
Dunbar	5500	LA	12	3	3.0
Kilian	5629	S. Africa	12	1	6.0
Ho	5233	TX	12	4	2.4

The geographic distribution of the enrollees appears to be adequate. With the exception of two single investigators in Ohio and one investigator in Wyoming who listed one co-investigator, the number of enrollees per investigator appears to be lower than most of the investigators listed in study 112.

CRF and Patient Profile audit

A random listing of 10% of the PIDs from study 110 was generated by the reviewing statistician. These 40 CRFs were carefully compared with the data as presented in the sponsor-generated Patient Profiles, to verify the authenticity of the data from which the sponsor's data tables were generated.

Ciprofloxacin + ampicillin/amoxicillin patients

PID	Investigator	Location	OK?	Comments
51350430	Nelson	MO	✓	
52220186	Baird	OH	✓	
52280333	Farrukh	UT	✓	
52330469	Ho	TX	✓	
52350067	Jauregui	OH	✓	
52390138	Plouffe	OH	✓	
52390299	"_"		✓	
52390442	"_"		✓	
52470215	Sherman	PA	✓	
54240166	Brown	CA	✓	<i>Patient profile lists investigator EOT assessment as "Not Assessable", but CRF shows it to be "Cure". Appropriately called "Failure" by sponsor at both EOT and EOS.</i>
54270144	Gammon	AL	✓	
55010330	Dowell	WY	✓	
55050232	Reinoso	TX	✓	
55560037	Honsinger	NM	✓	<i>Diagnosis of Chlamydia pneumoniae by four-fold rise in serum IgA titer.</i>
55560040	"_"		✓	
59910386	Schleicher	S.Africa	✓	<i>Called clinical cure after 6 days of therapy, and thus Rx stopped. Had appropriate length of f/u (to day 31), no additional antibiotics, thus I do not</i>
(b)(4)				
				<i>LFTs may have played a role in clinical decision to stop therapy at day 6.</i>
59920391	Dekock	S.Africa	✓	

Alatrofloxacin → trovafloxacin patients

PID	Investigator	Location	OK?	Comments
51350362	Nelson	MO	✓	<i>Called 'cure' but given Bactrim for days 33-42 for 'COPD Exacerbation'. Culture day 33 shows H. influenzae. See comments pages 26-7, below.</i>
51350364	"_"		✓	
51890353	Geckler	MD	✓	
52220188	Baird	OH	✓	<i>No micro specimen sent to reference lab.</i>
52220347	"_"		✓	
52340342	Jackson	WA	✓	
52390297	Plouffe	OH	✓	<i>Got 8 days of therapy; no explanation given.</i>
52390300	"_"		✓	
52400189	Renston	OH	✓	<i>Dizziness reported at day 5; was actually day 2 of oral trovafloxacin. May coincide with increased ambulation post-removal of IV.</i>
52400190	"_"		✓	
52430106	Rumans	KS	✓	
52430108	"_"		✓	<i>Patient had serum creatinine rise No mention of this as AE by investigator.</i>
52470216	Sherman	PA	✓	
54710275	Occhipinti	GA	✓	
55000126	Dunbar	LA	✓	
55010236	Dowell	WY	✓	<i>Given antibiotics day 17-29 for 'other infection' (acute bronchitis); called cure by investigator, not assessable by sponsor at EOS eval day 28. See discussion on pages 26-7, below.</i>
55010329	"_"		✓	
55050305	Reinoso	TX	✓	<i>Multiple crossouts/corrections!!</i>
59910398	Schleichter	S. Africa	✓	
59920407	De Kock	S. Africa	✓	
59920501	"_"		✓	
59920502	"_"		✓	
59930498	Beale	S. Africa	✓	

General comments:

1. No radiology reports were included in the CRFs for any patient in this study. When queried about this in reference to study 134, the sponsor was able to produce the baseline chest x-ray interpretations for all requested patients. It was not felt to be necessary to repeat this request for the patients in this study as well. The protocol for this study also stated, "For the assignment of outcomes all X-rays from a given patient will be read by a qualified radiologist and interpreted with respect to the baseline X-ray." Thus it remains unclear to this medical officer why such reports were not felt to be important elements of the data collected on each enrolled patient (and therefore worthy of inclusion in the CRF, along with Gram stain and culture reports).
2. As with the other CAP studies audited, the lab results for each patient never included a percentage reading for the WBC differential, even though >15% bands was included in the entry criteria for the study.
3. The diagnosis of pneumonia due to the 'atypical' agents is appropriately made via serology, as was performed in this study. However, a number of subjects (4 ciprofloxacin and 2 trovafloxacin) were diagnosed with Chlamydia pneumoniae pneumonia on the basis of a $\geq$ four-fold rise in serum IgA titers.

Trovafloxacin patients:

<u>PID</u>	<u>acute/convalescent</u>	<u>IgG</u>	<u>IgM</u>	<u>IgA</u>
52240357	acute convalescent			
55340447	acute convalescent			

Ciprofloxacin patients:

<u>PID</u>	<u>acute/convalescent</u>	<u>IgG</u>	<u>IgM</u>	<u>IgA</u>
52240319	acute convalescent			
55010225	acute convalescent			
55560037	acute convalescent			
55560118	acute convalescent			

* these values appear in table 5.3a of the Final Study Report; however, there are no laboratory reports in the CRF for this patient to document these results, so that the IgM and IgG results are not found.

There is no mention of the utility of an isolated rise in serum IgA in the diagnosis of Chlamydia pneumoniae infection in the most current edition of Mandell's Principles and Practice of Infectious Diseases. In a reference called Use and Interpretation of Tests in Medical Microbiology by J.B. Peter, MD, the author states: "The best evidence of an acute C. pneumoniae infection is a fourfold or greater rise in antibody titers between acute and convalescent serum samples, and the presence of C.pneumoniae - specific IgM by microimmunofluorescence of $\geq 1:16$. A single C.pneumoniae - specific IgG titer of $\geq 1:512$ or a single C.pneumoniae - specific IgM titer of $\geq 1:16$ is suggestive of acute infection."

From this definition, then, both of the trovafloxacin subjects have serologies that are suggestive but not diagnostic of acute C. pneumoniae pneumonia. Neither text referenced above mention the utility of a serum IgA titer in the diagnosis of this disease. Thus it can be concluded that patients so diagnosed in this and the other CAP studies should be eliminated from consideration when tallying numbers of subjects with specific pathogens, for the purpose of product labeling.

4. Use of concomitant and/or follow-up antibiotics for 'concomitant infections'.

The following table, taken from the sponsor's Final Study Report for study 110, details all subjects for whom the sponsor altered clinical responses from those that had been provided by the individual investigators:

Table A. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study			
Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Treatment			
5231-0201	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5231-0202	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 3)
5231-0290	Improvement	Failure	Concomitant antibiotic due to inadequate response (empyema (pneumonia failure)) (Day 6)
5231-0311	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 5)
5248-0257	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 6)
5466-0113	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5992-0390	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 6)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

TABLE F Continued on Next Page

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Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study			
Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Study			
5046-0328	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 7)
5135-0172	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for chronic obstructive pulmonary disease (Day 18)
5222-0185	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for surgical prophylaxis (Day 27)
5222-0346	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics (Day 6); subject discontinued treatment early due to adverse events
5222-0487	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics (Day 7); subject discontinued treatment early due to adverse events
5224-0282	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for chronic obstructive pulmonary disease (Day 14)
5224-0360	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic lung disease (Day 18)
5228-0072	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 7)
5231-0160	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics (Day 15)
5231-0201	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5231-0202	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 3)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

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Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study			
Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Study			
5231-0290	Cure	Failure	Concomitant antibiotic for empyema (Day 6)
5231-0291	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for meningitis ^a (Day 16)
5231-0311	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 5)
5235-0068	Cure	Failure	Concomitant antibiotic for concern of septic shock (Day 4)
5235-0198	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for sinus infection (Day 27)
5243-0477	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for persistent pleural effusion (Day 14)
5245-0049	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for bronchitis (Day 28)
5247-0213	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for sore throat (Day 13)
5248-0257	Not Assessed	Failure	Concomitant antibiotic due to inadequate response (Day 6)
5425-0087	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for prophylaxis secondary to bronchial obstruction (Day 15)
a When meningitis was diagnosed, this subject, who had no baseline pathogen, had a full workup and bacterial meningitis was excluded. Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

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Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study			
Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafloxacin: End of Study			
5430-0371	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic obstructive pulmonary disease (Day 31)
5466-0113	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 2)
5471-0273	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 8)
5501-0236	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for acute bronchitis (Day 17)
5992-0382	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 6)
5992-0390	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 6)
Ciprofloxacin/Ampicillin → Ciprofloxacin/Amoxicillin: End of Treatment			
5239-0138	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 7)
5239-0298	Improvement	Failure	Concomitant antibiotics due to inadequate response (Day 9)
5250-0129	Not Assessed	Failure	Concomitant antibiotic due to worsening of pneumonia (Day 1)
5424-0166	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 3)
5501-0226	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 8)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

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Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study			
Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Ciprofloxacin/Ampicillin → Ciprofloxacin/Amoxicillin: End of Study			
5135-0361	Cure	Failure	Failure (Day 7) carried forward
5222-0187	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for prophylaxis of urinary tract infections (Day 10)
5224-0183	Not Assessed	Relapse	Concomitant antibiotics due to inadequate response (Day 24)
5224-0281	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic obstructive pulmonary disease (Day 28)
5228-0333	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for <i>S. viridans</i> bacteremia (Day 16)
5233-0156	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 4)
5233-0469	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for exacerbation of chronic obstructive pulmonary disease (Day 16)
5234-0089	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for <i>E. coli</i> sepsis (Day 29)
5239-0138	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 7)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

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Table F. Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at the End of Treatment and the End of Study

Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Ciprofloxacin/Ampicillin → Ciprofloxacin/Amoxicillin: End of Study			
5239-0298	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 9)
5239-0442	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 8)
5248-0164	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for abdominal abscess (Day 25)
5250-0129	Not Assessed	Failure	Concomitant antibiotics due to worsening of pneumonia (Day 1)
5424-0166	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 3)
5466-0521	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 6)
5471-0274	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for a virus (Day 21)
5501-0205	Cure	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for unrelated upper respiratory tract acute infection (Day 17)
5501-0226	Not Assessed	Failure	Concomitant antibiotics due to inadequate response (Day 8)
5505-0229	Cure	Failure	Concomitant antibiotics due to inadequate response (Day 17)
5992-0403	Improvement	Not Assessed	Not clinically evaluable at EOS due to concomitant antibiotics for otitis media (Day 18)
5992-0424	Improvement	Failure	Failure (Day 11) carried forward
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

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To summarize the 'directionality' of these changes, the following table was compiled by the medical officer:

**Sponsor overrides at End of Study evaluation timepoint, Study 154-110,
as enumerated in Table F of sponsor's Final Study Report**

Investigator's interpretation	Sponsor's interpretation	Trovan (N = 27)	Cipro (N = 21)
Cure	Fail	7	4
Improved	Fail	4	1
Not assessed	Fail	1	6
Cure	Not assessed	10	6
Improved	Not assessed	5	3
Not assessed	Relapse	0	1

It would appear from this analysis that the sponsor has not biased these changes in a manner that is advantageous to trovafloxacin. There are no overrides that confirmed a better outcome than that assigned by the investigator. The only category in the above table that is of note is that which changed an investigator's 'not assessed' to 'fail'; there were 6 of these in the ciprofloxacin arm versus only one in the trovafloxacin arm. Review of each of these cases found the change to be appropriate; the investigator had deemed a patient not assessable because of the addition of concomitant antimicrobials due to 'inadequate response to study medication'.

The determination of what, in fact, constitutes an 'inadequate response' of the underlying disease being treated (in this case being community-acquired pneumonia) to the study drug, as opposed to the onset of a concomitant but 'unrelated' infectious illness, is a potential source of considerable bias. For example, here is a partial list of reasons provided by the investigator for the administration of concomitant antimicrobials during or following administration of study drug (this listing is only of those subjects who were rendered 'not assessable' by the sponsor):

**‘Cure’ or ‘Improvement’ per investigator to ‘Not Assessable’ changes by sponsor
Study 154-110**

	Trovafloxacin (N=15)	Ciprofloxacin (N=9)
concomitant antibiotics for other respiratory infectious processes:		
COPD exacerbation	4	2
bronchitis/upper resp. infection	2	1
otitis media	0	1
sinus infection	1	0
sore throat	1	0
persistent pleural effusion	1	0
prophylaxis:		
pre-surgical	1	0
bronchial obstruction	1	0
abdominal abscess	0	1
urinary tract infection	0	1
meningitis	1	0
bacteremia/sepsis	0	2
“a virus”	0	1
no reason specified	1	0
Study drug discontinued due to adverse event	2	0

Determining what constitutes a failure to treat the underlying pneumonia, as opposed to what constitutes an episode of bronchitis or ‘exacerbation of COPD’, is very difficult clinically. In such instances, the adequacy of the blind of the study becomes paramount. In general, the above numbers do not appear to indicate any sort of systematic bias on the part of the sponsor.

The two trovafloxacin discontinuations due to adverse events were on days 6 and 7 of therapy. The first, PID 52220346, had pruritus that was considered ‘not study drug related’ yet was switched to cephalexin on day 6, and followed up to day 31 of study. The second, PID 52220487, developed oropharyngeal thrush on therapy which resulted in the discontinuation of trovafloxacin and initiation of clarithromycin. Since both of these subjects received more than 5 days of study drug, they should be clinically evaluable and thus one could argue both should be clinical failures of trovafloxacin therapy. After all, trovafloxacin patient PID 59910386 was considered a ‘cure’ by the sponsor after having received only 6 days of therapy (see medical officer audit, page 17 of review).

These two cases lead to the question of how drug discontinuations due to adverse events should be handled in the assessment of outcomes. The IDSA guidelines call for “inability to complete the study because of adverse effects” to be one of the definitions of clinical failure. The sponsor has opted to ignore this aspect of the IDSA guidelines, along which all studies for this indication are ostensibly designed and executed.

Medical officer conclusions regarding efficacy results, study 110:

1. The overall design and conduct of this study was acceptable. There did not appear to be any systematic errors or biases in the interpretation of results that were unacceptable to the medical officer. The issues discussed in the above 'General Comments' do not invalidate the results of this study. The double-blind design of this study minimalizes the effect of some of the sources of bias discussed above.
2. The results of this study support the sponsor's assertion that trovafloxacin, given intravenously followed by orally, is as efficacious as ciprofloxacin (IV→ PO) plus amoxicillin/ampicillin in the treatment of CAP. At the EOS clinically evaluable assessment, the cure rates for trovafloxacin and ciprofloxacin were 106/140 (76%) and 130/165 (79%), respectively.
3. The number of subjects withdrawn during treatment, for any cause, was considerably higher in the trovafloxacin arm of this study (49/196 or 25%) than in the comparator arm (32/200 or 16%). Of those 49 withdrawn trovafloxacin patients, 23 were felt to be study drug related, and 13 of those were adverse events. Total number of patients having adverse events leading to study drug discontinuation (regardless of causality) were 21/196 (11%) in the trovafloxacin arm and 15/200 (8%) in the ciprofloxacin/ampicillin arm.
4. The use of change in serum IgA titers led to the diagnosis of *Chlamydia pneumoniae* pneumonia in two trovafloxacin-treated subjects in this study; these diagnoses will be discounted when tabulating total number of such subjects for the purposes of organism-specific labeling.

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Medical Officer Review of CAP study 154-111

1. Per Applicant

The synopsis of the applicant's final study report for study 111 is presented below, as excerpted from the electronic version of the NDA (section 2.H.2):

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN (CP-116,517) FOLLOWED BY ORAL TROVAFLOXACIN (CP-99,219) WITH INTRAVENOUS CEFTRIAXONE FOLLOWED BY ORAL CEFPODOXIME WITH OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Principal Investigators:

Warren Whitlock, MD	Stephen Green, MD	Juan Broquetas, MD
Charles Vánhook, MD	John Pullman, MD	Javier Solis, MD
W. Travis Ellison, MD	Frederick Whittier, MD	Jose Alegre Martin, MD
Charles Ballow, PharmD	James Leggett, MD	Joaquin Duran Cantoya, MD
Daniel Kett, MD	Daniel Musher, MD	Ronald Fergusson, MD
Edward Britt, MD	Rodney Wishnow, MD	Iain Gould, MD/ C. Christopher Smith, MD
Frank Byrne, MD/ Brian Zehr, MD	Gregory Kane, MD	Andrew Greening, MD
Timothy Kotschwar, PharmD	Phillip Masters, MD	Robert Masterton, MD
Ralph Steele, MD	Martin Tauber, MD	Robert Monie, MD
Michael Niederman, MD	Donald Graham, MD	Michael Pepperman, MD
Susan Pingleton, MD	Howard Koffler, MD	Robin Macmillan, MD
Curtis Sessler, MD	Sammy Campbell, MD	Clifford Leen, MD
Claude Tellis, MD	Arthur White, MD	D.R.T. Shepherd, MD
Scott Truab, PharmD	John Segreti, MD	Brent Richards, MD
J. Edwin Underwood, PharmD	Richard Pelligrino, MD	Martin Phillips, MD
Marcus Zervos, MD	J. Dewitte, MD	John Wilson, MD
David Grossman, MD	Eric Fournier, MD	Bruce Hall, MD
Dennis Mikolich, MD	Philippe Godard, MD	Patrick Carroll, MD
Kirk Jacobson, MD	Jean Paul Homasson, MD	Glenn Rice-Mcdonald, MD
Sadri Avsar, MD	Jean Jacques Larzul, MD	Raffaele Scicchitano, MD
David Bland, MB, BS	Marc Mathieu, MD	Charles Bredin, MD
Charles Ericsson, MD	Olivier Sitbon, MD	Shane O'Neill, MD
Selwyn Spangenthal, MD	Francois Steenhower, MD	P. Pillay, MD
Faroque Khan, MB	George Nouvet, MD	Luke Clancy, MD
Timothy Klein, MD	M. Peureax, MD	Etienne Marchand, MD
Donald Levine, MD	Yann Curran, MD	Claude Bonnet, MD
Benjamin Lipsky, MD	Luis Maestu, MD	Gavin Petrie, MD
Melvin Russell, MD	Jaime Martinez Del Rio, MD	Dharam Dhillon, MD
James Taylor, MD	Antoni Torres Marti, MD	Franz Daschner, MD
David Wisinger, MD	Ramon Estruch, MD	Raul Marques, MD

Study Publication: Not Applicable

Study Dates: 8 February 1995 - 22 March 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ceftriaxone followed by oral cefpodoxime, with optional erythromycin, for the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-111 was a randomized, multicenter, double-blind, double-dummy trial of alatrofloxacin administered intravenously for 2 to 7 days followed by oral trovafloxacin to complete 7 to 10 days of total treatment versus intravenous ceftriaxone for 2 to 7 days followed by oral cefpodoxime to complete 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

	Evaluation Groups^a:			
	Alatrofloxacin		Ceftriaxone	
	↓		↓	
	Trovafloxacin		Cefpodoxime	
Entered Study ^b	218		225	
All Treated	215	(100%)	222	(100%)
Completed Treatment	170	(79%)	172	(77%)
Completed Study	182	(85%)	183	(82%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	212	(97%)	221	(98%)
Clinically Evaluable	180	(83%)	187	(83%)
Bacteriologically Intent-to-Treat	92	(42%)	102	(45%)
Bacteriologically Evaluable	80	(37%)	85	(38%)
Assessed for Safety	215	(100%)	222	(100%)
Adverse Events	203	(94%)	205	(92%)
Laboratory Tests				

a The daily doses of alatrofloxacin and trovafloxacin were each 200 mg. The daily dose of ceftriaxone was 1000 mg and the daily dose of cefpodoxime was 400 mg (200 mg administered twice daily).

b Subjects who were randomized.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and initial intravenous therapy were eligible to participate in this study.

Drug Administration: Study drug was in the form of intravenous solution (alatrofloxacin and ceftriaxone); trovafloxacin tablets and cefpodoxime capsules, which was packaged in blister packs, using a double-dummy technique to maintain blinding.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum

chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Treatment groups were compared using the confidence interval approach. Confidence intervals (95%) were produced for the difference in success rates between treatments using the normal approximation method. Additionally, the Cochran-Mantel-Haenszel test controlling for centers was done. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

Efficacy Results: Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -3.6, 9.5 and -6.5, 8.1, respectively) and at the end of study (95% CI: -4.1, 11.9 and -5.2, 10.0, respectively).

Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects and pathogen eradication rates for bacteriologically evaluable and intent-to-treat subjects are presented in the following tables.

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Summary of the Sponsor's Assessment of Clinical Response (Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Alatrofloxacin ↓ Trovfloxacin (N=180)	Ceftriaxone ↓ Cefpodoxime (N=187)	Alatrofloxacin ↓ Trovfloxacin (N=159)	Ceftriaxone ↓ Cefpodoxime (N=169)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	178 (100%)	184 (100%)	159 (100%)	169 (100%)
Success (Cure + improvement)	160 (90%)	160 (87%)	136 (86%)	138 (82%)
Distribution of Clinical Response:				
Cure	102 (57%)	108 (59%)	128 (81%)	128 (76%)
Improvement	58 (33%)	52 (28%)	8 (5%)	10 (6%)
Failure	18 (10%)	24 (13%)	19 (12%)	25 (15%)
Relapse	NA	NA	4 (3%)	6 (4%)
(Clinically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Alatrofloxacin ↓ Trovfloxacin (N=212)	Ceftriaxone ↓ Cefpodoxime (N=221)	Alatrofloxacin ↓ Trovfloxacin (N=212)	Ceftriaxone ↓ Cefpodoxime (N=221)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed ^a	207 (100%)	214 (100%)	212 (100%)	221 (100%)
Success (Cure + improvement)	171 (83%)	175 (82%)	171 (81%)	173 (78%)
Distribution of Clinical Response:				
Cure	109 (53%)	115 (54%)	158 (75%)	153 (69%)
Improvement	62 (30%)	60 (28%)	13 (6%)	20 (9%)
Failure	36 (17%)	39 (18%)	37 (17%)	41 (19%)
Relapse	NA	NA	4 (2%)	7 (3%)
NA = Not Applicable				
a Five subjects in the alatrofloxacin/trovfloxacin group and seven subjects in the ceftriaxone/cefpodoxime group had missing assessments at the End of Treatment but were assessed at the End of Study.				
Ref.: Tables 5.1.1 and 5.1.2				

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Summary of Sponsor-Defined Pathogen Eradication Rates ^a (Bacteriologically Evaluable Subjects)						
Pathogen ^b	Alatrofloxacin ↓ Trovafoxacin (N=80)		Ceftriaxone ↓ Cefpodoxime (N=85)		Alatrofloxacin ↓ Trovafoxacin (N=68)	
	End of Treatment		End of Study		End of Study	
<i>S. pneumoniae</i>	28/31 (90%)	22/23 (96%)	25/27 (93%)	19/20 (95%)	13/15 (87%)	22/24 (92%)
<i>H. influenzae</i>	16/16 (100%)	23/26 (88%)	3/3	6/7	3/3	3/3
<i>S. aureus</i>	4/4	7/8	3/3	3/3	0/2	7/8
<i>M. catarrhalis</i>	5/5	3/3	2/2	2/2	7/8	8/10
<i>P. aeruginosa</i>	5/5	1/2	2/2	7/10	8/10	4/6
<i>C. pneumoniae</i>	4/4	9/9	7/10	9/10		
<i>L. pneumophila</i>	8/11	8/10				
<i>M. pneumoniae</i>	12/12	5/6				

Summary of Sponsor-Defined Pathogen Eradication Rates ^a (Bacteriologically Intent-to-Treat Subjects)						
Pathogen ^b	Alatrofloxacin ↓ Trovafoxacin (N=92)		Ceftriaxone ↓ Cefpodoxime (N=102)		Alatrofloxacin ↓ Trovafoxacin (N=92)	
	End of Treatment		End of Study		End of Study	
<i>S. pneumoniae</i>	31/37 (84%)	24/25 (96%)	29/34 (85%)	21/22 (95%)	15/17 (88%)	23/25 (92%)
<i>H. influenzae</i>	18/19 (95%)	23/26 (88%)	3/3	7/8	3/3	3/5
<i>S. aureus</i>	5/5	8/9	3/3	3/3	0/2	8/9
<i>E. coli</i>	4/5	4/6	5/5	6/6	4/4	9/11
<i>M. catarrhalis</i>	5/5	3/3	6/6	8/9	8/11	5/7
<i>P. aeruginosa</i>	5/5	1/2	4/4	11/12		
<i>C. pneumoniae</i>	4/4	9/9				
<i>L. pneumophila</i>	8/11	9/11				
<i>M. pneumoniae</i>	12/12	6/7				

NA=Not applicable
a Eradication rates = number of eradicated + presumed eradicated pathogens / number of pathogens.
b Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline. Non-eradicated pathogens were either persistent (confirmed microbiologically) or presumed persistent. For bacteriologically ITT, pathogens for subjects lost to follow-up were considered persistent.
Ref.: Tables 5.4.1 and 5.4.2

No subject in the alatrofloxacin/trovafoxacin group with a clinical outcome of failure had a microbiologically confirmed persistent pathogen.

Of the 11 subjects in the alatrofloxacin/trovafoxacin group and 20 subjects in the ceftriaxone/cefpodoxime group who died during this study, three subjects in the alatrofloxacin/trovafoxacin group and eight subjects in the ceftriaxone/cefpodoxime group died while receiving treatment or within 30 days following last treatment dose due to worsening of the disease under study. Two (2) alatrofloxacin/trovafoxacin subjects and five ceftriaxone/cefpodoxime subjects who died while receiving treatment or within 30 days following last treatment dose due to worsening of the disease under study were clinically evaluable treatment failures.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Alatrofloxacin ↓ Trovafloxacin (N=215)		Ceftriaxone ↓ Cefpodoxime (N=222)	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	177/215	(82%)	172/222	(77%)
Treatment-Related Adverse Events	70/215	(33%)	57/222	(26%)
Discontinuations From Treatment Due to an Adverse Event ^a	22/215	(10%)	18/222	(8%)
Clinically Significant Laboratory Values	121/203	(60%)	114/205	(56%)
a With the exception of eight subjects in the alatrofloxacin/trovafloxacin group and eight subjects in the ceftriaxone/cefpodoxime group who were discontinued due to unrelated adverse events, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related. Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, 7.1, and Appendix I, Table 3.1				

Eleven (11) subjects in the alatrofloxacin/trovafloxacin group and 20 subjects in the ceftriaxone/cefpodoxime group died during this study. With the exception of one death in the ceftriaxone/cefpodoxime group that occurred >30 days post-therapy and was considered by the investigator to be treatment related (upper gastrointestinal bleeding and pneumonia), all deaths were considered by the investigator to be unrelated to study drug. Thirty-four (34) subjects in the alatrofloxacin/trovafloxacin group and 47 subjects in the ceftriaxone/cefpodoxime group had serious adverse events. Two subjects in the alatrofloxacin/trovafloxacin group and two subjects in the ceftriaxone/cefpodoxime group who had serious adverse events that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or concomitant treatment.

Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were statistically equivalent for the sponsor-defined clinical success rate at the end of treatment for both intent-to-treat and evaluable subjects. Of the 11 subjects in the alatrofloxacin/trovafloxacin group and 20 subjects in the ceftriaxone/cefpodoxime group who died during this study, three alatrofloxacin/trovafloxacin subjects and eight ceftriaxone/cefpodoxime subjects died

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while receiving study medication or within 30 days of last treatment dose due to worsening pneumonia.

Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and at the end of study for baseline isolates of *S. pneumoniae* and *H. influenzae*. All subjects who had penicillin-resistant ($\text{MIC} \geq 0.1 \mu\text{g/mL}$) *S. pneumoniae* isolated at baseline (10 in the alatrofloxacin/trovafloxacin group and one in the ceftriaxone/cefepodoxime group) were clinical cures or improvements at the end of treatment and the end of study. No subject in the alatrofloxacin/trovafloxacin group with a clinical outcome of failure had a microbiologically confirmed persistent pathogen.

The percentage of subjects discontinued from treatment due to adverse events was 10% in the alatrofloxacin/trovafloxacin group and 8% in the ceftriaxone/cefepodoxime group. Nine (9) subjects in the alatrofloxacin/trovafloxacin group and two subjects in the ceftriaxone/cefepodoxime group were discontinued from treatment due to treatment-related adverse events. The most frequently occurring treatment-related adverse events that lead to discontinuation were those related to the intravenous insertion site (insertion site reaction, paresthesia, pruritus, thrombophlebitis, phlebitis) among subjects in the alatrofloxacin/trovafloxacin group and colitis and diarrhea among subjects in the ceftriaxone/cefepodoxime group. The overall percentage of all and treatment-related adverse events in the alatrofloxacin/trovafloxacin group was comparable to that of subjects in the ceftriaxone/cefepodoxime group (82% and 33% versus 77% and 26%, respectively). The most commonly reported treatment-related adverse events were dizziness (5%) and nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and diarrhea (7%) for subjects in the ceftriaxone/cefepodoxime group.

2. Per Medical Officer

APPROPRIATE
ON OPINION

A. Comments on comparator regimen

The chosen comparator regimen for this study is appropriate for use in the treatment of community-acquired pneumonia. Current labeling for ceftriaxone reads in part,

“Lower Respiratory Tract Infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus mirabilis*, or *Serratia marcescens*” at a dose of 1-2 grams given once daily or in equally divided doses twice daily depending on the type and severity of infection. The usual duration of therapy is 4 to 14 days; in complicated infections, longer therapy may be required.

For cefepodoxime: “acute Community Acquired Pneumonia caused by *Streptococcus pneumoniae* or non-beta-lactamase-producing *Haemophilus influenzae* ... at a dose of 200 mg bid for 14 days”.

The protocol-specified duration of 7-10 days for the comparator regimen is clearly less than the labeled duration of therapy for cefepodoxime, yet it exceeds the minimal duration of ceftriaxone specified in the labeling. The protocol does allow for a 14-day regimen to be given if the patient was felt to be adequately ill (defined as with bacteremia or requiring mechanical ventilation or high fractional O_2 [$>35\%$ to maintain PO_2 at >60]). A careful note will be made regarding the duration of therapy in the comparator arm and how it conforms to these labeling parameters.

Although these cephalosporins are not active against the agents of 'atypical' pneumonias, this protocol allowed for the addition of erythromycin, IV followed by tablets, if an atypical agent was suspected. Matching placebo was to be provided to the alatrofloxacin/trovafloxacin subjects.

B. Comments on study design and analysis

The design of this study is essentially identical to that of study 110, reviewed previously, aside from the difference in comparator regimen. The comments regarding design and analysis that were made in that portion of the Medical Officer review are appropriate for this study as well.

C. Medical officer comments on sponsor's analysis of study, and random audit of CRFs

ceftriaxone → cefpodoxime subjects

PID	Investigator	Location	OK?	Comments
50790075	Ellison	SC	✓	
50790105	"_"		✓	
50790235	"_"		•	<i>Called double infection with Klebsiella pneumoniae and Legionella pneumophila. Four-fold rise in titer documented but admission urinary antigen negative. X-ray shows lobar consolidation; patient smoker with purulent gram stain. Unlikely to be true co-infection; more likely to be false positive serology for legionellosis. See discussion below regarding issue of multiple pathogens in setting of positive serology for atypical agents.</i>
50791076	"_"		✓	
51080057	Britt	MD	✓	
51191051	Truab	MA	•	<i>Local lab claims sputum grew Strep pneumo; reference lab grew Serratia marcescens. Gram stain report shows Gram Positive Cocci, consistent with local lab diagnosis. Called clinically and microbiologically evaluable by sponsor.</i>
51220043	Grossman	OH	✓	
51710164	Ericsson	TX	✓	
51710177	"_"		✓	
51760015	Levine	MI	✓	
51760205	"_"		✓	
52000017	Pullman	MT	✓	
52060175	Leggett	OR	✓	<i>Called 'cure' at EOT (day 10), having been given cephalosporin but no erythromycin for what is serologically diagnosed as Chlamydia pneumoniae pneumonia. Lab result showing day 31 titer of 1:256 has "not clinically significant" written on it by investigator.</i>
53971162	Monie	UK	✓	
55150604	Daschner	Germany	✓	
56210729	Maestu	Spain	✓	
56210732	"_"		✓	
58330810	Bonnet	Belgium	✓	
59470926	Phillips	Australia	✓	
63401167	Dhillon	UK	✓	

alatrofloxacin → trovafloxacin subjects

PID	Investigator	Location	OK?	Comments
50790073	Ellison	SC	✓	
50791074	"—"		✓	
51161057	Pingleton	KS	✓	
51210141	Zervos	MI	•	<i>Patient received 13 days of trovafloxacin (6 IV then 7 PO) for blood culture positive Streptococcus pneumoniae infection. Called 'improvement' at EOT visit day 14, but then 2 days later admitted to ICU with recurrent Streptococcus pneumoniae sepsis, bilateral otitis media, and worsening sinusitis. Begun on tobramycin + ticarcillin at that point. Day 25 EOS evaluation initially called 'failure' by investigator; months later, crossed out and called 'cure'. AE of 'Streptococcal septicemia' initially ascribed to study drug; investigator crossed out and put 'illness or caused by illness' as cause of event. Sponsor agrees with both EOS and EOT assessments, though made patient 'not assessable' for Clin Eval population at EOS due to the flu antimicrobials. Local lab MICs of blood isolate vs PCN were ; reference lab claims MIC was ; thus sponsor includes this subject as an evaluable at EOT penicillin-resistant Streptococcus pneumoniae 'favorable outcome'. See comments below.</i>
51680146	Avsar	AL	•	<i>Patient received 9 days of trovafloxacin; had drug-related dizziness and nausea starting day 4 which prompted discontinuation of drug before 10 days. Given clarithromycin on study day 12 to 22; despite this, EOT assessment at day 12 called 'improvement' by investigator and sponsor agrees. If the patient is improving, why is an additional 10 days of clarithromycin indicated? EOS eval done day 40, called 'not assessable' by sponsor (out of window visit) but ITT 'cure' by investigator; again sponsor agrees. Isolate = beta-lactamase + Moraxella catarrhalis.</i>
51710162	Ericsson	TX	✓	
51740006	Khan	NY	✓	
51740225	"—"		✓	<i>Patient received 6 days of trovafloxacin (2 IV, 4 PO) and developed rash on day 5 which led to premature discontinuation day 6. (Nonetheless investigator claimed study drug was NOT cause of this rash.) Initial sputum culture grew both Staph aureus and Haemophilus parainfluenzae; called clinical cure and microbiologic eradication at EOT (day 11) by both investigator and sponsor, even though sputum culture on day 11 again grew H. parainfluenzae.</i>
51740226	"—"		✓	
51760219	Levine	MI	✓	
51760220	"—"		✓	
53970424	Monie	UK	✓	<i>This 77 year old patient received 10 days of trovafloxacin (6 IV, 4 PO) for a right lower lobe pneumonia. Sputum grew no pathogen but initial blood culture grew Streptococcus pneumoniae (penicillin MIC 0.06). Atypical agents were not suspected; no erythromycin [i.e. placebo] was given. At EOT evaluation day 13, investigator thought there was some clinical improvement, though chest x-ray was reported to be unchanged. Despite this assessment of 'improvement', a bronchoscopy was done day 16, and a thoracentesis on day 21; neither culture was positive. The investigator considered the patient to be a failure at EOS (day 30), and the sponsor did not override this. Because no repeat culture demonstrated Streptococcus pneumoniae, the sponsor considers this an eradication of this organism but a failure to treat Legionella. The convalescent serologies returned with a Legionella antibody rise from the urinary antigen was negative. It is debatable whether this case actually was a true case of Legionella, rather than pneumococcal pneumonia with bacteremia in which subsequent cultures while on trovafloxacin therapy did not grow the organism.</i>

alatrofloxacin → trovafloxacin subjects (con't)

PID	Investigator	Location	OK?	Comments
55080510	Curran	France	✓	
55461027	Koffer	PA	✓	
56070185	Campbell	AZ	✓	<i>Patient (67 year old male) presents with Streptococcus pneumoniae bacteremia; vitals show patient afebrile, pulse 77, respiratory rate normal, peripheral . Although CRF pages regarding addition of erythromycin indicate that no erythromycin [placebo in this case] was given, handwritten note on page with atypical serologies indicates that investigator, when cognizant of baseline , added erythromycin to regimen.</i>
56271140	Martin	Spain	✓	
58350739	Cantoya	Spain	✓	
58351193	"_"		✓	
58351194	"_"		✓	
61151171	O'Neill	Ireland	✓	
61151172	"_"		✓	<i>Called clinically evaluable 'cure' at EOT visit (day 11), following 7 day course of trovafloxacin. On day 14, started on a seven day course of cefixime for 'infective exacerbation of COPD' and appropriately called 'not assessable' by the sponsor at EOS visit (day 32). This case points out the need to use EOS rather than EOT as the crucial endpoint, and the problems inherent with using the ITT analysis at EOS as the endpoint (since by the sponsor's ITT rules, this patient gets called a 'cure' despite the use of additional antimicrobials).</i>
62540916	Scicchitano	Australia	✓	
62540937	"_"			
63401166	Dhillon	UK	✓	

General Comments regarding CRF audit:

1. No radiology reports were provided for any of the CRFs for this study. A previous request to provide such reports for one of the other CAP studies (134) was made to the sponsor, and the appropriate documents were forthcoming. It is not necessary to repeat this exercise with this study as well.
2. The comments made above point out some questions raised by the interpretation of the clinical data provided to the sponsor in the CRFs. In general, the evaluability criteria and assignment of outcome categories specified in the Final Study Report appear to have been followed. The cases highlighted in the above comments do raise several points that are worthy of further discussion:
 - cases 50790235 and 53970424 raise the question of the validity of claiming a patient has a dual infection, when one of the putative agents is being diagnosed indirectly (i.e., by serology rather than by culture). How many patients in this study diagnosed with an atypical agent were also ascribed a bacterial pathogen (or pathogens) based on sputum or blood culture results? Of the 25 trovafloxacin-treated patients who were given an atypical diagnosis (as listed in Table 5.3a of the Final Study Report), 10 had one or more respiratory pathogens in the sputum and/or blood. Of these 10, 4 were considered Not Assessable at the EOS evaluation. Of the 27 ceftriaxone-treated subjects, only 5 had positive sputum and/or blood cultures; of these, one was Not Assessable. (See the overall Medical Officer conclusions for the CAP indication for a complete discussion of this issue.)
 - the issue of post-therapy use of additional antimicrobials for 'unrelated' infectious diagnoses (particularly 'exacerbation of COPD' or 'bronchitis') is once again raised by this study. Since such patients were called 'not assessable' at EOS evaluation by the sponsor, use of the Clin Eval at EOS subset will eliminate such patients from consideration. The larger issue is if and when such patients should be considered failures that are retained in this population. From a review of Table 2.4, Appendix 1 of Final Study Report, entitled "Listing of Concomitant Antibiotics Taken During Study", the explanations given for additions or changes to study drug regimen were as follows:

Reason stated in CRF	trovafloxacin	ceftriaxone/cefpodoxime
Inadequate response	15	24
Other respiratory diagnoses	12	8
Discontinued early due to side effects	12	4
Total N (all randomized patients)	218	225

It should be pointed out that the above determinations were made while the study was still blinded, both from the investigators and sponsors point of view. The above breakdown reveals that there were 4 more subjects in the trovafloxacin arm who were given additional or subsequent antimicrobials due to related 'other' respiratory infections. This difference is not considered to be of any consequence in the overall analysis. The last category, early discontinuation due to AEs, appears to be appreciably larger in the trovafloxacin arm. This has been described in other studies, both for this as well as other indications, and will be further discussed in the integrated summary of safety.

3. The comments regarding subject PID 51210141, the Trovan-treated patient with Streptococcus pneumoniae sepsis who was admitted to the ICU two days after being assessed as 'improvement', were related to the sponsor for clarification:

Please take a look at the patient profile and CRF for this subject. I need to follow the logic which categorized this subject as an EOS 'not assessable' by Clin Eval/'cure' by ITT at day 25, when he became bacteremic with Strep pneumo three days following completion of his oral trovan, leading to admission to the ICU. (This event happened 2 days after he had been categorized as an 'improvement'.)

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The following email response was provided by the sponsor:

This patient was discussed in the study report in the section "Subjects with Positive Blood Cultures at Baseline"- as follows:

"One subject (Subject 5121-0141) in the alatrofloxacin/trovafloxacin group had a follow-up culture that showed persistence of *S. pneumoniae* in the blood. A narrative for this subject is presented below:

Subject 5121-0141, a 25-year-old white male randomized to the alatrofloxacin/trovafloxacin treatment group, entered the study with a congenital immunodeficiency associated with recurrent bacterial infections including pneumonia, sinusitis, and bacteremia. This subject had an improvement in pneumonia by Day 10 and a complete resolution by Day 16 (per chest X-ray) and a negative blood culture on Day 3 for *S. pneumoniae*, indicating resolution of bacteremia. On Day 16, however, the subject had recurrent *S. pneumoniae* that was associated with sinusitis. This subject's MIC for *S. pneumoniae* was _____ at baseline and _____ on Day 16."

This patient should not have been enrolled with an immunodeficiency. He had had frequent pneumococcal infections related to this immunodeficiency. The investigator was clear that the pneumonia had resolved but the patient had another pneumococcal infection related to a sinusitis (per the investigator typical of his immunodeficiency). For this reason (another infection not related to the original pneumonia) he was excluded from final assessment.

The manner in which this subject was assessed again points out the inadequacy of using the EOT timepoint as the primary efficacy endpoint. At least when using the EOS Clinically Evaluable subset, such patients are dropped from the analysis. In this particular case, since the patient is noted on page 2 of the CRF to have hypogammaglobulinemia as an underlying diagnosis, it would have been reasonable to say he should not have been enrolled and therefore was a protocol violation. The sponsor, however, chose to include this patient in the analysis. (The Patient Profile shows him to be an Clinically Evaluable EOT 'improvement' by sponsor evaluation; he is 'not assessable' at EOS.)

4. As far as duration of therapy is concerned, table 3.1 of the Final Study Report demonstrates that the median duration of therapy for the comparator arm was 10 days, vis 3 of ceftriaxone and 7 of cefpodoxime. Of note, no patient received longer than 12 days of cefpodoxime. Recall that cefpodoxime (as monotherapy) is labeled for a 14 day course of therapy in the treatment of CAP. It is likely that an initial regimen of ceftriaxone should allow for some shortening of that 14 day regimen, but on average in this study a three day course of ceftriaxone (at a 1.0 gram per day dose) was followed by a seven day course of cefpodoxime. Might this difference contribute to the overall outcome of the study, in which the trovafloxacin arm in the EOS Clinically Evaluable analysis showed a slightly increased (81% vs. 76%) clinical cure rate? Perhaps. However, this difference was not of statistical significance. This dosing issue does not raise any major concerns about the overall applicability of this study to the requested indication.

ADDED TO THE FILE
02/27/2001

D. Medical Officer conclusions regarding CAP study 154-111:

Despite some questions regarding the interpretation and analysis of several individual subjects reviewed above, the medical officer's audit of this study did not reveal any evidence of systematic bias that would call the sponsor's results into question. It does, however, further emphasize the importance of using the EOS Clinically Evaluable population as the relevant group for efficacy analyses. As such, the trovafloxacin/alatrofloxacin subjects had an 81% clinical cure rate, compared to a 76% cure rate for the ceftriaxone/cefepodoxime arm.

The organism-specific eradication rates for this study are provided in the following table:

Pathogen-specific eradication rates at EOS (bacteriologically evaluable subjects)
Study 154-111

Pathogen	#eradicated (eradicated + presumed eradicated)/total	
	Trovan	Ceftriaxone/cefepodoxime
<i>Streptococcus pneumoniae</i>	25/27 (93%)	19/20 (95%)
<i>Haemophilus influenzae</i>	13/15 (87%)	22/24 (92%)
<i>Moraxella catarrhalis</i>	3/3	3/3
<i>Pseudomonas aeruginosa</i>	2/2	0/2
<i>Staphylococcus aureus</i>	3/3	6/7
<i>Chlamydia pneumoniae</i> *	2/2	7/8
<i>Legionella pneumoniae</i> *	7/10	8/10
<i>Mycoplasma pneumoniae</i> *	9/10	4/6

* these numbers include subjects co-infected with routine bacterial pathogens; see overall CAP conclusion for further discussion.

Medical officer review of CAP study 154-112

1. Per applicant

The synopsis of the applicant's final study report for study 112 is presented below; this is taken from the electronic submission, pages 11-16 of the Final Report (found in 8.G.1.A.1 of the NDA, under the 'Clinical Studies Relevant to the Claim Structure' section).

PROTOCOL 154-112: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN (CP-99,219) WITH AMOXYCILLIN AND OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Principal Investigators:

Dr. Alain Wurtz	Dr. P. Williams	Dr. Gerhard Neugart
Dr. Michel Arnould	Dr. J. A. Chapman	Dr. Marlis Pettelkau
Dr. Jean-Francois Bertrand	Dr. D. M. Allin	Dr. Mauersberger
Dr. M. Krigel	Dr. N. H. Patel	Dr. med R. Glanz
Dr. Jean-Marie Letzelter	Dr. D.A.J. Dutchman	Drs. med O Brückner and B. Kemmerich
Dr. Hubert Margraff	Dr. A. G. Thomson	Dr. Jochen Schaller
Dr. Pascal Raucourt	Dr. T.F.M. Cooper	Gerhard Ras, MD
Dr. Marc Steinberger	Dr. J. G. Geater	Dr. Johan Geysler
Dr. M. Aoun	Dr. B. M. Higginson	Dr. J. H. Mynhardt, MD
Dr. B. Le Chevalier	Dr. N. Wilson	Prof. G. S. Fehrsen, MD
Dr. D. Perret	Dr. M.J.H. Pimm	Dr. D. Verstraate
Dr. P. Veyssier	Dr. P. McGarry	Dr. Philippe Gris
Dr. G. Vienne	Dr. B. O'Doherty	Dr. Karine Laurent
Professor Patri	Dr. M. Canning	Dr. Daniel Rozen
Christoph Pison, MD	Dr. J. Casey	John Upchurch, MD
Dr. Daniel Piperno	Dr. B. Crowley	Marvin Bittner, MD
Dr. Bsaibes	Dr. B. Cuddihy	Lala Dunbar, MD
M. J. Callander, MD	Dr. D. Forde	Richard Honsinger, MD
Dr. Adams Strump	Dr. Hanson	Thomas Decker, MD
Dr. A. Burton	Dr. L. McEntee	David Schreck, MD
Dr. I. D. Caldwell	Dr. McGinnity	
Dr. B. Cross	Dr. T. McMahan	
Dr. H. A. Duncalf	Dr. Niall Walsh	
Dr. J. A. Hughes	Dr. Philip Wiehe	
Dr. S. Hutchison	Dr. M. B. McDonnell	
Dr. Kesson	Dr. P. McDonagh	
Dr. P. N. Kulkarni	Dr. P. Quinn	
Dr. T. G. Maxwell	Dr. E. Hartman	
Dr. J. P. Nagle	Dr. D. Dwyer	
Dr. R. F. Quigley	Dr. O. Muller and Dr. E. Klingelhofer	
Dr. R. N. Snook	Dr. Gerhard Orlovius	
Dr. D. Sutherland	Dr. Borrás	
Dr. Thomson	Dr. Luckau	

Study Publication: Not Applicable

Study Dates: 9 December 1994 - 12 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to amoxicillin, with optional erythromycin, for the treatment of subjects with community acquired pneumonia.

Study Design: Study 154-112 was a randomized, multicenter, double-blind, double-dummy trial of trovafloxacin administered orally for 7 to 10 days of total treatment versus amoxicillin administered orally for 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

	Evaluation Groups:			
	Trovafloxacin (200 mg/day)		Amoxicillin (500 mg TID)	
Entered Study ^a	151		152	
All Treated	150	(100%)	152	(100%)
Completed Treatment	136	(91%)	139	(91%)
Completed Study	140	(93%)	136	(89%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	148	(98%)	149	(98%)
Clinically Evaluable ^b	138	(91%)	141	(93%)
Bacteriologically Intent-to-Treat	60	(40%)	55	(36%)
Bacteriologically Evaluable	55	(36%)	52	(34%)
Assessed for Safety				
Adverse Events	150	(100%)	152	(100%)
Laboratory Tests	144	(96%)	148	(97%)

a Subjects who were randomized.
b Clinically evaluable at end of treatment.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia were eligible to participate in this study.

Drug Administration: Study drug was in the form of tablets (trovafloxacin) and capsules (amoxicillin), which were packaged in blister cards and/or bottles, using a double-dummy technique to maintain blinding.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Statistical Methods: Confidence intervals (95%) for differences in clinical success (no signs or symptoms of a primary infection) rates between treatments were calculated using the normal approximation method as the primary means to compare treatment groups. Safety results including adverse events, laboratory abnormalities, and vital signs were analyzed using descriptive statistics.

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Efficacy Results: Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment supported equivalence of the two treatment regimens for clinically evaluable (trovafloxacin: 93%, 128/137; amoxicillin: 91%, 128/140 [CI: -4.2, 8.2]) and intent-to-treat (trovafloxacin: 90%, 132/147; amoxicillin: 88%, 130/148 [CI: -5.2, 9.1]) subjects. Sponsor-defined pathogen eradication rates at the end of treatment for the most frequently isolated pathogens (*H. influenzae* and *S. pneumoniae*) were comparable between the two treatment groups for bacteriologically evaluable and intent-to-treat subjects. A trend towards higher pathogen eradication rates for *H. influenzae* was noted for subjects in the trovafloxacin group compared to subjects in the amoxicillin group at the end of treatment and end of study. Among bacteriologically intent-to-treat subjects, two in the trovafloxacin group had positive blood cultures for *S. pneumoniae* at baseline and at least one follow-up blood culture during the study. The post-baseline pathogen outcome for these pathogens was eradication. In addition, these subjects were clinically improved or cured at the end of treatment and end of study.

Sponsor-defined clinical response rates for clinically evaluable and intent-to-treat subjects and pathogen eradication rates for bacteriologically evaluable and intent-to-treat subjects are presented in the following tables.

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A Summary of the Sponsor's Assessment of Clinical Response				
(Clinically Evaluable Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=138)	Amoxicillin 500 mg TID (N=141)	Trovafloxacin 200 mg (N=122)	Amoxicillin 500 mg TID (N=127)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	137 (100%)	140 (100%)	122 (100%)	127 (100%)
Success (Cure + Improvement)	128 (93%)	128 (91%)	107 (88%)	110 (87%)
Distribution of Clinical Response:				
Cure	71 (52%)	75 (54%)	98 (80%)	97 (76%)
Improvement	57 (42%)	53 (38%)	9 (7%)	13 (10%)
Failure	9 (7%)	12 (9%)	9 (7%)	12 (9%)
Relapse	Not Applicable	Not Applicable	6 (5%)	5 (4%)
(Clinically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Trovafloxacin 200 mg (N=148)	Amoxicillin 500 mg TID (N=149)	Trovafloxacin 200 mg (N=148)	Amoxicillin 500 mg TID (N=149)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	147 (100%)	148 (100%)	148 (100%)	149 (100%)
Success (Cure + Improvement)	132 (90%)	130 (88%)	126 (85%)	126 (85%)
Distribution of Clinical Response:				
Cure	74 (50%)	75 (51%)	113 (76%)	112 (75%)
Improvement	58 (39%)	55 (37%)	13 (9%)	14 (9%)
Failure	15 (10%)	18 (12%)	16 (11%)	18 (12%)
Relapse	Not Applicable	Not Applicable	6 (4%)	5 (3%)
A Summary of the Sponsor's Assessment of Pathogen Outcome				
Sponsor-Defined Eradication Rates For the Most Frequently Isolated Baseline Pathogens ^a				
(Bacteriologically Evaluable Subjects)				
	End of Treatment		End of Study	
Pathogen	Trovafloxacin 200 mg (N=55)	Amoxicillin 500 mg TID (N=52)	Trovafloxacin 200 mg (N=53)	Amoxicillin 500 mg TID (N=44)
Number and Percentage (%) of Pathogens				
<i>H. influenzae</i>	21/21 (100%)	17/20 (85%)	19/20 (95%)	10/14 (71%)
<i>S. pneumoniae</i>	21/21 (100%)	17/19 (89%)	20/21 (95%)	15/18 (83%)
<i>M. catarrhalis</i>	5/5	3/3	4/4	3/3
<i>M. pneumoniae</i>	4/5	2/3	4/5	1/2
<i>C. pneumoniae</i>	1/1	4/4	1/1	2/2
Sponsor-Defined Eradication Rates For the Most Frequently Isolated Baseline Pathogens ^a				
(Bacteriologically Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
Pathogen	Trovafloxacin 200 mg (N=60)	Amoxicillin 500 mg TID (N=55)	Trovafloxacin 200 mg (N=60)	Amoxicillin 500 mg TID (N=55)
Number and Percentage (%) of Pathogens				
<i>H. influenzae</i>	22/23 (96%)	18/21 (86%)	20/21 (95%)	11/16 (69%)
<i>S. pneumoniae</i>	22/22 (100%)	18/21 (86%)	21/22 (95%)	15/20 (75%)
<i>M. catarrhalis</i>	5/5	3/3	5/5	3/3
<i>C. pneumoniae</i>	1/1	4/4	1/1	4/4
<i>M. pneumoniae</i>	5/6	2/3	5/6	2/3
^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (<i>C. pneumoniae</i> and <i>M. pneumoniae</i>); percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline. Ref.: Tables 5.1.1, 5.1.2, 5.4.1, and 5.4.2				

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events, and clinically significant laboratory values is presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Trovafloxacin (200 mg)		Amoxicillin (500 mg TID)	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	52/150	(35%)	44/152	(29%)
Treatment-Related Adverse Events	24/150	(16%)	22/152	(14%)
Discontinuations From Treatment Due to Adverse Events ^a	9/150	(6%)	7/152	(5%)
Clinically Significant Laboratory Values	49/144	(34%)	44/148	(30%)

a Five (5) and two discontinuations in the trovafloxacin and amoxicillin treatment groups, respectively, were treatment-related.
Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, 7.1, and Appendix I, Table 3.1

Twelve (12) subjects in the trovafloxacin group and 11 subjects in the amoxicillin group had serious adverse events. One subject in the trovafloxacin group had serious adverse events (sweating, faintness, vomiting, loss of consciousness, and allergic conjunctivitis) that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or concomitant treatment. Five (5) subjects in the trovafloxacin group and seven subjects in the amoxicillin group died during this study. None of the deaths was considered to be related to study drug.

Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxicillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were statistically equivalent for the sponsor-defined clinical success rates at the end of treatment for both intent-to-treat and evaluable subjects. Sponsor-defined eradication rates were comparable between the two treatment groups at the end of treatment for baseline isolates of *S. pneumoniae* and *H. influenzae*. All five trovafloxacin subjects who had penicillin-resistant (MIC ≥ 0.1 $\mu\text{g/mL}$) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study. One subject in the amoxicillin group had penicillin-resistant *S. pneumoniae* isolated at baseline and was a clinical failure at the end of treatment and end of study. Of the subjects with a clinical response of failure or relapse, none in the trovafloxacin group and two in the amoxicillin group had an outcome of persistence confirmed by microbiology. The percentage of subjects discontinued from treatment due to adverse events was 6% in the trovafloxacin group and 5% in the amoxicillin group. The overall percentage of all and treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the amoxicillin group (35% and 16% versus 29% and 14%, respectively). The most commonly reported treatment-related adverse events were

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dizziness (3%) and nausea (3%) for subjects in the trovafloxacin group and diarrhea (5%) and nausea (3%) for subjects in the amoxicillin group.

2. Per medical officer.

This study was designed and conducted in a manner similar to that of study 134. The study design and execution is consistent with IDSA guidelines for the design and conduct of clinical trials seeking the Community-Acquired Pneumonia indication.

The comparator regimen, amoxicillin ± erythromycin, does not provide coverage for beta-lactamase positive strains of organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis*; thus it is not surprising to see the comparator arm of this study showing reduced efficacy against these organisms. General recommendations for therapy of this disease in the US would call for an antimicrobial agent (or combination of antimicrobial with a betalactamase inhibitor) that has activity against such strains. This issue will need to be taken into account if the sponsor desires to make a claim of superiority to this comparator regimen.

Although a total of 86 investigators were listed as contributing to this study, only 45 of them eventually contributed enrolled subjects. Overall, the distribution of enrolled patients by geographic location was as follows:

Country	# enrolling investigators	# subjects enrolled
USA	5	23
UK	13	95
Ireland	12	118
France	7	27
Germany	3	20
S. Africa	4	19
Belgium	1	1
TOTAL	45	303

It can thus be seen that this study has disproportionate representation from Ireland and the UK, from which two countries came 213 out of the 303 enrollees. This relative paucity of enrollees from southern Europe and South Africa is a major reason why there were not as many isolates of penicillin-resistant *Streptococcus pneumoniae* as might otherwise have been.

The following ten investigators were the leading contributors to this study:

Investigator	ID#	location	N	#subinvestigators	subjects per investigator
O'Doherty	5294	Ireland	37	1	18.5
Maxwell	5342	UK	26	0	26.0
Quinn	5809	Ireland	23	0	23.0
McGarry	5292	Ireland	13	0	13.0
Allin	5675	UK	13	0	13.0
Dutchman	5744	UK	13	0	13.0
Thompson	5745	UK	13	0	13.0
Honsicker	5556	NM, USA	12	2	4.0
Geyser	6313	S. Africa	12	0	12.0
Veyssier	5365	France	11	0	11.0

The number of enrollees per investigator in this study is much higher than was seen in study 134. This is because the European investigators are all (with a rare exception) listed as the sole investigator at that study site, as opposed to the American investigators in study 134 who often listed multiple (as many as 26) subinvestigators. This may be a reflection of practice patterns (solo practitioner vs. large group practice) in Europe as opposed to the USA, more than anything else.

CRF and Patient Profile audit.

A random listing of 10% of the PIDs from study 112 was generated by the reviewing statistician. These 30 CRFs were carefully compared with the data as presented in the sponsor-generated Patient Profiles, to verify the authenticity of the data from which the sponsor's data tables were generated.

Amoxicillin ± erythromycin patients

PID	Investigator	Location	OK?	Comments
52940036	O'Doherty	Ireland	✓	
52940246	"_"		✓	
52940269	"_"		✓	
53590275	Walsh	Ireland	✓	22 year old; no erythromycin given
53650329	Veyssier	France	•	no CRFs found in file
55560921	Honsicker	NM, USA	✓	Called clinical cure; received amoxicillin alone (without additional erythromycin). Had 4-fold rise in <i>Chlamydia pneumoniae</i> IgA and thus diagnosed as clinical and bacteriologic cure of <i>Chlamydia pneumoniae</i> but never received antimicrobial active against this infectious agent.
56750487	Allin	UK	✓	
56750604	"_"		✓	Radiologist report stamped "Drug trial"
57440102	Dutchman	UK	✓	
57740901	Decker	NH, USA	✓	
58130021	Higginson	UK	✓	Baseline CXR read as "probable minimal change? Infective left lung base" and in follow-up investigator writes "I suspect that initial appearance on balance did not represent active infection."
63130121	Geyser	South Africa	✓	Blood and sputum culture + for <i>Strep pneumoniae</i> ; penicillin MIC 0.06.
64030133	Fehrsen	South Africa	✓	Sponsor called patient unassessable at EOS because of single dose administration of metronidazole for trichomoniasis; patient clinically cured on amoxicillin alone, despite diagnosis of <i>Chlamydia pneumoniae</i> by 4-fold rise in serum IgG.

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Trovafloxacin patients

PID	Investigator	Location	OK?	Comments
52920563	McGarry	Ireland	✓	
52940034	O'Doherty	Ireland	✓	<i>called clinically and bacteriologically evaluable and cured by both sponsor and investigator; however, f/u CXR report states "Despite the clinical symptoms, the remainder of the lung fields remain clear."</i>
52940271	"—"		✓	
52940666	"—"		✓	<i>Baseline CXR read as "pleural shadowing in right cardiophrenic angle; possibly acute, possibly chronic." Patient experienced nausea/vomiting/headache on day 2 of therapy, called unrelated to study drug by investigator and ascribed to migraines despite no listing of migraines in subject's past medical history at entry.</i>
53420070	Maxwell	UK	✓	<i>Specific mention of "inclusion in drug trial" on baseline radiology report.</i>
53650354	Veyssier	France	•	<i>Called clinically evaluable cure by ITT at EOS by sponsor at day 34, despite having been given ofloxacin from days 30 to 36 for 'prostatitis', and clamoxyl (amoxicillin) from days 24 to 28 for 'urinary tract infection' (Appropriately called 'not assessable' by sponsor at EOS.) Recall that this NDA seeks prostatitis and UTI indications for trovafloxacin. When reviewing the CRFs for this investigator, all the CRFs for this study site were signed by a Dr. Cevallos rather than the listed investigator. There are no co-investigators listed in Appendix 2 of the study report for study 112, and a full-text search of the electronic submission failed to reveal an entry for a Dr. Cevallos. Thus it would appear that this Dr. Cevallos is not authorized to sign these documents as an investigator, and therefore the evaluability of all subjects enrolled at this site (N = 11) is questionable. As can be seen in Attachment 1, which is the complete CRF for one of these patients, there are multiple crossouts and other changes that make review of the CRF extremely difficult.</i>
55000933	Dunbar	LA, USA	✓	<i>Patient given 10 days of outpatient therapy for blood culture + Strep pneumoniae pneumonia but self-discontinued after 7 days. Only AE reported as left leg edema that was judged unrelated to study medication by investigator (despite fact that patient self-discontinued study medication at that point). Patient well at EOS day 32.</i>
55560907	Honsicker	NM, USA	✓	<i>Reading of baseline CXR: "Indistinctness of left hemidiaphragm could represent an early infiltrate."</i>
55560922	"—"		✓	<i>Baseline CXR read as "There is a chronic infiltrate in both the right middle and upper lobes" yet f/u film on day 29 called "completely resolved".</i>
55560928	"—"		•	<i>This subject was treated with 10 days of oral trovafloxacin, but was admitted to hospital for the first four days. (This is not a protocol violation per se, though the reason for admission was not clear from the CRFs.) Called clinically unevaluable by sponsor because patient received Keflex for four days immediately following trovafloxacin therapy for treatment of a superficial phlebitis of the left hand, secondary to intravenous therapy (?fluids) given during hospitalization. This is interesting given that the trovafloxacin NDA also seeks a Skin and Soft Tissue Infection indication. The CRFs also document that the patient's sputum Gram stain was of good quality, revealing 2+ GPC's, and the culture grew out Staph aureus. The microbiology results in the Patient Profile only show "normal/mixed flora" as the result. Overall, I agree with the sponsor's decision to call this subject unevaluable. However, the discrepancy between Patient Profile and CRF is disconcerting.</i>

Trovafloxacin patients (continued)

PID	Investigator	Location	OK?	Comments
56750486	Allin	UK	✓	<i>Baseline CXR: "A little increased shadowing suggestive of increased pulmonary edema... in keeping with superadded inflammatory changes" and is stamped "DRUG TRIAL". In keeping with this finding, the two f/u films both show no change, confirming that trovafloxacin has limited utility as an afterload reducing agent. Nonetheless this 89 year old man received 7 days of trovafloxacin, was called 'improved' (based on clinical symptoms, which the CRF states did improve), and thus qualifies as a 'clinical success'.</i>
56890081	Patel	UK	✓	
57440103	Dutchman	UK	✓	
58600421	Mauersberger	Germany	✓	
63430483	Wilson	UK	•	<i>Although this patient appeared to be accurately presented in the patient profile, compared to the CRFs, I found it disturbing that the patient had been on amoxicillin for 6 days, finishing a bit over 72 hours prior to study entry (thus meeting protocol entry criteria). Presumably this therapy had not produced an adequate response, yet the investigator felt comfortable entering him into a randomized study in which the subject presumably could have been continued on this inadequate therapy. It is furthermore disturbing to see that the subject's sputum grew out a beta lactamase positive Haemophilus influenzae (thus explaining the poor initial response to amoxicillin prior to study entry), yet the subject was continued on 'blinded' therapy which, fortunately for the patient, just so happened to be trovafloxacin. Such cases lead the medical officer to wonder about the integrity of the study blind, at the very least for this particular investigator and, inevitably, to some degree for the study as a whole.</i>
63430611	"—"		•	<i>Selected language from the baseline CXR report for this 72 year old study subject: "Main diagnosis is CHF... intercurrent infection cannot be excluded... follow-up film post-diuretics is recommended." The 'entry' CXR was taken four days prior to study entry. The sponsor called this patient an EOT improvement (in accord with the investigator) but an EOS 'not assessable' because the patient was given ciprofloxacin from day 26 to 33 for "other further chest infection". The sponsor did change the investigator's EOS evaluation of 'improvement' to 'failure' for the ITT analysis. If the sponsor considers this subject to be clinically evaluable (which is questionable, given the dubious nature of the baseline CXR), then the subject should be an evaluable EOS failure because of the need for additional antimicrobial (this same investigator [6343] as the previous subject quite brilliantly selecting ciprofloxacin in this instance, following an apparent failure of 'blinded' therapy with either a supposedly superior quinolone or amoxicillin). Interestingly, this investigator had a different patient (6343 0482) discounted by the sponsor for a protocol violation ("baseline CXR done > 48 hours prior to administration of study drug") but the sponsor did not exclude patient 0611 even though the same exclusionary criteria should apply.</i>
64610585	Pimm	UK	✓	<i>Appropriately called clinical failure at EOS. Baseline CXR report bears legend "ICON Study", indicating that radiologist was aware of patient's status as drug study participant.</i>

Comments:

1. This study, unlike the other CAP studies in the electronic submission of the NDA, included all radiology reports of CXRs taken at entry and at follow-up. Review of these initial radiology reports was helpful for several reasons: it allowed for verification of the handwritten interpretation that the investigator (or study nurse) would enter onto the appropriate page of the CRF; it allowed the medical officer to see that

- a fair number of patients were enrolled with questionable or 'soft call' infiltrates; and it demonstrated which of the investigators were in situations in which the status of the patient as a drug study participant was plainly stamped on the radiology report. This latter issue was seen in a small minority of CRFs, but is nonetheless important because it may bias the radiologist towards calling something an infiltrate, thus allowing the subject to be entered into the study (and the investigator to get reimbursed for same). This type of bias, if real, would presumably distribute such patients evenly between the two treatment arms.
2. The great majority of audited charts showed patients receiving 10 days of therapy. In fact, Table 3.1 of the final study report for study 112 shows that of the 150 patients randomized to trovafloxacin, 94 received 10 or 11 days of therapy whereas 39 received 7 days of therapy.
 3. Study site 5365 is problematic, given that the name of the supposed investigator, Dr. Pierre Veyssier, appears nowhere on the CRFs. The printed name and signature on all CRFs for this study site are for a Dr. Cevallos. There is no listing for this person anywhere in the electronic submission, nor is there a CV for anyone other than Dr. Veyssier (a one-page CV) under center 5365. The results from this center should thus be disregarded. Eleven subjects were enrolled, of which 9 were considered clinically evaluable and one was clinically evaluable at end of study, with a baseline pathogen. There are seven sets of CRFs included in the CRF Casebook section of the NDA; thus, four of the enrolled subjects have no documentation whatsoever. Attachment 1 to this review demonstrates the condition of one of these CRFs. Also included (the last 2 pages of this attachment) is the "Baseline Chest X-Ray Interpretation" from an additional two subjects from this center. These two sheets, neither of which even identify the subject by name or PID number, are handwritten replicas of the Pfizer CRF page of the same title. Overall, this study site demonstrates poor data collection, multiple strikeouts/corrections/changes, and a total lack of any signature by the investigator of record.
 4. The total number of subjects contributed to the study by investigator 5365 was relatively small, and the total number of bacteriologically evaluable subjects at EOS was only one; therefore, removal of all these subjects from consideration will not fundamentally change the sponsor's conclusions from this study.
 5. There was only one CRO responsible for the monitoring of all the European and American study sites for study 112:
The findings listed above for study site 5365, along with the other Medical Officer comments from the CRF audit, appear to demonstrate a worrisome lack of attention to detail; if this is representative of the oversight provided by this CRO to the remaining investigator sites, then this study is fundamentally flawed and should not be considered supportive of the indication. The audit of the remaining CRFs did not appear to demonstrate the same degree of inept CRO oversight, although it did raise a question regarding the integrity of the study blind.
 6. As noted in the CRF audit, a patient with beta-lactamase positive H. flu who was previously treated with 6 days of amoxicillin was entered into the study, only to randomize to the trovafloxacin arm. This leads to the question: how many subjects in this study had a beta-lactamase positive isolate at baseline, and of these, how many randomized to trovafloxacin vs. amoxicillin? Table 18, Appendix 5 of the final study report for study 112 lists all microbiology isolates, including whether they were beta-lactamase positive or negative. A review of this table reveals the following:

Total number of baseline microbiology isolates characterized by beta-lactamase production, study 112

	<i>H. influenzae</i>		<i>M. catarrhalis</i>		<i>H. parainfluenzae</i>	
	β -lac +	β -lac -	β -lac +	β -lac -	β -lac +	β -lac -
trova	3	20	4	1	1	3
amox	3	21	2	1	0	5

Thus it can be seen that the beta-lactamase positive isolates in this study were fairly evenly distributed between the two treatment arms. This provides no evidence that the study blind was compromised.

7. Although the sponsor's summary and conclusions (page 5 of this review, highlighted) states that

All five trovafloxacin subjects who had penicillin-resistant (MIC ≥ 0.1 $\mu\text{g/mL}$) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study. One subject in the amoxicillin group had penicillin-resistant *S. pneumoniae* isolated at baseline and was a clinical failure at the end of treatment and end of study.

a review of Table 18, Appendix 5 of the study report reveals that of the trovafloxacin subjects with 'resistant' pneumococcal isolates recorded, eight had MICs of 0.12 $\mu\text{g/mL}$; of these, one isolate grew on follow-up sputum culture on day 32 (b)(4) and another of these isolates was cultured from a day 11 sputum specimen (b)(4). An additional four subjects had MICs of 0.25 $\mu\text{g/mL}$ recorded; of these, one (b)(4) was collected on day 4 of trovafloxacin therapy. It is unclear how the sponsor arrived at the assertion quoted above, but nonetheless there is a paucity of clinical and microbiological data in this study upon which to make any statement regarding the efficacy of trovafloxacin in the treatment of community-acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* (which to the best of my knowledge means an MIC of > 1.0 $\mu\text{g/mL}$).

Medical officer conclusions regarding study 112:

With the exception of one study site, study 112 appears to have been conducted in an adequate and well-controlled manner, and demonstrates the equivalence of trovafloxacin and amoxicillin in the treatment of community-acquired pneumonia. If the rate of beta lactamase producing strains had been equivalent to what is currently seen in the United States, the amoxicillin arm would probably have done substantially worse than the trovafloxacin arm; this was not the case.

No conclusions regarding activity of trovafloxacin against penicillin-resistant strains of *Streptococcus pneumoniae* can be reached from this study.

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Overall Medical Officer conclusions for Community Acquired Pneumonia indication

A. Clinical results

1. Oral studies (154-112, 154-134)

Both of these studies were well-designed double blind, double-dummy studies of large size and geographic distribution. Study 134 was predominantly domestic. It utilized a BID comparator that has an approved indication of pneumonia, including pneumonia caused by at least one 'atypical' agent (Mycoplasma pneumoniae). (NB: Clarithromycin is not labeled for pneumonia due to Legionella pneumophila or Chlamydia pneumoniae.) Study 112 was an international study, using a comparator that was somewhat less efficacious (amoxicillin ± erythromycin). It, too, was double-blind, double-dummy in design; however, given that amoxicillin is a TID drug, and erythromycin is a QID drug, the subjects in this study who were judged to require the addition of erythromycin (or placebo) to their regimen were taking a total of 16 tablets and/or capsules daily. This was presumably daunting to even the most motivated of study enrollees. (Such concerns over compliance would be shared equally between the two randomization arms.)

Combined clinical efficacy for these two studies at EOS in the Clinically Evaluable subset is presented in the following table:

Study	Clinical Outcome at End of Study (EOS) timepoint Clinically Evaluable subset		
	Cure	Improvement	Failure /Relapse
Study 112 amoxicillin ± erythromycin	112/149 (75%)	14/149 (9%)	23/149 (16%)
	trovafloxacin	113/148 (76%)	13/148 (9%)
Study 134 clarithromycin	113/144 (78%)	11/144 (8%)	20/144 (14%)
	trovafloxacin	108/135 (80%)	12/135 (9%)

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Thus it can be seen that the two oral comparative studies demonstrate clinical equivalence to two different approved comparative regimens. In reviewing these two studies, the medical officer was troubled to find that the radiologists' interpretation of the entry chest x-rays was not included in the original set of CRF data. Upon request, the sponsor was able to provide the appropriate entry radiology reports for all audited patients. (These reports were included in the CRFs for study 112 patients.) Otherwise, the medical officer's audit of these studies essentially confirmed the interpretations of patient outcomes provided in the Patient Profiles compiled by the sponsor. There were some questions regarding the clinical course and outcome of certain individual patients, but the overall conclusion was that the sponsor's Clinically Evaluable at EOS subset was valid.

2. IV → oral studies.

Studies 110 and 111 were the two large, phase 3, multicenter studies conducted to evaluate the efficacy of alatrofloxacin and trovafloxacin, given sequentially, in the treatment of CAP. As with the above oral only studies, these two studies were designed as double blind, double-dummy trials using comparator regimens that had been previously discussed with and agreed to by DAIDP during end-of-phase-2 deliberations. Once again, one of these studies (study 110) used a regimen that has no labeled activity against Legionella pneumophila, whereas the other allowed the addition of optional erythromycin (or placebo) if the investigator suspected an atypical agent in the differential diagnosis. As with the oral only studies, one of these were predominantly domestic (study 110 included 53 South African patients and 9 Canadian patients out of a total of 396 randomized), whereas the other (study 111) was truly international (including France, Spain, UK, and Australia).

One would assume that the patients in these two studies were more severely ill than those in the oral only studies. The protocols did, after all, state that in order to be eligible for enrollment, subjects should be ill enough to be "... requiring hospitalization and initial intravenous therapy". However, these two protocols make no attempt to prospectively identify characteristics that easily differentiate between the patients enrolled in these IV to oral studies, as compared to those enrolled in the oral only studies.

The sponsor presents the following two tables in discussing the underlying severity of disease in the oral only vs. IV to oral patients:

Table 5: Summary of Baseline Characteristics and Co-Morbidity at Baseline (Clinical Intent-to-Treat Subjects - CAP, Oral)				
Baseline Characteristic	Trovafloxacin (N=361)		Comparator Agents (N=367)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	52.3		52.2	
Minimum	16		16	
Maximum	90		95	
16-44	144	(40%)	144	(39%)
45-64	104	(29%)	107	(29%)
65-74	60	(17%)	70	(19%)
≥75	53	(15%)	46	(13%)
Sex				
Male	198	(55%)	181	(49%)
Female	163	(45%)	186	(51%)
Smokers	118	(33%)	122	(33%)
Co-morbidity				
Number of Subjects With at Least One Co-morbidity	125	(35%)	120	(33%)
Chronic Obstructive Lung Disease	68	(19%)	75	(20%)
Asthma	35	(10%)	36	(10%)
Congestive Heart Failure	23	(6%)	24	(7%)
Diabetes Mellitus	29	(8%)	18	(5%)
Hepatic Disease	5	(1%)	6	(2%)
Impaired Renal Function	6	(2%)	3	(<1%)

Ref.: Tables H.4.6.1.2, H.4.6.3

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**Table 9: Summary of Baseline Characteristics, Co-Morbidity and Risk Factors at Baseline
(Clinical Intent-to-Treat Subjects - CAP, IV/PO)**

Baseline Characteristic	Alatrofloxacin/Trovafloxacin (N=408)		Comparator Agents (N=422)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	57.4		58.2	
Minimum	16		17	
Maximum	94		95	
16-44	120	(29%)	119	(28%)
45-64	111	(27%)	109	(26%)
65-74	87	(21%)	99	(23%)
≥75	90	(22%)	95	(23%)
Sex				
Male	240	(59%)	264	(63%)
Female	168	(41%)	158	(37%)
Smokers	150	(37%)	162	(38%)
Co-morbidity				
Number of Subjects With at Least One Co-morbidity	245	(60%)	243	(58%)
Chronic Obstructive Lung Disease	134	(33%)	153	(36%)
Congestive Heart Failure	69	(17%)	63	(15%)
Diabetes Mellitus	69	(17%)	55	(13%)
Asthma	63	(15%)	55	(13%)
Impaired Renal Function	33	(8%)	22	(5%)
Hepatic Disease	13	(3%)	15	(4%)
Risk Factors				
Pleuritic Chest Pain	251/405	(62%)	249/420	(59%)
Fever (>38°C)	227/404	(56%)	235/420	(56%)
Respiration Rate ≥24/min	183/395	(46%)	200/412	(49%)
Severe Cough	107/405	(26%)	106/420	(25%)
Severe Dyspnea	95/405	(23%)	98/420	(23%)
Hypothermia (<37°C)	67/403	(17%)	89/417	(21%)
Bacteremia ^a	41/389 ^b	(11%)	38/397 ^c	(10%)
Hypotension (Systolic ≤90mmHg)	17/405	(4%)	14/420	(3%)
Leukopenia (WBC <4000)	6/382	(2%)	7/395	(2%)
a Includes all subjects with any organism isolated from a baseline blood culture. b Includes 28 <i>S. pneumoniae</i> c Includes 18 <i>S. pneumoniae</i> Ref.: Tables H.4.7.1.2, H.4.7.3, H.4.7.3.1, and H.4.7.4				

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As can be seen from these two tables, the patients in the oral only studies generally had less 'co-morbidity' than those in the IV → oral studies (35% vs. 60%). There are no data collected however which speak to severity of illness in the oral studies, as there are presented above for the IV studies under the subheading 'Risk factors'. (What, precisely, these 'risk factors' put the patient at risk for is not defined in the text of the Integrated Summary of Efficacy.) These parameters should be compared with the American Thoracic Society definition of 'severe' community acquired pneumonia, which is defined as a new infiltrate in the presence of one or more of the following: admission respiratory rate of > 35/min; need for mechanical ventilation; chest radiograph indicating a 50% increase in the infiltrate over baseline, or bilateral multilobar involvement; need for vasopressors; severe lung injury; urine output < 20 cc/hr; or acute renal failure.

These data do not support wording that would indicate that trovafloxacin has been studied in 'severe' community-acquired pneumonia.

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The following table presents the clinical outcomes for the Clinically Evaluable subset at the EOS timepoint for both IV→ oral studies submitted:

Study	Clinical Outcome at End of Study (EOS) timepoint Clinically Evaluable subset		
	Cure	Improvement	Failure/Relapse
Study 110			
ciprofloxacin/ ampicillin	130/165 (79%)	15/165 (9%)	20/165 (12%)
alatrofloxacin/ trovafloxacin	106/140 (76%)	14/140 (10%)	20/140 (14%)
Study 111			
ceftioxone/ cefpodoxime ± erythromycin	128/169 (76%)	10/169 (6%)	31/169 (18%)
alatrofloxacin/ trovafloxacin	128/159 (81%)	8/159 (5%)	23/159 (14%)

As can be seen, the overall cure rates are comparable between trovafloxacin and both comparator arms. The slightly higher rates for the comparator in study 110 and the trovafloxacin arm in study 111 are not of statistical significance.

In the Medical Officer's audit of CRFs from these two studies, several questions were raised concerning the interpretation of individual enrollees in both studies. None of the CRF audits revealed a pattern of outcome assignment that could be taken as evidence of bias. It is therefore concluded that these results are a valid reflection of the clinical efficacy of trovafloxacin in the setting of community acquired pneumonia.

B. Pathogen-specific results

1. 'Routine' respiratory pathogens

The combined results for the eradication rates for identified pathogens in the four studies collected above are presented in the following table. This table includes routine bacterial pathogens only; the discussion of atypical agents follows:

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**Eradication Rates for Identified Pathogens
Clinically and Bacteriologically Evaluable Subjects*
Community Acquired Pneumonia
(According to M-)
Study number, N**

Pathogen	Study number, N				Totals N = 241
	Study 110 N = 64	Study 111 N = 68	Study 112 N = 53	Study 134 N = 56	
<i>Streptococcus pneumoniae</i>	30/33	25/27	20/21	11/12	86/93 (92%)
<i>Haemophilus influenzae</i>	14/16	13/15	19/20	10/10	57/61 (93%)
<i>Moraxella catarrhalis</i>		3/3	4/4		7/7
<i>Klebsiella pneumoniae</i>	1/1				1/1
<i>Pseudomonas aeruginosa</i>		2/2			2/2
<i>Staphylococcus aureus</i>	3/3	3/3			6/6

* A subject could have more than one pathogen at baseline.

It is clear from this table that the sponsor has accumulated adequate numbers of *Streptococcus pneumoniae* and *Haemophilus influenzae* to warrant approval. It is also clear that the numbers of the remaining organisms are relatively scanty. These numbers are augmented somewhat if the results of the phase 2 study 154-102 are taken into consideration. This dose-ranging study did include a trovafloxacin arm that was dosed at the requested regimen (200 mg qd for 10 days), and was of a randomized, double-blinded design. The Final Study Report for this study includes the following numbers of pathogens in the clinically and bacteriologically evaluable subset of patients at EOS:

**Pathogens eradicated/pathogens isolated
Clinically and Bacteriologically Evaluable Patients at EOS
Study 102**

<i>Streptococcus pneumoniae</i>	2/2
<i>Haemophilus influenzae</i>	4/5
<i>Moraxella catarrhalis</i>	2/2
<i>Klebsiella pneumoniae</i>	6/6

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Even if these additional isolates are included in the tabulation, one is still left with a total of 9 *Moraxella catarrhalis*, 7 *Klebsiella pneumoniae*, 2 *Pseudomonas aeruginosa*, and 6 *Staphylococcus aureus* isolates.

The Divisional Points to Consider document addresses the issue of organism-specific labeling as follows:

- the requested organism must be generally considered to be pathogenic in that indication;

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- the requested organism must represent at least 10% of the evaluable cases OR 10 total (whichever is higher); and
- the eradication rate must be clinically acceptable

When considering other organisms for labeling when they do not meet the '10% rule', the following additional caveats are to be taken into consideration:

- the *in vitro* activity of the drug against the organism is at least similar to that of other pathogens more substantially evaluated in clinical trials;
- the mechanism of resistance is similar to that of other pathogens more substantially evaluated in clinical trials;
- no scientific data exist suggesting differences in the management of infections due to these pathogens more substantially

It is also reasonable to consider related indications that have been studied in separate trials; for example, if there were sufficient evaluable numbers of *Klebsiella pneumoniae* from the nosocomial pneumonia studies (and an acceptable rate of clinical response/bacteriologic eradication), then it might be reasonable to grant this organism in the CAP indication despite the fact that there were only 7 evaluable patients with this organism among the five clinical studies submitted. This, however, is not the case (see the Nosocomial Pneumonia review by Dr. Alivasatos). Since CAP patients with pneumonia due to *Klebsiella pneumoniae* are at risk of developing severe disease, it would seem imprudent to label trovafloxacin for the treatment of this organism with such a relative paucity of accumulated experience in either the CAP or the Nosocomial Pneumonia indications

In the course of discussing the numbers of individual pathogens that were accrued from these studies, the sponsor's numbers were found to be discrepant with those cited above. As the above numbers were taken from the sponsor's own summary tables, it was unclear initially how such discrepancies came about. Following discussion with the sponsor, it was ascertained that the summary tables for each study, which appear in the Final Study Report for each individual CAP study, did not include all evaluable subjects by pathogen. In some (but not all) of these summary tables, those organisms with less than three evaluable isolates at EOS were not included. These small numbers were, however, tallied in the sponsor's table (see Attachment 1 to this portion of the NDA review, entitled "TABLE {CAP.X.2a}: Sponsor Assessment of Clinical Response by Baseline Pathogen") which was presented as a facsimile document during the course of teleconference discussions over the approvability of the CAP indication. A summary of that table will be presented below for the pathogens requested in the product labeling:

Organism	Initial MOC assessment	Revised for sponsor table CAP X.2a
<i>Chlamydia pneumoniae</i>	9/12 (75%)	12/15 (80%)
<i>Haemophilus influenzae</i>	61/66 (92%)	61/67 (91%)
<i>Klebsiella pneumoniae</i>	7/7 (100%)	9/11 (82%)
<i>Legionella pneumophila</i>	8/11 (73%)	10/13 (77%)
<i>Moraxella catarrhalis</i>	9/9	16/16 (100%)
<i>Mycoplasma pneumoniae</i>	36/40 (90%)	37/40 (93%)
<i>Pseudomonas aeruginosa</i>	2/2	6/9
<i>Staphylococcus aureus</i>	6/6	14/14 (100%)
<i>Streptococcus pneumoniae</i>	88/95 (93%)	88/98 (90%)
Total N evaluable	258	283

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This slight augmentation in numbers brings a few of the requested organisms above the '10' mark, but also serves to increase the denominator and therefore the number required if using the '10% rule' as described in the Points To Consider document.

For the 'typical' (i.e., not 'atypical') pathogens under consideration, the revised numbers presented above do not make any substantive changes. An organism-by-organism discussion follows:

Streptococcus pneumoniae: numbers and outcome are adequate to approve labeling

Haemophilus influenzae: numbers and outcome are adequate to approve labeling.

Moraxella catarrhalis: numbers are borderline (> 10 but < 10% of evaluables) but MIC₉₀ is low (less than *Streptococcus pneumoniae*, against which trovafloxacin is clearly efficacious) and efficacy also demonstrated in other respiratory indications (AECB particularly). Furthermore, disease due to this organism is clinically similar to H. influenzae, for which the sponsor has presented sufficient information. Overall, the medical officer considers this organism appropriate to include in the product labeling for CAP.

Pseudomonas aeruginosa: does not appear to be approvable, since the number (9) remains inadequate.

Klebsiella pneumoniae: again, does not appear to be approvable. Although the revised numbers (11) bring the total isolates above 10, this is still considerably below the 28 that is necessary to meet the '10% rule'. Furthermore, this organism is not approvable in the nosocomial pneumonia indication because the number of evaluable patients was low in this indication as well (see review by Dr. Alivisatos). As an agent of community-acquired lobar pneumonia, this organism is predominantly seen in debilitated, elderly patients with coexisting medical conditions (particularly alcoholism, diabetes, and COPD) which serve to impair normal host respiratory tract defenses. Because of the necrotizing quality of the infection and the debilitated baseline condition of the patients who are predisposed to this disease, mortality is high. (A recent study by Jong et al [*Chest* 107(1): 214-17, Jan '95] of 28 alcoholic patients seen with *Klebsiella pneumoniae* CAP over a three-year period found an overall mortality rate of 64%.) CAP caused by *Klebsiella pneumoniae* is sufficiently severe to warrant the absolute requirement that it be studied in adequate numbers (i.e., 10% or 28 in this situation), in the opinion of the reviewing medical officer.

Staphylococcus aureus: the revised numbers bring the total from 6 to 14 patients, of whom 100% were reported to have a successful outcome (actually 12 cures out of 14). Again, these numbers fall in between the absolute '10' and the number mandated by the 'rule of 10%' (i.e., 28). The MIC₉₀ for this organism is less than that for *S. pneumoniae*, but one dilution greater than that of *Klebsiella pneumoniae*. If this organism appeared to be approvable for a related respiratory indication, this would be of interest; in the nosocomial pneumonia indication, however, the eradication rate was 12/19, or 63%. *S. aureus* was not granted for the sinusitis indication because the sponsor was unable to demonstrate in adequate numbers that this organism was the sole pathogen (rather than a possible colonizer) in this infection. A similar such reevaluation is underway for the AECB indication, in order to determine how many cases of *S. aureus* were accrued in which no co-pathogens were present. Regardless of the outcome of the AECB reanalysis, it is the opinion of this medical officer that the efficacy of trovafloxacin in this situation is not directly applicable to the pneumonia indication. CAP caused by *S. aureus* is adequately severe to warrant the absolute requirement that it be studied in adequate numbers (i.e., 10% or 28 in this situation) such that efficacy has been undisputably demonstrated rather than partially inferred from other respiratory indications. There were a total of 8 trovafloxacin-treated CAP patients who had *S. aureus* isolated as the sole respiratory pathogen; of these, 6 were cured and 2 were improved.

Requested labeling regarding penicillin-resistant *Streptococcus pneumoniae*:

Another issue to be considered in this discussion is the fact that the sponsor has requested wording in the label that reads "... *Streptococcus pneumoniae*, including penicillin-resistant strains...". Despite the robust numbers of *Streptococcus pneumoniae* isolates in the five combined studies submitted in support of this indication, there were not adequate numbers of such resistant isolates studied to warrant such labeling. In Table H.4.5.5 of the NDA, entitled

"Sponsor Defined Clinical Response and Pathogen Outcome of *Streptococcus pneumoniae* by Susceptibility to Penicillin for all Pneumonia Studies (Community Acquired and Nosocomial), End of Treatment Visit, Clinically Intent-to-Treat Subjects"

the sponsor tallies a total of four such patient isolates. Keep in mind that this is the most permissive, all-encompassing analysis possible: the clinically ITT subgroup at the EOT timepoint. Even casting this wide net (and allowing inclusion of all pneumonia studies), a total of 4 such isolates is inadequate to warrant such labeling. It should be noted that the statements made by the sponsor in some of the final study reports for the CAP indication, such as this one from study 112: "All five trovafloxacin subjects who had penicillin-resistant (MIC ≥ 0.1 $\mu\text{g/mL}$) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study" are defining 'resistant' strains as those with MICs that are considered 'intermediate' not 'resistant'. Some authors would define penicillin resistance in *S. pneumoniae* as an MIC of > 2.0 $\mu\text{g/mL}$; others use the breakpoint of > 1.0 $\mu\text{g/mL}$.

As detailed in the microbiologist's review of this NDA, the MIC₉₀ for trovafloxacin appears to be the same *in vitro* against both penicillin-resistant *S. pneumoniae* and penicillin-susceptible *S. pneumoniae*. Thus it may well be that this drug will eventually prove to be clinically efficacious in the management of such infections; at present, however, the data are not adequate in this NDA to support such a labeling claim.

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2. Atypical pathogens

The sponsor has also requested the three major bacterial agents of 'atypical' community-acquired pneumonia: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* (formerly TWAR agent), and *Legionella pneumophila*. Because of the difficulty in reliably culturing these agents from clinical specimens, it has become acceptable to utilize indirect methods of diagnosis to document these infections.

A number of more direct and specific methodologies are currently coming into use to detect the presence of these organisms. These techniques include PCR, radiolabeled nucleic acid probes, and antigen detection methods. With the exception of the urinary antigen detection test for *Legionella*, the sponsor chose to utilize only indirect (antibody-based) methods for diagnosis of these agents.

The following discussion is excerpted from a reference text entitled "Use and Interpretation of Tests in Medical Microbiology", by Dr. James B. Peter (Santa Monica: Specialty Laboratories, Inc., 1990). Because the sponsor has not included any test-specific information in the NDA to determine the exact methodology utilized in the study determinations, this discussion will only be considered as background information:

1. *Chlamydia pneumoniae*: "The best evidence of an acute *C. pneumoniae* infection is a fourfold or greater rise in antibody titers between acute and convalescent samples, and the presence of *C. pneumoniae*-specific IgM by microimmunofluorescence (micro-IF) $\geq$ 1:16. A single *C. pneumoniae*-specific IgG titer of $\geq$ 1:512 or a single *C. pneumoniae*-specific IgM titer of $\geq$ 1:16 is suggestive of acute infection. An IgG titer of $\geq$ 1:16 and $<$ 1:512 is evidence of past infection."
2. *Mycoplasma pneumoniae*: "EIA is preferred to CF because fourfold rises in CF titers are seen in only about 50% of patients, and because false-positives by CF can be seen in pancreatitis, bacterial meningitis, and other acute inflammatory diseases... Detection by EIA of *M. pneumoniae*-reactive IgM antibodies or demonstration of a significant increase of specific IgG antibodies is strong evidence for recent infection in the appropriate clinical setting. Fourfold increases in titer or fourfold increases AND titers $\geq$ 1:32 with CF employing lipid antigen yield sensitivities of 53% and 90%, respectively, in culture-positive *M. pneumoniae* pneumonia."
3. *Legionella pneumophila*: "Direct detection of *L. pneumophila* in respiratory specimens by DFA (sensitivity ~70%, specificity ~97%) or DNA probe (sensitivity ~70%, specificity ~99%) is useful for rapid diagnosis but lacks sensitivity when low numbers of organisms are present. *L. pneumophila* soluble antigen in urine by EIA (sensitivity >70%, specificity ~99%) and RIA (sensitivity 93%, specificity 100%) can be detected within one day of onset of symptoms. The only reliable serological evidence of recent *L. pneumophila* infection is a fourfold rise in titer to a level $\geq$ 1:128 between acute and convalescent specimens by IFA or EIA. A single result of $\geq$ 1: 256 is presumptive evidence of infection."

Given this discussion, several questions arise regarding the sponsor's methodology and interpretation of the tests utilized to diagnose these infections in the CAP studies:

- ◆ Is a fourfold rise of any magnitude sufficient, or does the antibody titer need to rise above a certain level in some of the assays?
- ◆ Is a rise of any antibody class (IgM, IgG, or IgA) acceptable, or are some more sensitive or specific than others?
- ◆ Is it of concern that such tests, which are usually used on individual patients when clinical suspicion warrants, have essentially been employed as screening tests in this patient population? Does such a use of these tests heighten concerns over false positive results?
- ◆ What are we to make of patients who are identified by standard culture techniques with one or more definite respiratory pathogen, in either the sputum or the blood, but who also are found

retrospectively to have a rise in antibody titer that is suggestive of an atypical infection as well? Is the clinical suspicion of the investigator at the time of enrollment worth considering?

The sponsor was queried as to the specific type of assay utilized for each of these diagnostic procedures. The following email responses were transmitted during the course of this review:

Serologies were not done at the sites. All serologies (and legionella urinary antigen) for Legionella and Mycoplasma were done on paired serum samples (baseline and day 30) using their standard assays. Chlamydia titers (also paired)

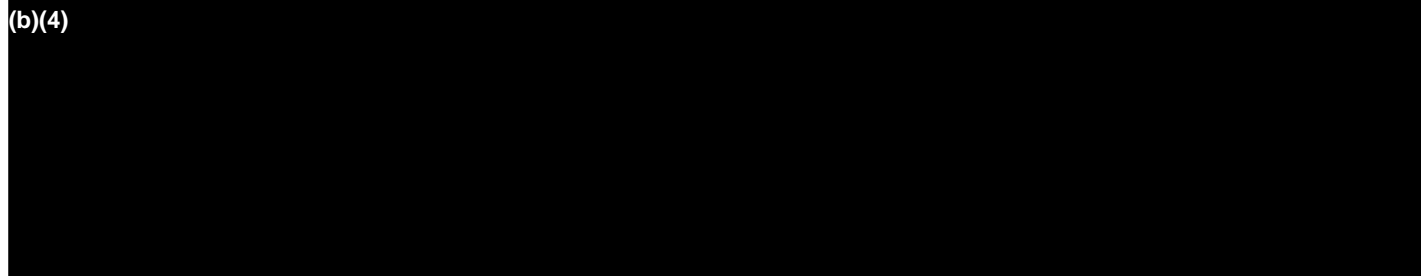
"specialty" assays

Chlamydia pneumoniae titers were done

Legionella titers

Mycoplasma titers were also

(b)(4)



1. Chlamydia pneumoniae

Intended use: "Since either the presence of antibodies to IgM or the detection of a fourfold IgG titer increase is highly diagnostic and indicative of acute or recent infection, it is recommended that both IgG and IgM determinations be performed on all patients suspected of Cp infection."

Prepared slides have wells labeled 'yolk sac', 'C.psittaci', 'C.trachomatis', and 'C.pneumoniae'. These other antigen spots "are provided as an aid to interpretation of the specificity of the C.pneumoniae serological reaction." In other words, this kit is not intended to diagnose C.psittaci infection. In fact, those patients who are claimed to have 'dual infections' probably have a nonspecific antibody and probably should be discounted.

Interpretation: a fourfold rise in antibody titer is highly diagnostic and indicative of active current or recent acute infection.

Limitations: "It is essential that all results from chlamydial serologies must be correlated with clinical history and other data available to the physician."

COMMENTS: The C.psittaci interpretations probably indicate nonspecificity and should be excluded. There is absolutely no mention of IgA; thus, these should be disregarded.

2. Mycoplasma pneumoniae IgG and IgM

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for the presence of circulating IgG and IgM antibodies to M.pneumoniae.
"A fourfold increase in antibody titer is considered diagnostic for a current infection if tested simultaneously" (run as paired sera).

Interpretation: (IgG) Flourescence at 1:64 but not more than 1:128 = equivocal results.
Flourescence at 1:128 or higher = active or past infection with M.pneumoniae

(IgM) Flourescence at 1:8 but not more than 1:16 = equivocal results
Flourescence at 1:16 or higher = active or recent infection with M.pneumoniae

Performance characteristics: utilizing the following criteria:

Negative: IgG of $\leq 1:32$ and IgM $\leq 1:4$
Borderline: IgG of $\geq 1:128$ and/or IgM of $\geq 1:8$
Positive: IgG of $\geq 1:128$ and/or IgM of $\geq 1:16$

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3. Legionella

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Assay: Detection and quantitation of antibodies to L. pneumophila serogroups 1-6. Polyvalent antiserum detects presence of IgG, IgM, or IgA in test serum that may bind to slide-fixed Legionella organisms.

Interpretation: "Serological evidence of a recent infection with LDB is indicated by a four-fold rise in titer between acute and convalescent sera. The rise in titer must be to $\geq 1:128$ to be considered as evidence of recent infection. A standing or single titer of $\geq 1:256$ is considered presumptive evidence of LDB infection at an undetermined time. Current data indicate that titers of 32 and 64 in the absence of detectable disease are common.

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The following table summarizes the sponsor's eradication numbers for the atypical pathogens requested in the NDA:

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**Eradication Rates for Identified Atypical Pathogens
Clinically and Bacteriologically Evaluable Subjects*
Treated with Trovafloxacin
Community Acquired Pneumonia**

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Pathogen	Study number, N				Totals N = 241
	Study 110 N = 64	Study 111 N = 68	Study 112 N = 53	Study 134 N = 56	
<i>Mycoplasma pneumoniae</i>	8/8	9/10	4/5	16/17	37/40
<i>Chlamydia pneumoniae</i>	2/4	2/2	1/1	5/6	10/13
<i>Legionella pneumophila</i> #	2/2	7/10	--	--	9/12

* A subject could have more than one pathogen at baseline.

Sponsor actually shows 10/13, but this includes one subject (111-56070186) who was not assessable.

This table does not include study 102; that study included an additional two *Chlamydia pneumoniae* patients who were treated with 200 mg of Trovan for 10 days and were evaluable at EOS; both of these were considered cured.

The above numbers do not take completely into account the definitions of a 'positive test' as provided in the package inserts to the assays utilized in this NDA. The following table examines these numbers more carefully by the precise serologic basis for the diagnosis of each organism in each study:

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**Clinically and Bacteriologically Evaluable Subjects
Treated with Trovafloxacin
Community Acquired Pneumonia
Atypical pathogens according to method of diagnosis**

Pathogen and method of diagnosis	# Cases / Total Clinical & Micro Evaluable at EOS					TOTALS N = 241
	Study 110 N = 64	Study 101 N = 68	Study 112 N = 53	Study 134 N = 56	Study 102 N = 10	
<i>Mycoplasma pneumoniae</i>						36/40 (90%)
4X rise in IgG and IgM	2/2	1/2		3/3		6/7
4X rise in IgG	5/5	8/8	5/6	12/13		30/32
4X rise in IgM	0/1					0/1
<i>Legionella pneumophila</i>[§]						6/11 (55%)
4X rise in IFA to 1:128*	1/2	3/4				4/6
4X rise in IFA*	1/2	4/7		1/1		6/10
Urinary antigen ⊕		0/1				0/1
<i>Chlamydia pneumoniae</i>[#]						9/14 (64%)
4X rise in IgG and IgM						
4X rise in IgG [@]	1/4	2/2	1/1	0/2		4/9
4X rise in IgM				3/3	2/2	5/5

footnotes:

§ Excludes two patients included in sponsor's final tally of N=13:

- 111-56070186, who was 'Not Assessable' (received 2 weeks of erythromycin at EOT)
- 111-56271159, who did not have a fourfold rise in titer documented and had *Streptococcus pneumoniae* bacteremia

* These two categories are not additive; those whose titer rose at least to 1:128 are a subset of those who had any sort of 4X rise in titer.

Of the 19 patients listed by the sponsor in table 5.3a of each study, the following were excluded to arrive at the denominator of 14:

- 102-50170247 (Not Evaluable)
- 110-50460304 (Not Evaluable)
- 111-51690166 (Not Assessable)
- 111-51900151 (Not Assessable)
- 134-52520242 (diagnosed on basis of isolated IgA rise only)

@ Includes two patients (110-52240357 and 110-55340447) who had single IgG titers of 1:1024 in the presence of a fourfold rise in IgA.

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The efficacy of the comparator regimens for Atypical CAP is shown in the following table:

**Clinically and Bacteriologically Evaluable Patients at EOS
Combined Comparator Regimens
CAP due to atypical agents**

Pathogen and method of diagnosis	# Cures / Total Clinical & Micro Evaluable at EOS					TOTALS N=241
	Study 101 N=74	Study 103 N=68	Study 102 N=53	Study 104 N=56	Study 102 N=16	
<i>Mycoplasma pneumoniae</i>	cipro + amp	ctx-ceftin ± erythro	amox ± erythro	clari	ceclor	23/27 (85%)
4X rise in IgG and IgM	1/1			3/4	1/1	5/6
4X rise in IgG	6/7		1/2	11/12		18/21
4X rise in IgM						
<i>Legionella pneumophila</i>						12/13 (92%)
4X rise in IFA to 1:128*	2/2	3/3				5/5
4X rise in IFA*	3/3	6/6				9/9
Urinary antigen ⊕	1/1	2/3				3/4
<i>Chlamydia pneumoniae</i> #						17/21 (81%)
4X rise in IgG and IgM	3/3		1/1		0/1	4/5
4X rise in IgG	4/4	4/4		3/4		11/12
4X rise in IgM		1/3		1/1		2/4

footnotes:

* These two categories are not additive; those whose IFA rose at least to 1:128 are a subset of those who had any sort of 4X rise in titer.

Excludes five patients diagnosed by sponsor on basis of IgA alone: 110-52240319; 110-55560118; 112-55560921; 134-50320097; and 111-51900001

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Medical Officer comments:

1. **Regarding *Mycoplasma pneumoniae*:** from the above table, it would appear that there is an adequate number of *Mycoplasma* patients to warrant inclusion of this organism in the CAP indication for trovafloxacin. Any of the three seroconversion definitions are acceptable for the diagnosis of this infection, as they conform to the diagnostic kit product labeling.

2. **Regarding *Chlamydia pneumoniae*:** the numbers are substantially lower than those accrued for *Mycoplasma*. Although greater than 10, the total of 14 accumulated cases falls short of the '10% rule', which would in this case require a minimum of 28 (10% of 283) accumulated subjects in order to consider approval of this pathogen for this indication. It should also be kept in mind that the diagnostic test kit utilized in this assay is not FDA approved; the labeling provided by the sponsor states that it is "For Investigational Use Only". Although this fact does not preclude the use of this test in the context of a clinical study filed as part of an NDA, the sponsor must present evidence to support the contention that this test is acceptable for use in this situation.

(It is readily acknowledged that there are no currently FDA-approved diagnostic tests for this pathogen.)

(It is also acknowledged that several recent product approvals for this organism were based on this same serological test, so it is reasonable to allow its use in this NDA as well.)

The eradication rate of 64% for trovafloxacin in *Chlamydia pneumoniae* pneumonia compares with an overall eradication rate of 81% (17/21) for the various comparator regimens utilized in these five studies.

Other factors to consider might include the efficacy of trovafloxacin against other Chlamydial infections in other requested indications (NGU, PID) in which other species of Chlamydia may be present; the in vitro activity of the drug against the pathogen, and what regulatory precedent exists.

The NDA for trovafloxacin also requests approval for nongonococcal urethritis due to *Chlamydia trachomatis*. Although this indication may appear to be approvable, it is difficult extrapolating the results of such studies to the CAP situation (different organisms and distinctly different anatomical sites).

Although there is not standardized in vitro susceptibility testing methodology for the chlamydiae, trovafloxacin is reported to have an MIC₉₀ of 0.25 µg/mL against *C. pneumoniae* (identical to the reported MIC₉₀ for *Mycoplasma pneumoniae*).

As mentioned above, recent product approvals for Sparfloxacin, Levofloxacin, azithromycin IV, and Grepafloxacin have all considered Chlamydia pneumoniae as a pathogen in community acquired pneumonia. The following regulatory actions were taken:

Recent regulatory experience with Chlamydia pneumoniae

Drug	Number eradicated / total evaluable	Number clinically & microbiologically evaluable for CAP indication (all pathogens)	Approval granted?
Sparfloxacin	19/22 (86%) eradicated	197	✓
Levofloxacin*	154/161 (96%)	370	✓
Azithromycin IV	19/21 (90%)	?	✓

* The number of patients in this application is extremely high because the case definition allowed for the inclusion of subjects who did not necessarily have serologic evidence of active infection.

During discussions with the sponsor regarding the CAP indication, the issue of relatively small numbers of evaluable *Chlamydia pneumoniae* patients was mentioned. The sponsor requested that the medical officer take into consideration a completed CAP study (154-136) that had been compiled but not submitted to the NDA. A Final Study Report for this study was provided to this medical officer during the final stages of the CAP review. This study was a randomized, double-blind, double-dummy trial comparing 7-10 days of trovafloxacin at a dose of 200 mg qd with high-dose amoxicillin at a dose of 1000 mg tid. The design and conduct of the study appeared to be similar to that of the CAP studies previously reviewed. During the conduct of this multicenter, international study, a total of 22 patients were enrolled in the trovafloxacin arm who were considered by the sponsor to have demonstrated serologic evidence of infection with *C. pneumoniae*. The medical officer reviewed these cases (although the CRFs and patient profiles were not available) to apply the same serologic criteria delineated above (i.e., a change in serum IgA titer alone was not sufficient for diagnosis). This resulted in the following additional cases:

**Chlamydia pneumoniae cases reported from non-NDA
CAP study 154-136
Trovafloxacin-treated patients**

APPROXIMATE DATE
01/10/2000

APPROXIMATE DATE
01/10/2000

PID#	(b)(4)	Diagnosed (EOS)	Clinical response	Comments
50340810		yes	cure	
50340814		no	--	--
50340833		yes	cure	
52120286		--	--	--
54130315		yes	cure	Strep pneumoniae (blood)
55550389		no	--	--
55550403		--	--	--
55700017		yes	cure	
55900096		yes	cure	
55900269		yes	cure	
55960297		yes	failure	Mycoplasma pneumoniae
56270334		yes	failure	
56270381		yes	cure	
56290425		yes	failure	
59920167		--	--	--
59920170		yes	failure	Strep pneumoniae
60430325		yes	cure	
63570191		yes	cure	
64160943		--	--	--
65480885		yes	cure	Staph aureus
65570904		--	--	--
65690905		yes	cure	Mycoplasma pneumoniae
65880410		yes	cure	

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Thus it can be seen that there are an additional 15 evaluable *Chlamydia pneumoniae* patients (diagnosed serologically by IgG titer rise only) in Study 136 who were treated with trovafloxacin and considered evaluable at the EOS timepoint. Of these 15 subjects, 11 (73%) were clinical cures. If these numbers are added to those tallied above (9/14), the total becomes 20/29 (69%) cured at EOS following 7-10 days of trovafloxacin therapy.

It should be noted that the medical officer only tallied 'cures' in the numerator (as indicated in the table for NDA studies 102, 110, 111, 112, and 134). If 'improvements' are also counted as a favorable outcome, an additional two patients should be added to the numerator, making the total 22/29 or 76%. This should be compared with efficacy rates of 86% for sparfloxacin and 90% for IV azithromycin. (Because of the inadequate case definition used in the levofloxacin review, this will be disregarded.)

The total of 29 accrued patients with Chlamydia pneumoniae appears to fulfill the '10% rule'; however, if one is to include these additional patients from study 136 to achieve a denominator of 29, this should also raise the total number of microbiologically evaluable subjects from which the 10% is calculated. If one disregards this for the moment and simply considers the relative efficacy rates, it remains troublesome that the trovafloxacin efficacy rate was only 76% while that of the various comparators in studies 102, 110, 111, 112, and 134 was a cumulative 17/21 or 81% cures (not cure + improved). It is also of note that in the European study 136, the sponsor tallies 22/26 (85%) cures for the amoxicillin arm.

These numbers, however, are too small to say with any statistical confidence that they are NOT equivalent

Regarding Legionella pneumophila: once again, the sponsor has accrued a relatively small number of such patients. Using the broadest definition of infection, the sponsor has provided clinical outcomes on eleven evaluable patients infected with this organism. Since the '10% rule' in this situation would indicate that somewhere in the order of 28 patients need to be studied in order grant such labeling for trovafloxacin, it would appear that there is insufficient information here to warrant approval. *Legionella pneumophila* is a respiratory tract pathogen which, along with the Gram-negative bacilli, is associated with severe disease. In a study of passive surveillance data on 3254 patients diagnosed with legionellosis from 1980 to 1989, Marston and colleagues [*Arch Int Med* 154(21): 2417-22, Nov 94] at the CDC found an overall mortality rate of 24%. Similar to Gram-negative bacillary pneumonia, this study found that risk of death was higher in patients with cancer, renal disease, immunosuppression, or advanced age. Thus, for legionellosis as well as Gram negative bacillary CAP, the need to study adequate numbers of patients is essential.

Although the small numbers make statements of equivalence problematic, the number of evaluable cures at end-of-study for the trovafloxacin arm (6/11 or 55%) appears to be less than that for the combined comparators (12/13 or 92%). The sponsor's tally, as provided in table CAP.X.2a (Attachment 1), shows 8 cures out of 13 subjects, or 62%.

The following table shows recent regulatory experience in granting the indication of CAP due to *Legionella pneumophila*:

Recent regulatory experience with Legionella pneumophila

Drug	Number eradicated / total evaluable	Number clinically & microbiologically evaluable for CAP indication (all pathogens)	Approval granted?
Sparfloxacin	not requested		
Levofloxacin	7/10	370	✓
Azithromycin IV	13/16	??	✓
Grepafloxacin	8/9	96	NO

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As can be seen from the above table, approval has been granted for levofloxacin with relatively low numbers of patients. This fact was brought forward by the sponsor in the process of discussing the approvability of the CAP indication. This precedent notwithstanding, it is the opinion of this medical officer that given the gravity of community-acquired pneumonia due to *Legionella pneumophila*, it is unacceptable to grant approval on a total of eleven evaluable patients, only six of which were deemed to be clinically cured at the end of study, particularly when the same double-blinded, double-dummy studies accrued a similar number of cases in the comparator arms (13) and 12 of these patients were cured.

The sponsor then requested that the legionellosis cases from a recently-completed European study (154-136), which had not been submitted to the NDA, be considered in addition to those tallied above. A Final Study Report for this study was provided to this medical officer during the final stages of the CAP review. This study was a randomized, double-blind, double-dummy trial comparing 7-10 days of trovafloxacin at a dose of 200 mg qd with high-dose amoxicillin at a dose of 1000 mg tid. The design and conduct of the study appeared to be similar to that of the CAP studies previously reviewed. During the conduct of this multicenter, international study, a total of 6 cases of legionellosis were accrued at five separate study sites. The following is a compilation of the *Legionella* cases from study 154-136:

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**Legionella cases from non-NDA
CAP study 154-136**

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PID#	(b)(4)	Available at BOS?	Clinical response
trovafloxacin patients			
5627-0372		yes	cure
5627-0381		yes	cure
5627-0433		yes	cure
5992-0166		yes	cure
6043-0322		yes	cure
6116-0081		yes	cure
amoxicillin patients			
5573-0022		yes	failure (NB: also showed 4X rise in <i>Chlamydia pneumoniae</i> IgG)
5627-0336		yes	cure
5627-0382		yes	failure (NB: also showed 4X rise in <i>Chlamydia pneumoniae</i> IgM)
5627-0435		yes	failure
6043-0321		yes	cure
6043-0326		yes	cure

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According to the sponsor, the serologies done in this European study were performed in a manner identical to those done for the previously-reviewed CAP studies: the Zeus test kit was utilized, and was performed by the contracted central laboratory service, Scior. Recall from the previous discussion of this test that the definition of a positive IgG rise, according to the product labeling, was:

"a four-fold rise in titer between serum taken during the acute phase of illness (within the first week) and convalescent phase (3 to 6 weeks after onset). The rise in titer must be to $\geq 1:128$ to be considered as evidence of recent infection."

Using this definition, the last two trovafloxacin subjects listed above cannot be diagnosed as having Legionella as the cause of their acute illness. In the previously reviewed CAP studies, there were no serum samples obtained at days 9-10, so these two patients would never have been called positive in those studies to begin with. Furthermore, one of these two (6116-0081) also had Strep pneumo grown from a sputum sample.

If these four additional cases are added to the tally for all the CAP studies submitted to the NDA, the resulting numbers are 10/15 (67%) clinical cures at EOS. This number remains well below the 28 called for by the '10% rule' of the Points to Consider document, but approximates the 16 that were tallied in the NDA submission for intravenous azithromycin, another Pfizer product recently reviewed and subsequently approved by FDA.

(The efficacy of amoxicillin in this study was interesting. If one discounts the two patients who had evidence of infection with *Chlamydia pneumoniae*, amoxicillin in this study cured 3/4 *Legionella* patients. If one uses the serologic criteria applied above, the one evaluable amoxicillin patient was cured.)

Because these numbers are so small, it cannot be determined with any reasonable degree of confidence that 10/15 is equivalent to [or inferior to] 13/16 (the numbers tallied in the IV azithromycin NDA). (NB: since these azithromycin numbers include 'cures' plus 'improvements' in the numerator of 13, it should be pointed out that there were two trovafloxacin subjects called 'improvement' who were not tallied in the above table, which is entitled "# Cures/total...". The appropriate comparison is 12/15 for trovafloxacin, to 13/16 for IV azithromycin.)

When discussing this issue with the entire Trovan review team, it was pointed out by Dr. Alivasatos that there were a few cases of legionellosis in the two Nosocomial Pneumonia studies. The study reports from studies 154-113 and 154-137 were examined and the following trovafloxacin-treated subjects were found: (NB: these studies both utilized IV doses of 300 mg qd, followed by 200 mg PO when changed to oral therapy.)

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Synopses of trovafloxacin-treated subjects in nosocomial pneumonia studies
diagnosed with Legionellosis

113-53860200 61 female received 5 days of Trovan for nosocomial pneumonia. Initial sputum showed an adequate Gram stain for culture; a pathogen (*Haemophilus parainfluenzae*) was isolated. Trovan was discontinued due to an adverse event (Hallucinations) that was considered study drug-related. Therapy changed to ampicillin. Patient called an evaluable cure at EOS by sponsor. Serologies showed a fourfold rise in *Legionella* titer from _____.

Comment: although the protocol allowed patients with at least five days on study drug to be considered evaluable, it is difficult to ascribe the clinical outcome to drug exposure here. Most references call for diagnosed cases of legionellosis to be treated with 21 days of erythromycin.

113-53860249 65 year old male ex-smoker s/p CABG, admitted to ICU for management of nosocomial pneumonia. Initial sputum called 'normal respiratory flora' on CRF but the following organisms all described as pathogens: *H. influenzae*, *Klebsiella oxytoca*, and *Staphylococcus aureus*. Received 3 days of IV therapy, then changed to PO trovafloxacin to complete 12 days of therapy. Serologies noted to show rise in *Legionella* titers from _____.

Comment: aside from the issue of the diagnostic test needing to rise to or above 1:128, this case appears to be appropriate for inclusion. The issue of sputum co-pathogens has been discussed previously.

137-59450136 62 year old Australian male ex-smoker with underlying hepatic disease (baseline SGOT/PT 149/102) admitted to this open study and randomized to Trovan. Given 8 days IV therapy (at 300 mg qd), then switched to PO to complete a total of 23 days of Trovan therapy. Initial sputum showed normal flora; initial CXR read as "minimal atelectasis left base, lungs otherwise clear". No followup CXR obtained. _____

Comment: unimpressive radiograph would make eligibility for entry into study questionable. Nonetheless, patient has serology consistent with diagnosis of legionellosis, and has no other sputum pathogens. Rationale for duration of therapy not provided by investigator.

137-59780398 48 year old German male smoker admitted to ICU for treatment of nosocomial pneumonia. Initial sputum culture grew *Acinetobacter baumannii* and *Escherichia coli*. Patient treated with 300 mg IV Trovan for XX days then changed to 200 mg orally to complete 10-day course. Called evaluable EOS cure by sponsor; presumed eradication of *A. baumannii*, *E. coli*, and *Legionella pneumophila* based on a baseline serology showing a titer of 1:1024 and a negative urinary antigen. The convalescent _____, and thus the diagnosis of legionellosis was made on a >4X drop in titer.

Comment: a drop in titer is not considered diagnostic. This is not mentioned in the product labeling nor is it discussed in the standard Infectious Disease reference text (Mandell's Principles and Practice of Infectious Diseases). A single titer of such magnitude may be used as an indicator of acute infection. However, since this antibody test may give false positives in the presence of concomitant gram negative bacillary disease, it is quite possible that the serology may represent a false positive in this case. If the sputum had not shown other pathogens, this case would have been considered acceptable for inclusion.

The medical officer will consider patients 113-53860249 and 137-59450136 as acceptable additions to the tally for cases of legionellosis for the CAP indication. Since both of these subjects are cures, this brings the total tally for this organism in this indication to 14 cured or improved out of 17 evaluable cases.

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The medical officer is asked to make a recommendation concerning approval of this indication not on the basis of 'adequate' numbers of evaluable subjects and a comparable rate of clinical response, but on the basis of precedent within the agency (not all of it consistent with the tenants of the Points to Consider document) and in the face of an apparently similar response rate (12/13) in the pooled comparator arms (many of whom were not treated with the gold standard comparator, erythromycin).

Since the *in vitro* activity of trovafloxacin against *Legionella pneumophila* indicates that this drug should be clinically efficacious in this infection, and since the number of accumulated evaluable cases (17) is at least as large as the number of cases described in the medical officer's review of the IV azithromycin NDA (16), and since the efficacy was similar (82% for trovafloxacin and 81% for IV azithromycin), it is the opinion of this medical officer that the CAP indication in the INDICATIONS AND USAGE section of the product labeling should include *Legionella pneumophila*. However, since patients treated with the nosocomial pneumonia dosage (300 mg IV qd) were included in this analysis, the DOSAGE AND ADMINISTRATION section will need to reflect this fact.

**APPEARS THIS WAY
ON ORIGINAL**

C. Recommended action

The medical officer recommends inclusion of the following language in the INDICATIONS AND USAGE section of the Trovan® product labeling:

"Community acquired pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, *Legionella pneumophila*, or *Chlamydia pneumoniae*."

Under DOSAGE AND ADMINISTRATION:

The column heading "Infection/location and type" should include an entry entitled "Community Acquired Pneumonia";

The column heading "Daily unit dose and route of administration" should read "200 mg oral or 200 mg IV followed by 200 mg oral";

The column heading "Total duration" should read "7-14 days".

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ON ORIGINAL**

(Please see attached addendum to this conclusion.)

/S/

Philip E. Coyne, J.D. MD
Medical Officer
HFD-590

concurrency: HFD-590/DivDir/Goldberger
HFD-590/TL/Leis

/S/

/S/

cc:
original NDA 20-759, 20-760
HFD-590
HFD-590/DepDivDir/Albrecht
HFD-590/MO/Alivasatos
HFD-590/Pharm/Ellis
HFD-590/Biopharm/Colangelo
HFD-590/Stats/Silliman
HFD-590/CSO/

**APPEARS THIS WAY
ON ORIGINAL**

Medical officer addendum to review of Community Acquired Pneumonia

Date: 16 December 1997

The sponsor has taken issue with the stated intention of the agency to deny the inclusion of *Klebsiella pneumoniae* as a listed organism in the CAP indication. An electronic communication was received on 12 December which read, in part, as follows:

Klebsiella pneumoniae

--Across nosocomial pneumonia and CAP, 18/24 *Klebsiella pneumoniae* isolates were successfully treated. Eight were from Nosocomial pneumonia with 4 clinical successes, while 16 were from double blind, randomized, controlled trials in CAP, with 14/16 successfully treated (EOS). From p. 407 of the medical officer's review of levofloxacin, it appears that there were only 6 clinically evaluable subjects with this isolate, several of which appear to have originated in the non-comparative trial #M92-075. The medical officer did not recommend approval for this organism, however, there is a reference on p. 427 to additional data from supportive trials in an 'addendum', which is not available to Pfizer.

--The only other recent reference to *Klebsiella pneumoniae* is the levofloxacin package insert clinical trials section, where a figure of 10 isolates, all successfully treated, is cited.

--We regard this as a 'level playing field issue'. The primary source of the *Klebsiella pneumoniae* for the levofloxacin label was from an unblinded study (vs. ceftriaxone/cefuroxime) which was justly criticized by the medical officer because of this and other deficiencies. The only further data seem to have come from a non-comparative study, as reported in the clinical trials section. The trovafloxacin CAP data on *Klebsiella pneumoniae* are from much more robust double blind studies. More *Klebsiella pneumoniae* were studied in the trovafloxacin CAP program, by a considerable margin than in the levofloxacin program.

--The agency may fairly take the position that it has made an egregious error in the levofloxacin label and will not include organisms on such flimsy data in the future. However, the trovafloxacin data are much more robust and much greater in quantity. To not include *Klebsiella pneumoniae* would be unfair.

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ON ORIGINAL

Medical officer comments:

1. The sponsor's total of 16 patients in combined CAP clinical studies apparently includes 5 from study 136, which was not submitted formally as part of the NDA. (The matter of this study and its applicability to NDA 20-759/760 was not raised until final discussions were underway regarding the approvability of the CAP indication. The final study report for 136 was submitted to the NDA on 3 December 1997, two weeks before the PDUFA due date.) It was agreed, in previous discussions with the sponsor, to consider this European study only in the context of discussions regarding the approval of atypical agents of CAP, specifically *Legionella*. (The sponsor made the appropriate observation that legionellosis is a respiratory disease which occurs as small epidemics, and the only way to capture cases in the context of an NDA-driven clinical trial is by being lucky enough to catch an epidemic while conducting the trial. Study 136 did so.) If the study in its entirety is to be taken into consideration, in order to consider additional organisms such as *Klebsiella pneumoniae*, it would most likely be considered as a major clinical amendment to the NDA, mandating an additional 3 months of review time.

2. The sponsor's total minus study 136 would then be 11. In looking over Tables 5.3.1 and 5.4.1 for each study report of the 5 studies (102, 110, 111, 112, and 134) in the electronic NDA submission, and noting that only the 200 mg arm of study 102 is of interest here, the following numbers are found:

Clinical Response at End Of Study
Clinically and Bacteriologically Evaluable CAP patients with *Klebsiella pneumoniae*
(Source: table 5.4.1, studies 102, 110, 111, 112 and 134)

<u>Study</u>	<u>number clinical successes/number evaluable</u>
102	4/4
110	1/1
111	2/2
112	1/1
134	0/1
Total	8/9

Clinical Response by Baseline Pathogen
Clinically Evaluable CAP patients with *Klebsiella pneumoniae*
(Source: table 5.3.1, studies 102, 110, 111, 112 and 134)

<u>Study</u>	<u>number clinical successes/number evaluable</u>
102	6/6
110	1/1
111	2/2
112	0/1
134	0/1
Total	9/11

The sponsor was asked to explain the difference in these numbers. Specifically:

- how the one *Klebsiella pneumoniae* patient in study 112 could be a failure in the analysis presented in table 5.3.1, and a success in table 5.4.1; and
- how an additional two patients in study 102 were included as successes in table 5.3.1, as compared to table 5.4.1.

The sponsor (Dr. Debra Williams, phone conversation 17 Dec 97) that the patient in study 112 was a clinical failure but had a f/u sputum culture done which did not grow *Klebsiella pneumoniae*; therefore this patient was counted as a bacteriologic eradication even though a clinical failure. The two patient difference in study 102 was due to the fact that two patients were considered (by the sponsor) to have persistent productive cough at EOS, and therefore a f/u sputum should have been obtained. They were considered to have clinically successful outcomes, and were so counted in table 5.3.1; however, they were considered bacteriologically unevaluable on this basis and thus do not appear in table 5.4.1.

It would seem reasonable to allow inclusion of the additional two patients from study 102 who were considered clinical cures, even though they had some residual productive cough (not at all unusual in this population of patients, many of whom have underlying chronic bronchitis). Thus, the 9/11 numbers are accepted.

Is it reasonable to take the *Klebsiella pneumoniae* patients from Dr. Alivasatos' review of the nosocomial pneumonia indication (studies 113 and 137) into consideration? The two diseases are pathophysiologically quite similar; the basis for their distinction as separate clinical entities is, to a large degree, based on the difference in microbial etiologies between the two clinical syndromes. There are differences in the patient populations (nosocomial pneumonia patients generally being more ill, with higher degree of comorbidity) that make the application of CAP clinical trial subjects to consideration of the nosocomial pneumonia indication quite problematic. However, it would seem reasonable to apply the results of nosocomial pneumonia studies to the setting of the CAP indication.

According to Dr. Alivasatos, by her analysis there were a total of 4/8 *Klebsiella pneumoniae* patients in studies 113 and 137 who were clinically and bacteriologically cured at EOS.

If these additional patients are added to the 9/11 noted above from cumulative tables 5.3.1 of the CAP studies, the total *Klebsiella pneumoniae* experience then becomes 13/19, for an eradication rate of 69%.

The medical officer considers these revised numbers to be adequate, and an eradication rate of nearly 70% to be acceptable for this indication, particularly in light of the higher rate in those patients from the actual CAP studies. Therefore, the inclusion of *Klebsiella pneumoniae* to the organism list for CAP is acceptable.

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OF ORIGINAL

In the same electronic communication of 12 December, the sponsor also took issue with the division's stance that *Staph aureus* had not been studied in adequate numbers to warrant inclusion in the CAP indication:

Staphylococcus aureus

--In Nosocomial pneumonia alone, there were 21 *S. aureus* isolated and 14 successfully clinically treated at EOS (67%) in the two trovafloxacin protocols, results equal to the overall outcomes. The figures for the comparators are 10/21 (48%). The somewhat better efficacy with trovafloxacin is not surprising since trovafloxacin is at least an order of magnitude more active than ciprofloxacin or ceftazidime. In CAP, 18/18 were successfully treated in the trovafloxacin arms.

--*S. aureus* was included in the levofloxacin CAP indication, apparently on the basis of successful outcomes in 15/17 cases, as reported in the clinical trials section of the package insert. As noted below however, the levofloxacin CAP studies were very weak in key design areas (one was unblinded and the other non-comparative).

--*S. aureus* was included in the recent Zosyn label for Nosocomial pneumonia apparently on the sole basis of organisms acquired in the single pivotal trial vs. ceftazidime in which 155 patients were randomized to Zosyn. From the medical officer's review (p. 75), it is apparent that approval was gained on the basis of 13 successful courses out of 16 isolates.

--We regard this as a 'level playing field' issue. We believe we have studied adequate numbers that are at least equal to those studied in recent approvals. We do not believe the sponsors of levofloxacin and Zosyn were required to specially 'prove the validity' of this particular isolate as Pfizer was, for an organism that is generally regarded as a pathogen in these infections.

Medical officer comment:

The sponsor is correct in noting that the levofloxacin NDA was approved for *Staph aureus* in CAP on the basis of 15 successes out of 17 cases. It should also be noted that there was no analysis done in the levofloxacin review that looked specifically at how many of those 17 cases were instances in which *Staph aureus* was the sole pathogen identified. Thus, the sponsor makes a valid observation. The total number of *Staph aureus* isolates, again from the two tables noted above for the five studies submitted for the CAP indication in the NDA, were as follows:

Clinical Response at End Of Study
Clinically and Bacteriologically Evaluable CAP patients with *Staphylococcus aureus*
(Source: table 5.4.1, studies 102, 110, 111, 112 and 134)

<u>Study</u>	<u>number clinical successes/number evaluable</u>
102	0/0
110	3/3
111	3/3
112	1/1
134	7/7
Total	14/14

Clinical Response by Baseline Pathogen
Clinically Evaluable CAP patients with *Staphylococcus aureus*
(Source: table 5.3.1, studies 102, 110, 111, 112 and 134)

<u>Study</u>	<u>number clinical successes/number evaluable</u>
102	0/0
110	3/3
111	3/3
112	1/1
134	7/7
Total	14/14

In the text of the sponsor's comments, the number 18 is used for the number of *Staph aureus* CAP isolates. The difference between 14 and 18 is the 4 *Staph aureus* isolates from study 136. It is the opinion of this medical officer that full consideration of this study, in the absence of its designation as a 'major amendment', sets an undesirable precedent which would allow a sponsor to submit additional last-minute clinical information with no impact on the PDUFA-mandated action date.

The sponsor's claim that their numbers (14/14) are somehow qualitatively 'better' than the 15/17 successes in the levofloxacin CAP indication, because of differences in study design, is difficult to factor into consideration.

Returning to the discussion in the overall CAP conclusions in this Medical Officer's review, the following observations were made:

Staphylococcus aureus: the revised numbers bring the total from 6 to 14 patients, of whom 100% were reported to have a successful outcome (actually 12 cures out of 14). Again, these numbers fall in between the absolute '10' and the number mandated by the 'rule of 10%' (i.e., 28). The MIC₉₀ for this organism is less than that for *S. pneumoniae*, but one dilution greater than that of *Klebsiella pneumoniae*. If this organism appeared to be approvable for a related respiratory indication, this would be of interest.... CAP caused by *S. aureus* is adequately severe to warrant the absolute requirement that it be studied in adequate numbers (i.e., 10% or 28 in this situation) such that efficacy has been undisputably demonstrated rather than partially inferred from other respiratory indications. There were a total of 8 trovafloxacin-treated CAP patients who had *S. aureus* isolated as the sole respiratory pathogen; of these, 6 were cured and 2 were improved.

Since the recommendation has now been made that the nosocomial pneumonia indication should include *Staph aureus* (see Dr. Alivasatos' review), the situation now exists in which a closely related respiratory indication (in fact, one in which the patients are, in general, sicker) has been approved for this pathogen. This medical officer thus concludes that it is reasonable to allow the inclusion of this organism to the list of pathogens for the CAP indication as well. The overall numbers (14/14) are essentially identical to those of the levofloxacin review (15/17); this conclusion is based neither on a judgment of the 'quality' of these numbers based on underlying trial design, nor on the basis of additional numbers from a study that was never submitted as a major clinical amendment to this NDA.

Philip E. Coyne, Jr., MD
Medical Officer
HFD-590

concurrence: HFD-590/DivDir/Goldberger
HFD-590/TL/Leissa

Medical Officer's Review of NDAs 20-759 and 20-760

Complicated Intra-abdominal Infections

- 1.1 NDAs : 20-759 (oral tablets) and 20-760 (injection)
- 1.2 Applicant identification
 - 1.2.1 Pfizer Central Research
 - 1.2.2 Address and telephone number:
Eastern Point Road
Groton, CT 06340
- 1.3 Submission/review dates
 - 1.3.1 Date of submission : 27 December 1996
 - 1.3.2 CDER stamp date : 30 December 1996
 - 1.3.3 Date submission received by reviewer : 6 January 1997
 - 1.3.4 Date review begun : 4 June 1998
 - 1.3.5 Date review completed : 12 December 1997
- 1.4 Drug identification
 - 1.4.1 Generic name : trovafloxacin mesylate (tablets)
alatrofloxacin mesylate (solution for injection)
 - 1.4.2 Proposed trade name : **TROVAN™**
 - 1.4.3 Other names used during development: CP-99,219 (tablet)
CP-116,517 (IV)
- 1.5 Pharmacologic Category : fluoronaphthyridone
- 1.6 Dosage form : See 1.1 above
- 1.7 Route of Administration : intravenous (20-760) and oral (20-759)
- 1.8 Proposed Indication & Usage section :

COMPLICATED INTRA-ABDOMINAL INFECTIONS, including post-surgical infections caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus viridans*, *Bacteroides thetaiotaomicron*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Staphylococcus aureus*, *Beta Streptococcus* Group B, *Peptostreptococcus* species, *Prevotella* species, *Enterobacter* species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

1.9 Proposed Dosage and Administration section :

300 mg I.V. followed by 200 mg oral for a total of 7-14 days.

NOTE: Where the BernhardMod BT font is used in this document, this represents text copied from the applicant's submission.

1.10 Related Drugs : See 1.4.3 above.

1.11 Material Reviewed : NDAs and amendments

1.12 Regulatory Background

A) Anti-Infective Drug Products Approved For This Indication

The following products are approved for "INTRA-ABDOMINAL INFECTIONS" (NOTE: some labels specify "including peritonitis"):

amikacin, aztreonam, cefoperazone, cefotaxime, ceftazidime, clindamycin, imipenem/cilastatin (PRIMAXIN®), metronidazole, mezlocillin, netilmicin, ticarcillin, ticarcillin/clavulanate (TIMENTIN®), tobramycin,

Piperacillin/tazobactam (ZOSYN) is approved for "**Appendicitis (complicated by rupture or abscess) and peritonitis** caused by piperacillin resistant, beta-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group; *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, Or *B. vulgatus*. The individual members of this group were studied in less than 10 cases."

Parenteral ciprofloxacin (CIPRO) is approved for "**Complicated Intra-Abdominal Infections** (used in conjunction with metronidazole) caused by *E. coli*, *P. aeruginosa*, *P. mirabilis*, *K. pneumoniae*, or *B. fragilis*" at a dose of 400 mg q12 hrs.

Owing to the recent approval (1996) of meropenem (MERREM; NDA 50-706) for CIAI, the MO reviewed the original MOR. In piecing together the MERREM history, this MO noted the following highlights from the MOR:

In the original NDA submission (1993), clinical experience for CIAI included a single North American and three foreign studies:

- 3591US/0007 -- considered by the original MO as a single adequate and well-controlled study for complicated appendicitis - meropenem 1g q8h vs. clindamycin + tobramycin (double-blind study)
- 194660/0300
- 194660/0301
- 194660/0402

**APPEARS THIS WAY
ON ORIGINAL**

The original MO concluded that a confirmatory trial was needed for intra-abdominal/pelvic cavity infections. Submitted data from foreign studies were considered inadequate. Therefore, the indication was considered not approvable.

The MERREM resubmission consisted of three foreign, open-label studies (conducted between 1989-1991):

- 14660/0300 - meropenem 1g q8h vs. cefotaxime + metronidazole (Europe and S. Africa)
- 14660/0301 - meropenem 1g q8h vs. imipenem/cilastatin (Europe)
- 14660/0402 - same as 301 (Europe)

In the company's presentation of the data, they pooled data across studies.

As discussed in the original MOR, to be considered evaluable, the following criteria were used:

- Documentation that the operative site was evaluated.
- Follow-up ≥ 7 days post-therapy.
- For failure: Received a minimum of 48 hours of study drug.

**APPEARS THIS WAY
ON ORIGINAL**

The studies were designed with the end-of-therapy visit as the primary efficacy endpoint. However, since the original MO wanted a minimum of 7 days post-therapy follow-up to be considered evaluable, the FDA evaluable population dropped to 30%.

The MO concluded that MERREM was equivalent to Primaxin but inferior to cefotaxime/metronidazole. Furthermore, efficacy was considered too low (5/11) to include *E. faecalis* in the listing of approved pathogens in the INDICATIONS AND USAGE section. In addition to that shown above, the following labeling eventually was approved in 1996:

B) Regulatory Guidance

1992 DAIDP "Points to Consider" document (PTC)

The PTC states that for the treatment indication "complicated intra-abdominal infections" (CIAI):

- only a single study is needed
- only patients that require surgical intervention, including penetrating and blunt trauma should be studied.
- at least 80% of clinically evaluable patients should be microbiologically evaluable
- for an anaerobic claim, the drug product under review needs to establish effectiveness in either at least one other infection (with anaerobes) or establish in-vitro susceptibility and animal data effectiveness.

- need a reasonable mix of intra-abdominal infections – if not, a labeling restriction may be necessary
- it is expected for this indication to be granted, that efficacy also must be established in gynecologic infections at the same dosing and duration.
- tissue distribution studies are expected. (PK/PD)

IDSA/FDA Guidelines (Clinical Infectious Diseases; 15, Suppl. 1; Nov. 1992)

The guidelines make the following points about CIAI:

- Appropriate diseases for CIAI: where surgical intervention is needed (including percutaneous drainage). viscous perforation frequently resulting in peritonitis and/or abscess (including liver, pancreas, & spleen), periappendiceal abscess, perforated appendicitis, following emergency or elective operation with associated problems noted above.
- Inappropriate diseases for CIAI: diverticulitis, acute cholecystitis, non-operative management of acute appendicitis, Crohn's, ulcerative colitis (NOTE: w/o perforation), postoperative abdominal wound infections, spontaneous bacterial peritonitis, and CAPD-associated peritonitis perinephric infections, female genital tract infections, acute appendicitis, suppurative appendicitis

The IDSA/FDA Guidelines go on to comment on specific CIAIs:

- Acute gastric and duodenal perforations: if perforation occurs <24 hours prior to surgery, mostly gram-positive organisms and cultures only reflect intraluminal flora and therefore NOT appropriate for CIAI. However, if >24 hours, then gram-negative facultative and obligate anaerobes are present and culture results should correlate well with the isolation of this organism as a true pathogen.
- Traumatic perforations and transmural necrosis of the intestine: appropriate to include in CIAI study if surgery occurs >12 hours after perforation.
- Infections arising from the distal small bowel, appendix, and colon/rectum: need abscess or peritoneal fluid with WBCs and isolation of organisms from the infected site.
- Infections that occur following emergency or elective operation: constitute approx. 25% of intra-abdominal infections. May include resistant pathogens due to the failure of prophylaxis. Activity against resistant bugs (e.g., *P. aeruginosa* and *Enterobacteriaceae*) is important here.

The Guidelines discuss the following miscellaneous points:

- Parenteral therapy is usually continued until the patient is afebrile, WBC <12,500/mm³, and return of bowel function - generally after a 7-day course.
- Infection must be documented at the time of surgery or during radiographically-directed drainage procedure.
- Patients should not be enrolled if the APACHE score >35
- Minimum total treatment duration (IV + PO) is typically 5 days; maximum is 14 days. If patients require >14 days of treatment, they should be considered failures. The minimum parenteral therapy is typically 3 days prior to switching to oral therapy.
- Patients who receive additional antimicrobial agents for nosocomial infections outside of the abdomen ≥5 days into the trial should be evaluated on the day on which therapy these agents are initiated. If there is no evidence of intra-abdominal sepsis at this time and there is no evidence of recurrent intra-abdominal infection during the subsequent clinical course, the patients should be considered clinically cured.

Clinical evaluability summarized (per IDSA/FDA Guidelines)

- Appropriate diagnosis (abscess, peritonitis, etc.) - diagnosed and treated via laparotomy or radiographically-directed drainage procedure.
- Survive >48 hours
- APACHE score <35 at entry
- For gastric & duodenal perforations: Need >24 hours since perforation prior to defining surgery
- For traumatic perforation, need >12 hours since perforation prior to defining surgery

Microbiological evaluability summarized (per IDSA/FDA Guidelines)

- Clinically evaluable AND
- (+) culture within 24 hours of defining surgery -- blood and/or site culture

Clinical outcomes summarized (per IDSA/FDA Guidelines):

Cure

- Minimum duration of therapy to be considered a cure is 5 days (first 3 days of therapy should be IV)
- To be evaluable for cure, the patient needs a valid 4-6 week follow-up visit after study entry

Failure

- additional surgical procedures needed
- treatment prolonged >14 days

- Any modification of therapy
2. Table of Contents: not applicable
 3. Chemistry/Manufacturing Controls:
 4. Animal Pharmacology/Toxicology:

CP-99,219 was found efficacious in a rat abscess model relative to control animals and comparable in effect with animals treated with clindamycin/gentamicin. (SOURCE: Onderdonk AB, BWH, Channing Labs; personal communication.) The preliminary data from this study are presented in the following table. This experimental model of intra-abdominal sepsis has been shown to consist of two phases: early peritonitis and abscess development in surviving recipients of a fecal inoculum. During the early, acute peritonitis stage, *Escherichia coli* and other Gram-negative organisms are numerically dominant and appear to be responsible for mortality. The second and more chronic stage of the disease, abscess formation, requires the presence of obligate anaerobes, such as *Bacteroides fragilis*. Quinolones, such as ciprofloxacin, do not prevent abscess formation when used alone in this animal model. Thus, the finding of only 2 of a possible 17 abscess formations in animals treated with CP-99,219 is further evidence suggesting the potential of this agent as sole treatment of intra-abdominal infections.

	Control	CP-99,219	Clindamycin-gentamicin
Mortality (%)	13/19 (68.4%)	1/18 (5.6%)	0/19 (0.0%)
Abscess (%)	6/6 (100%)	2/17 (12%)	3/19 (16%)
Organisms recovered	<i>E. coli</i> <i>Gr. D. Strept</i> <i>Lactobacillus</i> <i>C. perfringens</i> <i>B. fragilis</i> <i>Fusobacterium</i>	<i>E. coli</i> <i>Lactobacillus</i>	<i>E. coli</i> <i>Gr. D. Strept</i> <i>Lactobacillus</i>

Table : Preliminary data from rat abscess model treated with CP-99,219 (20 mg SC three times daily for 7 days), clindamycin (15 mg SC three times daily for 7 days) and gentamicin (2 mg IM three times daily for 7 days), or placebo (Control).

5. Microbiology:

The MIC_{90s} of trovafloxacin for pathogens commonly associated with intra-abdominal infections are listed in the following table:

Pathogen	MIC ₉₀ range (µg/mL)	median MIC ₉₀ (µg/mL)
AEROBES		
Gram (+)		
<i>S. agalactiae</i>	0.12-0.5	0.25
<i>S. aureus</i> (MSSA + MRSA)	1-8	2.0
viridans group streptococci	0.06-0.5	0.25
<i>E. faecalis</i> (vanc S)	0.25-8	2.0
<i>E. faecalis</i> (vanc R)	8-16	8.0
<i>E. faecium</i> (vanc S)	0.78-4	2.0
<i>E. faecium</i> (vanc R)	4-32	8.0
Gram (-)		
<i>Acinetobacter baumannii</i>	>8	>8
<i>C. freundii</i>	0.25-4	0.375
<i>E. coli</i>	<0.015-4	0.06
<i>E. cloacae</i>	0.05-2	1.6
<i>K. pneumoniae</i>	0.06-1	0.12
<i>M. morganii</i>	0.12-2	0.5
<i>Proteus mirabilis</i> (indole -)	0.12-4	0.5
<i>Proteus vulgaris</i> (indole +)	0.25-1	0.5
<i>Providencia stuartii</i>	0.5-2	2.0
<i>P. aeruginosa</i>	1->16	2.0
STRICT ANAEROBES		
<i>B. fragilis</i> group		
<i>B. fragilis</i>	0.5-2	1.0
<i>B. fragilis</i>	≤0.25-2	0.5
<i>B. thetaiotaomicron</i>	0.5-4	1.0
<i>B. ovatus</i>	1-2	2.0
<i>B. distasonis</i>	0.5-1	1.0
<i>B. vulgatus</i>	0.5-4	4.0
<i>B. uniformis</i>	2-4	4.0
<i>Prevotella</i> spp.		
<i>P. bivia</i>	1-2	1.0
<i>P. bivia</i>	1-2	1.0
<i>P. intermedia</i>	1	1.0
<i>P. melaninogenica</i>	1-2	1.5
<i>C. perfringens</i>	0.12-0.25	0.25
<i>Peptostreptococcus</i> spp.	0.25-1	1.0
<i>Fusobacterium</i> spp.		
<i>F. nucleatum</i>	0.5-2	1.0
<i>F. nucleatum</i>	0.25-0.5	0.375

6. Human Pharmacokinetics/Pharmacodynamics: See biopharm review.

The peak blood level (C_{max}) of alatrofloxacin at the 300 mg intravenous dose (trovafloxacin equivalent dose) used for intra-abdominal infections is 4.4 µg/mL with a half-life of 10.8 hours. The fluid/serum concentration ratio of trovafloxacin in peritoneal fluid after IV administration of 200 mg alatrofloxacin was 0.39. Mean tissue/serum concentration ratios for gynecologic tissues (ovary, uterus, myometrium, cervix and fallopian tubes) ranged after single or multiple doses of oral trovafloxacin 200 mg. Thus, based upon its pharmacokinetic profile, single daily intravenous doses of 300 mg alatrofloxacin will exceed the MIC₉₀ values of pathogens commonly involved in intra-abdominal and acute pelvic infections.

7. Human Clinical Experience: not applicable

8. Clinical Studies:

8.1 Protocol Overview:

**APPEARS THIS WAY
ON ORIGINAL**

Study: 154-124

Protocol Title: A Randomized, Double-Blind, Multicenter Trial Assessing The Safety and Efficacy of Intravenous CP-116,517 (alatrofloxacin) Followed by Oral CP-99,219 (trovafloxacin) Compared to Intravenous Imipenem/Cilastatin (PRIMAXIN®) Followed by Oral Amoxicillin/Clavulanic Acid (AUGMENTIN®) for the Treatment Of Complicated Intra-Abdominal Infections

Study Dates: 12 April 1995 - 20 June 1996

**APPEARS THIS WAY
ON ORIGINAL**

Study objective : To compare the safety and efficacy of alatrofloxacin (intravenous prodrug) followed by oral trovafloxacin with the combination of intravenous imipenem/cilastatin followed by oral amoxicillin/clavulanic acid in the treatment of subjects with complicated intra-abdominal infections.

Subjects with suspected complicated intra-abdominal infections were randomized in a double-blind fashion to receive either a regimen of intravenous alatrofloxacin and oral trovafloxacin (300 mg/day intravenously followed by 200 mg/day orally for a maximum of 14 days of total therapy) or a combined regimen of imipenem/cilastatin (maximum dose of 1 gram intravenously every 8 hours) followed by amoxicillin/clavulanic acid (500 mg orally every 8 hours). Switching from parenteral to oral medication was to be determined by the investigator when oral intake had been re-established.

**APPEARS THIS WAY
ON ORIGINAL**

Adequacy of comparator:

PRIMAXIN® (imipenem/cilastatin) is FDA-approved in the INDICATIONS AND USAGE section for the treatment of:

**APPEARS THIS WAY
ON ORIGINAL**

MO Comment : PRIMAXIN® is an adequate comparator.

Although AUGMENTIN® is not FDA-approved for intraabdominal infections, the applicant argues:

Amoxicillin/clavulanic acid is clinically accepted as follow-up oral therapy in the treatment of severe infections, in particular those involving β -lactamase producing organisms and anaerobic organisms responsible for intra-abdominal infections (e.g. *Bacteroides* sp.).^{1,2}

¹Ball P, Watson T, Mehtar S. Amoxycillin and clavulanic acid in intra-abdominal and pelvic sepsis. *J Antimicrob Chemother* 1981; 7:441-444.

²Yashioka K, Youngs DJ, Keighley MR. A randomised prospective controlled study of ciprofloxacin with metronidazole versus amoxicillin/clavulanic acid with metronidazole in the treatment of intra-abdominal infection. *Infection* 1991; 19:25-29.

MO Comment : Pfizer's rationale to use AUGMENTIN® as the follow-up oral therapy to PRIMAXIN® is acceptable.

Sample size: A total of 300 subjects were to be enrolled in this study. Recruitment was to cease when 300 subjects had been enrolled, even if some centers had not reached their projected recruitment targets.

MO Comment : The applicant enrolled a total of 414 patients instead.

Noteworthy Inclusion Criteria :

- 1) Subjects who are found to have one of the following infections requiring anti-infective therapy and an operative procedure or percutaneous drainage. Subjects must have physical examination findings consistent with an intra-abdominal infection (e.g. signs of peritoneal irritation, mass) as well as systemic evidence of inflammation (for example, fever [body temperature ≥ 38.5 °C], WBC $> 12,500$ cells/mm³, hypotension [systolic blood pressure < 90 mmHg], etc.). Physical findings may also include clinically-documented serosal inflammation and/or presence of localized or diffuse abdominal wall rigidity, mass, or ileus. Where appropriate, imaging studies may support signs and symptoms of an intra-abdominal infection.
- intra-abdominal abscesses
 - bacterial peritonitis
 - appendicitis with evidence of a perforation or abscess; duration of symptoms ≥ 24 hours
 - acute perforations of the stomach or duodenum only if not operated on within 24 hours of perforation
 - traumatic perforations of the small bowel (excluding duodenum) or large bowel only if not operated on within 12 hours of perforation
 - perforations unrelated to trauma of the small bowel (excluding duodenum) or large bowel
 - intra-abdominal infections related to previous intra-abdominal surgery
 - intra-abdominal infections following penetrating and blunt trauma.

MO Comment : The protocol specifies that "Findings at operation must confirm the presence of an intra-abdominal infection (e.g. presence of purulent exudate and inflamed or necrotic tissue)."

- 2) Duration of the treatment of the intra-abdominal infection is anticipated to be at least 3 days.
- 3) Subjects may be included into the study after receiving prior anti-infective therapy under the following conditions:
 - the previous anti-infective therapy was given for < 24 hours of therapy with a drug which requires ≥ 7 days duration of therapy
 - subjects with a known intra-abdominal abscess may be enrolled into the study despite receiving empirical therapy for several days if pre-treatment cultures at time of surgery or percutaneous drainage yield bacterial pathogens susceptible to the study drugs
 - subjects infected with an organism that is resistant *in vitro* to the anti-infective drug initially used, provided that the organism causing the infection is recovered within _____ before enrollment and is susceptible to the study drugs.

Noteworthy Exclusion Criteria :

**APPEARS THIS WAY
ON ORIGINAL**

- 1) Subjects with any of the following disease states:
 - perinephric infections
 - infections of the female genital tract (gynecological infections)
 - spontaneous bacterial peritonitis
 - peritonitis associated with chronic peritoneal dialysis
 - acute (< 24 hours) perforations of the stomach or duodenum
 - traumatic perforations of the small or large bowel and operated on within 12 hours of the perforation
 - transmural necrosis of the intestine due to acute embolic or thrombotic occlusion
 - acute cholecystitis with infection confined to the gallbladder
 - early acute or suppurative (nonperforated) appendicitis unless there is evidence of an abscess or free peritoneal fluid containing leukocytes and microorganisms suggestive of regional contamination
 - pancreatic and peripancreatic sepsis.

- 2) Baseline APACHE II score > 35 obtained within 48 hours prior to randomization into double-blind therapy.
- 3) Subjects who require "open abdomen" techniques for management. However, when clinically-indicated, temporary closure of the abdominal incision using Marlex® (or equivalent) with a subsequent, *planned* surgical procedure to close the abdomen within 72 hours of the initial surgical procedure will be allowed.
- 4) Subjects with any infections that require treatment with an anti-infective agent other than the study drugs. Subjects requiring antibiotic irrigation of the abdominal cavity or surgical wound are not suitable for entry.
- 5) Immunocompromised patients

APPEARS THIS WAY
ON ORIGINAL

MO Comment : The applicant's criteria are entirely consistent with the IDSA/FDA Guidelines. The MO agrees with the applicant's use of them.

Evaluation Visits :

Patients were to be evaluated at baseline (day 1; within 48 hours prior to the start of therapy), daily between days 1-14, at end of therapy (EOT), and long-term follow up (EOS; days 28-42). Clinical response to therapy was to be assessed by the investigator at the end of the double-blind treatment period as well as at follow-up (day 30).

MO Comment : From a practical standpoint, the applicant used EOS as ≥ 21 days of study. Although the IDSA Guidelines recommend a 4-6 weeks post-therapy test-of-cure follow up visit, the MO considers this visit window acceptable. Furthermore, MERREM was recently approved for this indication based on a minimum follow-up visit of 7 days post-therapy.

At entry into the study, based on the findings from the illness-defining procedure, the investigator was instructed to capture the following information on the CRF:

UNDERLYING DISEASE (check all that apply) :

- ◇ Appendicitis with perforation or abscess ≥ 24 hours
- ◇ Acute perforation of stomach or duodenum with surgery ≥ 24 hours
- ◇ Perforation (non-traumatic) of small or large bowel
- ◇ Traumatic perforation of small bowel or large bowel with surgery ≥ 12 hours
- ◇ Intra-abdominal infection following penetrating or blunt trauma
- ◇ Intra-abdominal infection related to previous intra-abdominal surgery
- ◇ Other (specify) _____

APPEARS THIS WAY
ON ORIGINAL

SITES OF INTRA-ABDOMINAL INFECTION (check all that apply):

- ◇ Distal esophagus/stomach/duodenum
- ◇ Appendix
- ◇ Pancreas

- ◇ Biliary tree
- ◇ Colon
- ◇ Proximal small bowel
- ◇ Liver
- ◇ Distal small bowel
- ◇ Spleen
- ◇ Other (specify) _____

**APPEARS THIS WAY
ON ORIGINAL**

TYPE OF INFECTION (check all that apply):

- ◇ Single abscess
- ◇ Multiple abscesses
- ◇ Peritonitis

Protocol Prohibitions

- Intraluminal use of antibiotics was not allowed during the study.

Microbiology

**APPEARS THIS WAY
ON ORIGINAL**

The protocol stipulated,

- pre-treatment blood and peritoneal fluid specimens for culture were to be obtained within 48 hours prior to initiation of therapy or, with peritoneal fluid samples, up to 12 hours after the initiation of therapy. Each probable pathogen was to be identified to the species level.”
- blood cultures (more than 1) must be obtained from all subjects.

The following susceptibility testing was employed for this study:

Criteria	CP-99,219 ¹	Imipenem-cilastatin ²		Amoxicillin-clavulanic acid ²	
	MIC µg/mL	Zone 10-µg disk	MIC µg/mL	Zone 30-µg disk	MIC µg/mL
Susceptible	≤ 2	≥ 16	≤ 4	≥ 18	≤ 8
Intermediate	4	14 - 16	8	14 - 17	16
Resistant	≥ 8	≤ 13	≥ 16	≤ 13	≥ 32

¹tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing

²NCCLS criteria

According to the protocol, subjects need not be discontinued from the study drug if they do not have a pathogen isolated at baseline or because the pathogen is

resistant to any of the study medications. Rather, the investigator could choose to continue the patient in the study if there was evidence of clinical improvement.

Outcome Definitions

APPEARS THIS WAY ON ORIGINAL

Clinical response

At each visit, clinical response was assessed for the presence or absence of intra-abdominal pain/tenderness, abdominal rigidity, swelling, induration, surgical wound discharge, mass, ileus, bowel sounds, formed bowel movements, flatulence, hypotension and leukocytosis on the CRF. The following clinical response definitions were used by the applicant.

Cure : Typically, a successful outcome may be characterised by resolution of signs and symptoms of an inflammatory response (e.g. fever [body temperature ≥ 38.5 °C], elevated white blood cell count [WBC $\geq 12,500$ cells/mm³], hypotension [systolic blood pressure < 90 mmHg]) and intra-abdominal distress (localized or diffuse abdominal wall rigidity and/or mass and/or ileus, pain/tenderness, abdominal swelling, discharge, induration, and lack/presence of bowel sounds).

MO Comment : As stated above, the IDSA/FDA Guidelines state that the minimum duration of therapy to be considered a cure is 5 days and that the first 3 days of therapy should usually be administered parenterally. The MO asked the applicant to identify "clinically evaluable" patients in both treatment arms who transitioned from IV to oral within 3 days of study onset. The applicant responded that for the "cure" rate was 3/6 (50%) and 9/12 (75%) for the TROVAN and PRIMAXIN→AUGMENTIN treatment arms, respectively.

APPEARS THIS WAY
ON ORIGINAL

Improvement : Resolution of some but not all intra-abdominal symptoms and no requirement for additional antibiotic. The investigator will determine if the subject is improved from baseline, rather than cured or failed antibiotic therapy.

Failure will be defined by one or all of the following conditions:

- lack of resolution of all signs and symptoms of an intra-abdominal infection (as defined above).
- the need for additional antibacterial therapy for the treatment of the intra-abdominal infection. The reason for additional antibiotic therapy must be documented in the subject's Case Report Form.
- the need for greater than 14 days of antibiotic therapy.
- the need for more than one surgical procedure (with the exclusion of replacement of peritoneal drainage tubes). However, if assessed independently

by a blinded panel of investigators and the sponsor that the initial surgical procedure is considered inadequate, then the subject should be considered non-evaluable (see below). Subjects who require temporary closure of the abdominal incision using Marlex® (or equivalent) with a subsequent, *planned* surgical procedure to close the abdomen within 72 hours of the initial surgical procedure will be considered as having a single surgical procedure. Thus, this delayed closure procedure will not be considered a treatment failure.

The occurrence of any of the following conditions will supersede the evaluation of response as cure, improvement, or failure and will result in the reassignment of outcome by the sponsor as follows:

- for subjects who were previously assessed as failures, the outcome will always be failure at subsequent time points.
- for subjects who were given a concomitant systemic antibiotic prior to an evaluation time point, response will be classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.

According to an August 1995 protocol amendment: For subjects who stopped double-blind therapy because of no apparent response, response will be classified as failure.

According to a November 1995 protocol amendment : Clinical response will also be determined at initiation of concomitant antibiotic therapy. Patients who receive additional antimicrobial agents for any infections outside of the abdomen ≥ 5 days into the study must be evaluated on the day on which therapy with these agents is initiated.

MO Comment : The MO asked the applicant to identify patients in the clinically evaluable population considered "successes" (cure or improvement) who received a systemic anti-infective drug product ≥ 5 days into the study considered "unrelated" to the intra-abdominal infection. The applicant noted 19 and 14 patients in the TROVAN and PRIMAXIN→AUGMENTIN treatment arms, respectively, who met these criteria. Example reasons included pneumonia, UTI, wound suppuration, tooth abscess, change in therapy due to the development of an adverse event, and "prophylaxis".

Bacteriologic Response

APPEARS THIS WAY ON ORIGINAL

Bacteriologic response was usually presumptively determined based on the subject's clinical outcome. Possible responses included : **eradication**, **presumed eradication**, **persistence**, **superinfection** (new pathogen during therapy), and **presumed microbiological persistence**.

MO Comment : The MO agrees with the applicant's outcome definitions.

Evaluability Definitions**APPEARS THIS WAY
ON ORIGINAL****(1) Evaluable population**

To be considered fully evaluable for clinical response, a subject must have :

- a. an intra-abdominal focus of established infection documented by operative intervention or by a radiographically-controlled drainage procedure
- b. signs and symptoms of an intra-abdominal infection

**APPEARS THIS WAY
ON ORIGINAL**An indeterminate clinical outcome assessment was made (i.e., made nonevaluable), if the subject fulfilled any of the following criteria:

- a. Insufficient therapy: received < 5 days of double-blind therapy unless considered a failure
- b. inapplicable diagnosis (i.e. subject did not meet entry criteria for intra-abdominal infection).
- c. Concomitant systemic antibacterials given for intercurrent illness. However, if a subject receives additional antimicrobial agents for nosocomial infections outside the abdomen ≥ 5 days into the trial, the reason should be documented by the principal investigator or his designate and noted on the subject's Case Report Form. If no evidence of an intra-abdominal infection, nor evidence of a recurrent intra-abdominal infection during the subsequent clinical course exists, then this subject may be considered evaluable and, accordingly, a clinical cure.³
- d. Missing post-baseline clinical assessments: no visit at evaluation point unless subject was previously designated as a treatment failure.
- e. Inadequate initial operative procedure. An operation is considered inadequate if not all communications between the gastrointestinal tract and the peritoneal cavity are closed and/or if necrotic intestine is left and/or if an infected collection was missed at the initial drainage. Prior to the blind being broken, a panel of investigators and the sponsor will consider those cases which have questionable evaluability. Operative notes or percutaneous drainage notes will be reviewed and a decision will be rendered on the evaluability of these subjects.
- f. Death: subjects who die within 48 hours after initiation of double-blind therapy.
- g. if appropriate, other criteria may be added.

**APPEARS THIS WAY
ON ORIGINAL**An indeterminate bacteriologic outcome assessment was made (i.e., made nonevaluable), if the subject fulfilled any of the following criteria:**APPEARS THIS WAY
ON ORIGINAL**

³Solomkin JS, Hemsell DL, Sweet R, Tally F, Bartlett J. Evaluation of new anti-infective drugs for the treatment of intra-abdominal infections. *Clin Infect Dis* 1992; 15(Suppl 1):S33-S42.

- a. relevant post-baseline cultures are not obtained, unless it is a result of the absence of adequate purulent culture material (to be considered presumptive microbiologic eradication as defined below) or concomitant antibiotic use due to bacteriologic persistence
- b. concomitant antibiotic use for treatment of an intercurrent illness
- c. the subject was not considered clinically evaluable.

(2) Modified Intent-to-Treat population (protocol defined)

To be evaluable for the MITT analysis,

Subjects with inappropriate primary diagnoses (e.g., no clinical signs or symptoms at baseline, or having entered the study more than once) will be excluded. Otherwise, all randomized subjects will be included in the modified ITT analysis. Subjects with no clinical information after the baseline evaluation will be considered as clinical treatment failures.

Clinical Intent-to-Treat Subjects (from study summary)

The clinical intent-to-treat subjects subset included those subjects in the all randomized subjects subset who had confirmed intra-abdominal infection and underwent surgery or percutaneous drainage at baseline. Some subjects in this subset may never have received any study medication.

Bacteriological Intent-to-Treat Subjects (from study summary)

The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline in either peritoneal fluid or blood culture. Subjects in this subset may never have received any study medication.

Efficacy Analyses

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According to a November 1995 protocol amendment, the primary efficacy parameter:

will be *sponsor-defined* clinical response at follow-up (day 30).

The same amendment states :

The following secondary efficacy outcome parameters will be tabulated and compared between treatment groups:

- *sponsor-defined* clinical response at end of double-blind therapy
- *investigator-defined clinical response at the end of double-blind therapy and at follow-up*
- *sponsor-defined organism outcome at end of treatment and at follow-up*
- changes in baseline APACHE score on days 4, 7, 10, and 14 after start of double-blind therapy
- time post-operatively spent in the hospital (days)
- time of post-operative fever (days)
- time to recovery (days)
- duration of intravenous therapy (days)
- proportion of subjects with nosocomial infection
- proportion of subjects receiving additional antibiotics

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Schedule of Study Evaluations

Study day Allowable Window:	Day 1 -48 hours	Day 4 Day 3-5	Day 14 ^a Day 10-14	Day 30 Day 28-42
Treatment Period	Day 1 to Day 14 ^a			
Follow-up period	Day 15 to Day 42			
Informed consent	X			
Demographic information	X			
Physical examination of the abdomen ^b	X-----X		X	X
Maximum body temperature ^b	X-----X		X	X
Vital signs	X	X	X	X
Concomitant medication	X	X	X	X
APACHE scoring	X	X ^c	X	
Dosing record		X	X	
Clinical signs & symptoms ^b	X-----X		X	X
Assessment of bowel function ^b	X-----X		X	X
Microbiology culture & sensitivity				
• blood	X	X ^d	X ^d	X ^d
• peritoneal	X ^c			
Safety laboratory tests				
• hematology	X	X	X	abn
• biochemistry	X	X	X	abn
• urinalysis	X	X	X	abn
• pregnancy test ^f	X			
Adverse events	X-----X			X
Investigator's assessment of clinical response ^g			X	X
Time of recovery	X-----X			X
Health care resource utilization	X-----X			X

^aor end of double-blind therapy if sooner

^bperformed daily during the hospitalization period

^crecorded also on days 7 and 10

^donly if clinically indicated (e.g., time of discontinuation or previously positive culture)

^eor up to a 12-hour period after start of therapy

^fto be done locally for women of child bearing potential

^gand to be done at the time of discontinuation, if applicable

abn=to be done only if abnormal at previous visit or clinically significant adverse event

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8.3 Study Results

MO Comment : The Medical Officer reviewed the applicant's patient data and, in general, agreed with their assignment of patients to populations and outcome responses. Therefore, for the purposes of this review, the MO's and applicant's efficacy and safety populations are the same.

INVESTIGATORS:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5133	Dennis Mikolich, MD
	5204	Stanley Klein, MD
	5229	Michael Neill, MD
	5429	John Yatsu, MD
	5431	Steven Mintz, MD
	5486	David Borgstrom, MD
	5495	George Mueller, MD
	5497	Joseph Wentzky, Jr, MD
	5524	C. Gene Cayten, MD
	5525	David Smith, MD
	5526	Gene Coppa, MD
	5529	Vinod Dhawan, MD
	5530	Philip Donahue, MD
	5532	Blaine Enderson, MD
	5533	Michael Esser, MD
	5534	Richard Greenberg, MD
	5535	David Longworth, MD
	5537	Luis Jauregui, MD
	5542	Carey Page, MD / Ronald Stewart MD
	5545	Robert Martindale, MD
	5549	Michael Metzler, MD
	5550	Ronald Simon, MD
	5552	John Oropello, MD
	5553	Russell Postier, MD
	5557	William Stahl, MD
	5560	Richard Wait, MD
5562	Bienvenido Yangco, MD	
5563	Thomas Berne, MD	
	Albert Yellin, MD	
5599	Jefferson Stowers, MD	
5606	Robert Gainer, II, MD	
5608	Lawrence Nastro, MD	
5610	Jon White, MD	
5613	Peter Krumpke, MD	
5614	Amir Neshat, MD	
5615	Kathaleen Porter, MD	
5616	David Redfield, MD	

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States (continued)	5617	Joseph Solomkin, MD
	5619	Barry Miskin, MD
	5661	Norman Zinner, MD
	5739	James Wagner, MD
	5761	John Mazuski, MD
	5910	Joseph Portoghese, MD
	5931	Carol Kemper, MD
	5970	Alan Sugar, MD
	5998	Kenneth Courington, MD
	6006	Richard Kohler, MD
	6012	Corrado Marini, MD
	6044	Alexander Robbins, MD
	6046	E. Robert Harris, MD
	6047	Joseph Scoma, MD
	6048	Mark Sherman, MD
	6052	Craig Schaefer, MD
	6053	Ronald Nichols, MD
	6055	Jan Elston, MD
	6067	Larry Danziger, PharmD
	6068	Leon Smith, MD
	6069	Judith Wolf, MD
	6090	Burke Cunha, MD
	6099	Manuel Ramirez, MD
	6100	Vinod Rustgi, MD
	6107	Dana Edwards, MD
	6151	Gregory Timberlake, MD
	6155	Ellis Caplan, MD
	6170	Eduardo Gonzales, MD
	6246	Michael Hellinger, MD
	6287	Nicholas Price, MD
	6344	William O'Riordan, MD
	6367	Del Dehart, MD
	6380	John Dawson, MD
	6381	Bruce Harris, MD
	6382	Jay Harviel, MD
	6383	Carol Leitner, MD
	6395	Gaylord Kavlie, MD
6398	Patrick White, MD	
6409	Ronald Jackson, DO	
6424	H. Scott Bjerke, MD	
6425	Edward Condon, MD	
6431	Martin Schrieber, MD	
6498	Thomas Lawson, Jr., MD	
6499	Robert Cohen, MD	
France	5187	Dr. Didier Grange
	5199	Dr. Paul Teniere
	5990	Dr. Francois Fraisse
	6013	Dr. Georges Goursot
	6014	Dr. Francis Bur

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
France (continued)	6016	Dr. Jean Dupeyron
	6017	Dr. Philippe Duvaldestin
	6018	Dr. Luc Guyot
	6019	Dr. Claude Jacquot
	6020	Dr. Patrick De Rohan Chabot
	6095	Dr. G. Kohlmann
	6311	Dr. Patrick Cougard
	6436	Dr. Ghassan Ferzli
	6437	Dr. Fariborz Hakami
	6439	Dr. Jean-Michel Kerrenneur
	6440	Dr. Michel Ossart
	6441	Dr. Jean-Claude Otteni
	6442	Dr. Philippe Lallemand
	6444	Dr. Christian Virenque
Canada	5155	Sylvie Trottier, MD
	5598	Frederick Brenneman, MD
	5921	Frank Baillie, MD
	6365	Marvin Gerson, MD
	6384	Jean Ledoux, MD
	6451	Claude Lemieux, MD
	6465	Jean-Francois Bellemare, MD
	6467	Vivian Mcalister, MD
6468	Murray Girotti, MD	
Poland	6517	Dr. Otmar Gedliczka
	6518	Dr. Zygmunt Mackiewicz
	6521	Dr. Bogdan Lazarkiewicz
	6522	Dr. Bruno Szczygiel
	6523	Dr. Andrzej Karwowski
	6524	Dr. Wojciech Noszczyk
Belgium	6092	Dr. Bernard Broze
	6093	Dr. Claude Chastel
	6496	Dr. Yves Van Laethem
United Kingdom	6255	Dr. Roger Leicester
	6256	Dr. Eric Taylor
	6258	Dr. Peter Donaldson

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The study was conducted in several countries and many centers were enlisted (120 total centers: 80 USA, 9 Canada, and 31 Europe).

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Number of Patients Evaluated in Each Group		
	Alatrofloxacin ↓ Trovafloracin	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid
Randomized	204	210
Randomized, not treated	3	3
All Treated	201 (100%)	207 (100%)
Completed Treatment	167 (83%)	170 (82%)
Completed Study	181 (90%)	184 (89%)
Evaluated for Efficacy ^a		
Clinical Intent-to-Treat	200 (98%)	199 (95%)
Clinical Intent-to-Treat with Abscesses	118 (58%)	102 (49%)
Clinical Intent-to-Treat with Peritonitis	111 (54%)	115 (55%)
Clinically Evaluable ^b	156 (76%)	152 (72%)
Clinically Evaluable with Abscesses	96 (47%)	82 (39%)
Clinically Evaluable with Peritonitis	87 (43%)	85 (40%)
Bacteriologically Intent-to-Treat	171 (84%)	164 (78%)
Bacteriologically Evaluable	135 (66%)	131 (62%)
Assessed for Safety		
Adverse Events	201 (100%)	207 (100%)
Laboratory Tests	198 (99%)	205 (>99%)
a	Based on the number of randomized subjects.	
b	Evaluability determined at the end of study.	

A total of 414 patients (204 Trovan vs. 210 Primaxin → Augmentin) were randomized into the study. There was no significant difference between treatment arms in the proportion represented in the various study populations.

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Summary of Baseline Demographic Characteristics		
	Alatrofloxacin ↓ Trovafoxacin	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid
Baseline Demographic Characteristic	Number and Percentage (%) of Subjects	
	(N=156 ^a)	(N=152 ^b)
Gender		
Male	114 (73%)	95 (63%)
Female	42 (27%)	57 (27%)
Race		
Black	20 (13%)	15 (10%)
White	87 (56%)	94 (62%)
Other (primarily hispanic)	49 (31%)	43 (28%)
Weight (kg)		
males (mean)	77.1	79.6
females (mean)	68.9	67.9
Age (years)		
Mean	42.6	45.4
Minimum		
Maximum		
16-44	94 (60%)	78 (51%)
45-64	39 (25%)	45 (30%)
≥65	23 (15%)	29 (19%)
Diseases/Syndromes at Baseline^b	(N=201 ^c)	(N=207 ^c)
COPD	13 (6%)	20 (10%)
Diabetes Mellitus	13 (6%)	14 (7%)
Hepatic Disease	7 (3%)	4 (2%)
Impaired Renal Function	6 (3%)	5 (2%)
Congestive Heart Failure	5 (2%)	7 (3%)

COPD = chronic obstructive pulmonary disease.
a Clinically evaluable subjects.
b Not all treated subjects were assessed for intercurrent disease/syndrome at study entry.
c Treated subjects.

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Among the clinically evaluable study population, proportionally more males were studied in each arm. Otherwise, the two treatment arms appeared similar with regard to other demographic features.

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Summary of Baseline Risk Factors Associated with a Possible Unfavorable Outcome (Clinically Evaluable Subjects)		
	Alatrofloxacin ↓ Trovafoxacin (N=156)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)
Risk Factors	Number and Percentage (%) of Subjects	
Subjects with at Least One Risk Factor*	109 (70%)	91 (60%)
APACHE score		
Mean	6.4	7.0
Median		
Maximum		
Type of Infection		
Abscess only	69 (44%)	67 (44%)
Peritonitis only	60 (38%)	70 (46%)
<i>Abscess and Peritonitis</i>	27 (17%)	15 (10%)
Site of Infection		
<i>Multiple</i>	19 (12%)	18 (12%)
Underlying Disease		
Appendiceal rupture	81 (51%)	71 (47%)
Peptic ulcer perforation	32 (21%)	32 (21%)
<i>Post/op abscess or perforation</i>	32 (21%)	30 (20%)
Extreme Age		
>75	6 (4%)	12 (8%)
Health Insurance		
None	53 (34%)	47 (31%)

* *italicized* titles listed above represent "risk factors" (according to the applicant)

For the clinically-evaluable population, risk factors were similarly distributed between the two treatment groups at baseline with the exception of the infection type "abscess and peritonitis" being higher in the Trovan arm. (17% vs. 10%)

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Summary of Premature Discontinuations From Treatment				
(All-Treated Subjects)				
	Alatrofloxacin ↓ Trovafoxacin (N=201)		Imipenem/Cilastatin ↓ Amoxicillin/Clavulanac Acid (N=207)	
Number and Percentage (%) of Subjects				
Total Discontinued	34	(17%)	37	(18%)
Discontinuations Related to Study Drug:	21	(10%)	14	(7%)
Adverse Event	13	(6%)	6	(3%)
Insufficient Response	7	(3%)	8	(4%)
Laboratory Abnormality	1	(<1%)	0	
Discontinuations Unrelated to Study Drug:	13	(6%)	23	(11%)
Adverse Event	5	(2%)	9	(4%)
Did Not Meet Randomization Criteria	1	(<1%)	1	(<1%)
Laboratory Abnormality	0		1	(<1%)
Lost to Follow-Up	0		2	(<1%)
Other	2	(<1%)	6	(3%)
Subject Died	3	(1%)	1	(<1%)
Protocol Violation	1	(<1%)	1	(<1%)
Withdrawn Consent	1	(<1%)	2	(<1%)

Reasons for premature discontinuation were comparable between study arms.

Clinical Efficacy

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Summary of Sponsor-Defined Clinical Response Rates					
at the End of Treatment and the End of Study					
(Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafoxacin (N=156)		Imipenem/Cilastatin ↓ Amoxicillin/Clavulanac Acid (N=152)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	155	(100%)	142	(100%)	
Success (Cure + Improvement)	136	(88%)	122	(86%)	(-5.9, 9.5)
Distribution of Clinical Response:					
Cure	119	(77%)	104	(73%)	
Improvement	17	(11%)	18	(13%)	
Failure	19	(12%)	20	(14%)	
End of Study:					
Number of Subjects Assessed	156	(100%)	152	(100%)	
Success (Cure + Improvement)	129	(83%)	127	(84%)	(-9.2, 7.5)
Distribution of Clinical Response:					
Cure	128	(82%)	125	(82%)	
Improvement	1	(<1%)	2	(1%)	
Failure	27	(17%)	25	(16%)	

For the clinically-evaluable population, by the end of treatment and end of study visits, efficacy was similar between treatment arms. Similar results were seen for the clinical intent-to-treat population. (See next table.)

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A Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinical Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Alatrofloxacin ↓ Trovafoxacin (N=200)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=199)	Alatrofloxacin ↓ Trovafoxacin (N=200)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=199)
	Number and Percentage (%) of Subjects			
Number of Subjects Assessed	198 (100%)	193 (100%)	200 (100%)	199 (100%)
Success (Cure + improvement)	168 (85%)	163 (84%)	161 (81%)	162 (81%)
Distribution of Clinical Response:				
Cure	146 (74%)	136 (70%)	157 (79%)	156 (78%)
Improvement	22 (11%)	27 (14%)	4 (2%)	6 (3%)
Failure	30 (15%)	30 (16%)	39 (20%)	37 (19%)

According to the applicant, "Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -5.9%, 9.5% and -6.8%, 7.5%, respectively) and at the end of study (95% CI: -9.2%, 7.5% and -8.6%, 6.8%, respectively)."

Summary of Clinical Signs and Symptoms at Baseline, EOT, and EOS (Clinically Evaluable Subjects)						
	Alatrofloxacin ↓ Trovafoxacin			Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid		
	Baseline	EOT	EOS	Baseline	EOT	EOS
Sign/Symptom^a	Percentage of Subjects With Clinical Signs and Symptoms					
Intra-abdominal Pain/Tenderness	92%	12%	7%	92%	16%	7%
Abdominal Rigidity	36%	0%	<1%	33%	0%	0%
Swelling	38%	2%	2%	46%	3%	<1%
Induration	11%	1%	<1%	9%	2%	2%
Surgical Wound Discharge	16%	16%	10%	13%	16%	10%
Mass	7%	0%	<1%	12%	1%	0%
Ileus	40%	<1%	<1%	39%	2%	0%
Hypotension	4%	1%	<1%	5%	<1%	0%
Leukocytosis	77%	16%	14%	74%	24%	13%
Bowel Sounds	55%	94%	94%	49%	95%	95%
Formed Bowel Movements	17%	75%	86%	16%	78%	85%
Flatulence	26%	76%	78%	24%	77%	84%
Intra-abdominal Pain/Tenderness	92%	14%	8%	91%	18%	8%
Abdominal Rigidity	34%	3%	<1%	32%	0%	<1%
Swelling	36%	5%	2%	41%	5%	2%
Induration	11%	2%	<1%	7%	2%	2%
Surgical Wound Discharge	16%	17%	10%	15%	17%	10%
Mass	8%	<1%	<1%	12%	2%	<1%
Ileus	37%	2%	<1%	38%	2%	0%
Hypotension	5%	4%	1%	5%	1%	0%
Leukocytosis	76%	18%	14%	74%	24%	13%
Bowel Sounds	56%	92%	94%	51%	94%	95%
Formed Bowel Movements	19%	71%	85%	15%	75%	83%
Flatulence	27%	75%	80%	24%	79%	83%

EOT=End of Treatment; EOS = End of Study
a Not all subjects were evaluated for all signs/symptoms at all timepoints.

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For the clinically evaluable subjects, intra-abdominal signs and symptoms were comparable between populations at baseline, end of treatment, and end of study.

Other Indirect Measurements of Clinical Success (Clinical Intent-to-Treat Subjects)		
	Alatrofloxacin ↓ Trovafoxacin (n=200)	Imipenem/Cilastatin ↓ Amoxicillin/Clavulanic Acid (n=199)
Time to recovery (days)	(n=179) 7.9 ± 5.8*	(n=189) 8.2 ± 6.9*
Duration of post-op fever (days)	(n=199) 3.3 ± 3*	(n=197) 3.2 ± 3*
Duration of post-op hospitalization (days)	(n=193) 14.3 ± 14.5*	(n=195) 14.0 ± 14.2*
Median duration of hospitalization (days)	9	9

* = mean ± SD

As shown above, time to recovery, duration of post-op fever, duration of post-op hospitalization, and median duration of hospitalization was comparable between the two treatment arms.

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Microbiologic Efficacy:

Summary of Clinical Success (cure + improved) Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens ^a (Clinically Evaluable Subjects)				
	Alatrofloxacin ↓ Trovafoxacin (N=156)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)	Alatrofloxacin ↓ Trovafoxacin (N=156)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)
	Number of Subjects		Number of Subjects	
Pathogen	End of Treatment		End of Study	
Gram Positive Aerobes				
Alpha-haemolytic streptococci	9/12	4/4	8/12	6/6
Beta-hemolytic streptococci, Gp. B (≠ <i>S. agalactiae</i>)	0/1	1/1	0/1	0/1
<i>S. viridans</i>	18/20 (90%)	19/23 (83%)	18/20 (90%)	18/23 (78%)
<i>S. anginosus</i>	7/10	8/8	6/10	8/8
<i>Streptococcus</i> sp.	27/30 (90%)	38/41 (93%)	26/30 (87%)	40/43 (93%)
<i>E. faecium</i>	3/4	5/6	3/4	5/6
<i>E. faecalis</i>	7/13	12/16 (75%)	6/13	12/17 (71%)
<i>Enterococcus</i> sp.	7/10	13/18 (72%)	7/10	15/20 (75%)
<i>S. aureus</i>	8/11	1/3	8/11	1/3
Gram Negative Aerobes				
<i>E. coli</i>	72/77 (94%)	52/58 (90%)	66/77 (86%)	51/59 (86%)
<i>E. aerogenes</i>	3/3	2/2	3/3	2/2
<i>E. cloacae</i>	6/7	5/7	5/7	6/7
<i>Enterobacter</i> sp.	2/3	1/1	2/3	1/1
<i>K. pneumoniae</i>	12/15 (80%)	10/14	10/15 (67%)	10/14
<i>P. aeruginosa</i>	15/16 (94%)	14/17 (82%)	14/16 (88%)	15/18 (83%)
Gram Positive Anaerobes				
<i>Peptostreptococcus</i> sp.	12/14	7/8	11/14	6/8
<i>Clostridium</i> sp.	4/5	8/9	4/5	9/10
<i>Corynebacterium</i> sp.	3/3	5/5	3/3	6/6
Gram Negative Anaerobes				
<i>Prevotella buccae</i>	1/2	1/2	1/2	1/2
<i>Prevotella intermedia</i>	1/1	0	1/1	0/0
<i>Prevotella</i> sp.	10/13	2/4	10/13	3/5
<i>B. fragilis</i>	30/31 (97%)	28/34 (82%)	26/31 (84%)	27/36 (75%)
<i>B. thetaiotaomicron</i>	14/18 (78%)	13/13	11/18 (61%)	12/13
<i>B. uniformis</i>	7/7	9/10	5/7	9/10
<i>B. vulgatus</i>	5/7	7/7	5/7	7/7
<i>Bacteroides</i> sp.	7/9	11/12	7/9	11/13
<i>F. necrophorum</i>	3/3	2/2	3/3	2/2
<i>F. nucleatum</i>	1/2	1/1	1/2	1/1
<i>Fusobacterium</i> sp.	6/7	2/2	6/7	2/2

^a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Comparable bacteriologic efficacy (often presumptively determined based on clinical response) was observed in both treatment arms for the majority of pathogens isolated at the time of the defining surgery. However, TROVAN appeared (albeit small numbers) to have lower efficacy against *B. thetaiotaomicron* compared to the control arm. (11/18 vs. 12/13)

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For those patients who received repeat cultures at follow up, the development of resistance to trovafloxacin was not seen.

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Safety

Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Alatrofloxacin ↓ Trovafoxacin (N=201)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=207)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	128/201 (64%)	120/207 (58%)
Treatment-Related Adverse Events	29/201 (14%)	23/207 (11%)
Discontinuations from Treatment Due to an Adverse Event: All Causality	19/201 (9%)	19/207 (9%)
Discontinuations Due to a Treatment-Related Adverse Event	13/201 (6%)	6/207 (3%)
Clinically Significant Laboratory Abnormalities	142/198 (72%)	153/205 (75%)
Deaths*	11	11
Deaths during study period (entry → 30 days post-therapy)	7	5

Adverse event reporting (all causality and treatment-related) was similar between the two treatment groups.

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Deaths

Eleven (11) deaths were reported for both treatment groups. Seven and five patients, respectively, died during the study period (entry to 30 days post-therapy). Narrative summaries for these 12 patients are provided below.

Four subjects in the TROVAN group (Subjects 5525-0068, 5533-0110, 6256-0404 and 6524-0918) and two subjects in the comparator regimen (Subjects 5533-0086, and 6052-0806) died while receiving therapy. None of these deaths were considered by the investigator to be related to study drug.

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**NARRATIVES OF ALL REPORTED DEATHS
(On Therapy or Within 30 days Posttherapy)**

Phase II/III Studies - Complicated intra-abdominal infection

Alatrofloxacin/Trovafloxacin

Subject 154-124-5525-0068	This 63-year old white male underwent radiation therapy for treatment of anal carcinoma. He was admitted to a center in the US for surgical repair and treatment of radiation therapy-associated perforation of the small bowel with abscess formation. His previous medical history was significant for anal carcinoma and hypertension. The subject was maintained on erythropoietin for the treatment of underlying anemia at the time of hospital admission. The subject was treated successfully with a 7-day course of 300 mg alatrofloxacin daily. His clinical course improved and he was transferred on day 4 from the surgical intensive care unit (SICU). On day 6, his condition rapidly deteriorated following a cardiopulmonary/pulmonary arrest due to mucous plugging and anoxia, and he was transferred back to the SICU. The patient expired on day 8 secondary to complications resulting from the cardiopulmonary/pulmonary arrest.
Subject 154-124-5533-0110	This 79-year old white male presented to the Emergency Department at a center in the US with acute lower quadrant pain, low grade fever, and multiple episodes of nausea. The subject was found surgically to have an acute appendicitis with an-inflamed terminal ileum and cecum requiring resection. He was randomized into study on day 1 and treated for 11 days with intravenous alatrofloxacin 300 mg daily; one dose was missed. No chronic medications were listed at screening nor was his previous medical history significant for cardiac disease. The subject suffered a cardiac arrest on day 7 which was considered to be due to a pulmonary embolism. The subject continued to deteriorate and multiple organ failure was diagnosed on day 10. The subject was made "do not resuscitate" on post-operative day 11, the family requested all medication to be discontinued including study drugs, life support was withdrawn, and the patient expired on the same day.
Subject 154-124-6151-0603	This 77-year old white female with a 6-month history of abdominal pain and 3-month progressive weight loss (15 lb.) underwent a left and sigmoid colectomy for perforated sigmoid colon with fecal peritonitis at a center in the US. Previous medical history was significant for angina, constipation, COPD, and peptic ulcer disease. She was treated with alatrofloxacin 300 mg IV daily for 4 days. Her hospital course was complicated by thrombocytopenia which was thought to be related to study drug, recurrent pleural effusions (starting on day 3) and hemorrhage from the right chest tube (day 22) secondary to diffuse metastatic lung carcinoma, and acute renal failure on day 21. The subject expired on day 23 from cardiorespiratory arrest secondary to chronic obstructive pulmonary disease, lung carcinoma, and coronary disease.
Subject 154-124-6256-0404	This 68-year old white male underwent a sigmoid colectomy and Hartmann's closure of the rectal stump for peritonitis resulting from a nontraumatic perforation of the sigmoid colon at a center in the UK. Previous medical history was not significant for any underlying diseases nor was the subject maintained on chronic therapy. However, his prognosis was poor with a baseline APACHE II score of 27. The subject was treated with alatrofloxacin 300 mg IV daily for 3 days. The subject experienced multiple organ failure secondary to the disease under study and expired on post-operative day 3.

**NARRATIVES OF ALL REPORTED DEATHS
(On Therapy or Within 30 days Posttherapy)**

Phase II/III Studies - Complicated intra-abdominal infection	
Subject 154-124-6451-0721	This 64-year old white female with peritonitis underwent surgical repair of perforated small bowel felt secondary to amyloidosis at a center in Canada. Concurrent active medical conditions included COPD, congestive heart failure, angina, and hepatic disease. The subject was maintained on cardiac drugs at time of hospital admission. She was randomized into study and received 8 days of intravenous alatrofloxacin 300 mg daily. The subject experienced severe restrictive cardiomyopathy, amyloidosis, and acute pulmonary decompensation on day 3. Her clinical course further deteriorated and on day 14, she had a cardiac arrest that was considered secondary to the COPD, restrictive cardiomyopathy, congestive heart failure, and amyloidosis. She subsequently lapsed into unconsciousness and expired on the same day.
Subject 154-124-6518-0934	This 72-year old white male underwent surgery for a perforated gastric ulcer at a center in Poland. Two weeks post-operatively, the subject underwent further surgery for peritonitis and drainage of multiple abscesses related to an anastomotic leakage from the prior surgery. He was subsequently randomized into study and received 14 days of alatrofloxacin 300 mg IV daily. The subject was maintained on multiple concomitant medications, including gastrointestinal agents, blood transfusions, anticoagulants, cardiac drugs, and an antifungal agent (fluconazole). His clinical course improved until day 11 when signs and symptoms of peritonitis were again noted. Surgical cleaning of the wound was performed on day 14 and no further antibiotics were administered. The subject expired on day 20 of multiple organ failure due to the disease under study. Autopsy findings included anastomotic healing, fibrocaseous peritonitis, nephritis, partial necrosis of tissue surrounding the pancreas, advanced cerebral and peripheral atherosclerosis, and lung venostasis.
Subject 154-124-6524-0918	This 68-year old white female with peritonitis secondary to bowel perforation from rectal carcinoma underwent a Hartmann's procedure at a center in Poland. The subject was treated with alatrofloxacin 300 mg daily IV for 7 days. Previous medical history was significant for COPD, congestive heart failure, and ischemic heart disease which were maintained with respiratory and cardiac drugs. Prognosis was poor and the subject expired on day 7 due to multisystem failure.

**APPEARS THIS WAY
ON ORIGINAL**

Comparator

Subject 154-124-5533-0086	This 72-year old Hispanic female had motor vehicle accident-related multisystem trauma with upper extremity fractures, ileal perforation, and evolving sepsis. The ileal perforation was surgically repaired at a center in the US. She was treated with imipenem/cilastatin 1000 mg IV every 8 hours for 10 days. She had no significant previous medical history nor maintained on chronic drug therapy prior to hospitalization. During her hospital stay, she received concomitant medications consistent with the disease under study and the associated surgical procedure. Chest x-rays confirmed adult respiratory distress syndrome caused by evolving sepsis on day 6 and the subject continued on respiratory support throughout her hospitalization. Her clinical course worsened on day 9 with evidence of an abdominal site infection and sepsis; the antibiotic therapy was switched to ampicillin/sulbactam and metronidazole on day 10. She expired on day 13 due to complications associated with the motor vehicle accident.
Subject 154-124-5553-0695	This 64-year old white male underwent drainage of a retroperitoneal abscess which developed from a previous enterolysis for small bowel obstruction at a center in the US. Previous medical history was significant for COPD, asthma, bladder and prostate cancer, and metastatic carcinoma of the right lung and left retroperitoneum. His pre- and post-operative course was complicated by cardiac arrhythmias (supraventricular tachycardia, atrial flutter with atrioventricular block). He also had a proximal femoral vein deep venous thrombosis pre-randomization. He was treated with imipenem/cilastatin 1000 mg every 8 hours for 8 days. His clinical course deteriorated, the subject was ventilator-dependent, and he was hemodynamically stabilized on dopamine and hyperalimentation. Due to his deteriorating neurologic status and end-stage condition, all supportive measures were withdrawn on day 14. The subject expired due to cardiac arrest on day 17.
Subject 154-124-6018-0497	This 82-year old white male was hospitalized for digestive hemorrhage due to hiatal hernia at a center in France. He underwent a vagotomy with pyloroplasty and then developed post-operative acute respiratory failure. He subsequently developed peritonitis secondary to the previous abdominal surgery and was randomized into study. His APACHE II score at baseline was 32. He was treated with imipenem/cilastatin 500 mg IV every 6-8 hours for 14 days. His previous medical history was significant for COPD, coronary insufficiency, transient ischemic accidents, renal impairment, and an abdominal aortic aneurysm. His clinical course deteriorated with multiple surgeries for acute cholecystitis, fistulization of the pyloroplasty, and evisceration of the surgical abdominal wound. The subject developed worsening respiratory failure, renal failure, and cardiac failure, and expired on day 26 due to multisystem organ failure.
Subject 154-124-6052-0806	This 86-year old white male underwent appendectomy for a perforated appendix with diffuse peritonitis at a center in the US. Previous medical history was significant for stroke, hypertension, and urinary tract infection. The subject was treated with imipenem/cilastatin 250 mg every 6 hours for 13 days; one dose was missed on day 3. He was diagnosed with aspiration pneumonitis by chest x-ray on day 1 following surgery. On day 5, there was evidence of a new cerebrovascular accident confirmed clinically by seizure-like activity. The subject expired on day 13 due to the recurrent stroke.

**APPEARS THIS WAY
ON ORIGINAL**

Subject 154-124-6441-0525

This 79-year old white male underwent surgical repair of a perforated duodenal ulcer at a center in France. Previous medical history was significant for impaired renal function and an adrenal gland tumor which was diagnosed at time of randomization. The subject was treated with imipenem/cilastatin 1000 mg IV every 12 hours for 2 days, then 500 mg IV every 12 hours for 1 day, then 500 mg IV every 8 hours for 11 days. Abdominal cultures were positive for *Candida albicans* at baseline, and on days 3, 6, and 11; blood cultures were positive for *Candida albicans* on days 9, 10, 12 and 19. The subject was treated with fluconazole and amphotericin B. On day 19, his clinical course deteriorated and the subject was intubated for adult respiratory distress syndrome. The subject expired on day 23 from *Candida* septicemia and disease under study.

**APPEARS THIS WAY
ON ORIGINAL**

9. Conclusions:

Compared to Primaxin → Augmentin (an adequate comparator), the MO believes Pfizer has shown TROVAN to be safe and effective in the treatment of complicated intra-abdominal infections due to numerous pathogens.

In their proposed labeling, Pfizer requests the following be included in the INDICATIONS AND USAGE section:

COMPLICATED INTRA-ABDOMINAL INFECTIONS, including post-surgical infections caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus viridans*, *Bacteroides thetaiotaomicron*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Staphylococcus aureus*, *Beta Streptococcus* Group B, *Peptostreptococcus* species, *Prevotella* species, *Enterobacter* species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

As discussed in the 1992 DAIDP Points-to-Consider document, to include an organism in a treatment indication, the following criteria are recommended:

1. the organism is generally considered pathogenic AND
2. the organism represents at least 10% of the evaluable cases OR
3. the organism represents 10 total (whichever is higher) AND
4. the eradication rate must be clinically acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

The PTC document goes on to discuss how one might include a pathogen in labeling where <10% of cases were associated with the "pathogen":

1. generally accepted to be a pathogen at the site of infection
2. in vitro activity is at least similar to that of other pathogens more substantially evaluated in clinical trials
3. the mechanism of resistance is similar to that of other pathogens more substantially evaluated in clinical trials

4. no scientific data exist suggesting differences in the management of infections due to these pathogens

Although not discussed in the PTC document, the following caveats should be considered in the approval of pathogens for treatment indications:

1. If this is the first time a pathogen is to be included in the INDICATIONS AND USAGE section of product labeling (i.e., no other label is approved for this pathogen), perhaps a higher standard of evidence may be appropriate.
2. All pathogens *should* be fully speciated for each treatment indication in the INDICATIONS AND USAGE section with the exception of viridans group streptococci and *Peptostreptococcus spp.* (e.g., *Bacteroides spp.* would be unacceptable because *in vitro* susceptibility can vary significantly between species of bacteroides within the genus).
3. It's feasible to use pathogen data from other treatment indications to support efficacy in the treatment indication under study as long as that extrapolation is appropriate and reasonable (clinically and pharmacodynamically). For example, anaerobes for complicated intra-abdominal infection and GYN infections could be combined in inferring a drug's *in vivo* efficacy against pathogens included in approved product labeling. However, for example, the extrapolation of *E. coli* efficacy from UTI studies to intra-abdominal infections would not be appropriate. (NOTE: Severity of treatment indication as well as dose and duration should be considered in making this extrapolation from one treatment indication to another.)

MO Comment : The MO does not believe that GYN/Pelvic infection efficacy data can be extrapolated to support the CIAI indication, because CIAI patients are often sicker (e.g., mortality is not rare in CIAI; it is rare in GYN/Pelvic infections).

The MO believes Pfizer has presented substantial evidence supporting approval for the following pathogens:

Escherichia coli, *Bacteroides fragilis*, *Streptococcus viridans*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Peptostreptococcus spp.*, and *Prevotella spp.*

MO Comment : Following discussion with the reviewing microbiologist, "viridans group streptococci" is the preferred collective name for *S. viridans* including other streptococci. e.g., *Streptococcus anginosus*.)

MO Comment : Following review of the NDA, the MO could not find convincing *in vitro* or clinical data suggesting that different prevotella species demonstrate variable susceptibility patterns or clinical outcomes to TROVAN. Therefore, the MO recommends approval of "*Prevotella species*" for this treatment indication.

The MO does not believe the following bacteria should be included in this treatment indication:

Bacteroides thetaiotaomicron : As noted previously, efficacy appears to be lower for this pathogen (relative to the comparator regimen) in the clinical study AND *in vitro* data show the MIC₉₀ for trovafloxacin to be high: 1.5 mcg/mL. Therefore, *in vitro* susceptibility testing support this clinical concern.

Staphylococcus aureus : Following the above discussion, there were 135 bacteriologically-evaluable TROVAN recipients. Ten percent of 135 is 14. Only 11 *S. aureus* were isolated. This number does not meet the points-to-consider guidance.

As already discussed above, the Agency has been reluctant to include genus information alone (without speciation) in the INDICATIONS AND USAGE section of product labeling, because susceptibility testing may differ for species within a genus. Therefore, unlike prevotella, the MO recommends the following unspciated pathogens/organisms not be included in product labeling:

Enterobacter species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

Unfortunately, the applicant did not speciate these organisms during the trial and this information cannot be inferred.

10. Recommendations:

The MO recommends addition of the following information in the INDICATIONS AND USAGE section as it pertains to this indication:

IS!

**APPEARS THIS WAY
ON ORIGINAL**

Brad Leissa, MD
Medical Officer/HFD-590

cc: Orig. NDA
Division file
HFD-590/MO/Leissa
HFD-590/MO/Alivisatos
HFD-590/MO/Cox
HFD-590/CSO/Kimzey

Concurrence only: DivDir/Goldberger

IS! 11/4/98

**APPEARS THIS WAY
ON ORIGINAL**

TROVAFLOXACIN ADVERSE EVENTS/HEPATOTOXICITY/PANCREATITIS

**Medical Officer's Review
Post-Marketing Adverse Events
NDA 20-759 and 20-760**

Dates of Submissions: April 1998 – June 1998
Date MOR Started: May 7, 1998
Date MOR completed: August 31, 1998

Applicant: Pfizer Inc.
235 East 42nd St.
New York, NY 10017-5755

Drug: Trovafloracin
Alatrofloracin

Dosage Form: Tablets and IV

Pharmacologic Category: Synthetic Fluoroquinolone

Date of NDA Approval: December 18, 1997

Abbreviations Used:

MO = the current MO, Dr. Alivisatos.
RMO = the pre-NDA medical officer.

Overview:

Trovafloracin, a synthetic fluoroquinolone for oral administration and alatrofloracin, the IV formulation, were approved on December 18, 1997 (NDA 20-759, NDA 20-760). The applicant submitted 19 indications for approval with a database of approximately 10,000 patients. A major part of the NDA review was the safety assessment. The majority of the issues which were discovered during the pre-approval NDA review phase related to the CNS and specifically to the development of severe dizziness in all segments of the population but most frequently in young females. Specific attention however was also paid to the assessment of liver abnormalities.

The trovafloracin NDA review team found no patients in the safety database (0/6500) that developed liver failure or necrosis. Additionally, minor LFT abnormalities were seen in only _____ of the patients studied per indication. The exception to the above was the prostatitis indication. This indication was the sole indication for which information was submitted for a duration of therapy for > 14 days. From a safety standpoint, the MO found, as did the sponsor that, 5/140 trovafloracin-treated subjects were discontinued due to increased LFTs that were considered treatment-related by the investigator. An additional 10/140 patients developed LFT abnormalities during the course of therapy or immediately after therapy that were not considered treatment-related by the investigators. In the MOR, the MO disagreed with this determination because "the pattern of the abnormalities was consistent with that of the previously listed 5 patients in whom they were attributable to the study drug, both in terms of the timing of the events as well as the duration (approximately 3 – 4 weeks of trovafloracin usually without an associated increase in bilirubin and with apparent resolution after 6 – 10 weeks off therapy." The MO determined that 14/140 (10%) of treated prostatitis patients developed increased transaminases to $\geq 3x$ normal after approximately 3 to 4 weeks of therapy. Additionally, 15/140 (10.7%) of prostatitis patients developed an increase of transaminases to $\geq 2x$ normal. These abnormalities were not associated with clinical symptoms or with concomitant increases in alkaline phosphatase, bilirubin, or gGT. The LFT abnormalities resolved after therapy with trovafloracin was discontinued over the course of 6 – 10 weeks. This was compared to an incidence of LFT abnormalities on the comparator ofloxacin arm of 1/132 (0.8%).

**APPEARS THIS WAY
ON ORIGINAL**

At the conclusion of the prostatitis review in July 1997 the MO contacted the applicant and requested that revisions to the proposed labeling with regard to hepatotoxicity be made. The applicant's original proposal was determined to be inadequate and after negotiation during the NDA approval meetings, final labeling was agreed upon by the applicant and the DSPIDPs with regard to this issue. Specifically the original approved label, (pertinent sections at conclusion of document) was determined to accurately reflect the magnitude of LFT abnormalities that were noted during the NDA review. The MO was of the opinion that trovafloxacin induced a chemical hepatitis (i.e. asymptomatic) after > 14 days of therapy and that these abnormalities resolved after 8 – 12 weeks off therapy.

During the review of a periodic report submitted in April, 1998, the MO noted 3 reports of increased transaminases associated with liver biopsy findings of eosinophilic infiltration of the liver in patients who had received trovafloxacin for therapy of less than 14 days duration. At this point on April 30, 1998, the MO contacted HFD-735 to request information about reports of increased transaminases and/or eosinophilic infiltration of the liver associated with trovafloxacin usage.

Concerns with regard to the potential hepatotoxic effect of trovafloxacin had been raised during the IND phase of this antimicrobials development. The MO has provided a brief review of these events below.

Historical Perspective:

The initial trovafloxacin IND

The original reviewing MO expressed concern over increased LFTs found in 2/8 dogs studied (increased serum LFTs at 2 months and histologic findings at 6 months). The MO re-reviewed this study (93-783-16, Supplemental Preclinical Information), originally submitted on October 11, 1994 and found that of 8 beagle dogs that received 50mg/kg of the study drug daily for 6 months, 2, a male and a female developed elevations of ALT, AST and gGT during the study. These abnormalities were from 2 to 16 times normal levels. On microscopic exam these enzyme abnormalities were correlated with findings of centrilobular hepatocellular vacuolar degeneration and necrosis of moderate degree in the male dog and marked in the female. A second group of dogs that received a lower dose of 15 mg/kg daily did not have similar abnormalities and thus a no observed adverse effect level (NOAEL) was established. The MO converted the mg/kg/day dosing schema to mg/m^2 (utilizing the conversion table of Freireich E. J. et al. *Cancer and Chemotherapeutics* 50(4): 219 –244, 1966), and found that the 50 mg/kg/day dog dose was equal to a dose of $1000 \text{ mg}/\text{m}^2$. The 15 mg/kg/day dog dose was equal to $300 \text{ mg}/\text{m}^2$. A human dose of 300 mg/day in a 60 kg person or 5 mg/kg/day was equal to $185 \text{ mg}/\text{m}^2$. Therefore there was appeared to be a margin of safety of 5.4 between the toxic animal dose of 50 mg/kg/day and the maximum planned human dose of 300 mg/day. The margin between the NOAEL dog dose of 15 mg/kg/day and the maximum human dose was only 1.6. The MO also compared dog and human C_{max} and AUCs at the respective doses and found that at the 50 mg/kg/day dose the dogs had a mean C_{max} of 6.7 mcg/mL and an AUC of 40.2 mcg-hr/mL. The human values at the 300 mg dose or 5 mg/kg/day were 4.3 and respectively. The AUCs were comparable because of the longer half-life in humans (10.5 hours) versus dogs (2.5 hours). Thus the animal dose at which toxic effect was found, was extremely close to the maximum planned human dose. This data raised concerns of potential hepatotoxic effects in humans.

Of interest was the finding of hepatic abnormalities in a 6 month rat study where 3 doses were utilized, a low (25 mg/kg/day), medium (75 mg/kg/day), and high (200 mg/kg/day) dose. As per the pharm/tox reviewer, a higher incidence of minimal to mild hepatic fatty change was noted in the mid- (7/15) and high (11/15) dose males relative to the low dose (4/15) and the control (4/15) males.

The original RMO reviewing the planned Phase II protocols requested that clinical studies be limited to 14 days duration and at the end-of-Phase II meeting, August 29, 1994, it was requested that prior to proceeding to Phase III studies, the applicant perform a study to assess the reversibility of these hepatic lesions in dogs. This study (94-783-23) was performed at a dose of 50 mg/kg/day for 6 months. 4/16 dogs were found to have increased LFTs (primarily ALT), which returned to baseline after treatment discontinuation on days 67 to 89. There was microscopic correlation, that is findings of hepatocellular

necrosis and periportal infiltration in 3 of the animals. The histologic changes were all found to be reversible at necropsy.

At this point the original RMO determined that it was safe to proceed with all planned Phase III studies of < 14 days duration of therapy as well as the prostatitis study. This study was originally planned for 6 weeks duration, however it was allowed to proceed only after the duration of therapy was limited to 4 weeks for the trovafloracin-treated patients. Additionally, the RMO revised the protocol to provide for laboratory reevaluations at day 21 of the study and weekly thereafter.

Current Trovafloracin Labeling (as approved 12/97):

WARNINGS: " Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions, vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis, acute renal failure or insufficiency, hepatitis, jaundice, acute hepatic necrosis or failure...

PRECAUTIONS: "Because TROVAN® can cause elevations of liver function tests during or soon after prolonged therapy (i.e. ≥ 21 days), periodic assessment of hepatic function is advisable. The safety and efficacy of TROVAN® given for > 4 weeks have not been studied."

ADVERSE REACTIONS: GASTRONINTESTINAL: "abdominal pain, altered bowel habit, constipation, diarrhea-Clostridium difficile, dyspepsia, flatulence, loose stools, gastritis, dysphagia, increased appetite, gastroenteritis, rectal disorder, colitis, pseudomembranous colitis, enteritis, eructation, gastrointestinal disorder, melena, hiccup."

LABORATORY CHANGES: Changes in laboratory parameters without regard to drug relationship, occurring in > 1% of TROVAN®-treated patients were: " increased ALT (SGPT), increased AST (SGOT), and alkaline phosphates;... It is not known whether these abnormalities were caused by the drug or the underlying condition being treated."

"The incidence and magnitude of liver function abnormalities with TROVAN® were the same as comparator agents except in the only study in which oral TROVAN® was administered for 28 days. In this study (chronic bacterial prostatitis), 9% (13/140) of TROVAN®-treated patients experienced elevations of serum transaminases (AST and/or ALT) of ≥ 3 times the upper limit of normal. These liver function test abnormalities generally developed at the end, or following completion of, the planned 28-day course of therapy, but were not associated with concurrent elevations of related laboratory measures of hepatic function (such as serum bilirubin, alkaline phosphatase, or lactic dehydrogenase). Patients were asymptomatic with these abnormalities, which generally returned to normal within 1 – 2 months after discontinuation of therapy."

**APPEARS THIS WAY
ON ORIGINAL**

Post-marketing Events:

Subsequent to the review of a periodic report submitted in April, 1998, wherein MO noted 3 reports of increased transaminases associated with liver biopsy findings of eosinophilic infiltration of the liver in patients who had received trovafloracin for therapy of less than 14 days duration and after reviewing the animal and human trovafloracin-related hepatotoxicity data from the IND and NDA phases of development (see above), the MO presents post-marketing case reports submitted both to Pfizer and to the agency through June 30, 1998. The Pfizer-generated reports were submitted to the DSPIDPs after the institution of a Trovan®-monitoring system to capture all hepatic and pancreatic AEs meeting a case definition proposed by the review team. This case definition was communicated to Pfizer over the course of 2 telecons on May 12 and 14, 1998, and after the receipt of additional reports of hepatotoxicity as well as pancreatitis.

During the aforementioned telecons, Pfizer agreed to submit all serious as well as non-serious reports meeting the case definition to the DSPIDPs within 15 days of receipt. They agreed to communicate with the reporters and to ask event-specific follow-up questions as requested by the MO. This agreement included the review of all in-house non-serious reports already received by Pfizer and held for the next planned periodic report. Terms that contributed to a hepatitis case-definition included the finding of one of the following verbatim terms in the text of a MedWatch form:

- Hepatitis
- Hepatic Enlargement or Hepatomegaly (as evidenced by physical exam or abdominal US or CT or MRI)
- Pancreatitis
- Liver biopsy
- Liver transplantation
- Jaundice
- Right upper quadrant pain
- Elevated LFTs (AST, ALT, and Alk. Phos, or bilirubin)

The elevation of LFTs as evidenced by the finding of:

- AST or ALT > 2 x ULN (where normal ranges reported), or > 80 if normal ranges not known
- Alkaline phosphatase > 2 x ULN
- Direct bilirubin > 1.0 mg/dL or indirect bilirubin > 3.0 mg/dL
- Amylase > 2 x UNL

Specific follow-up questions were outlined as follows:

- History of previous fluoroquinolone usage in the recent or distant past.
- History of other liver disease risk factors including ETOH, DM, medications, viral etiologies, GB or BT disease.
- Complete enzyme and bilirubin profile
- Time to resolution of the condition
- CBC with differential to assess for eosinophilia
- Liver biopsy results.

At the time this document was prepared, the agency was in receipt of 38 case reports, 11 serious and 27 non-serious. 7 cases were of pancreatitis, 31 of hepatitis (with 1 patient with both). No deaths had been reported. All cases are prefaced by the MCN (manufacturer's control number), a seven-digit number. Few cases were reported directly and only to the agency and are prefaced by a 4 to 6-digit number only. In cases where reports were received by both Pfizer and the agency, the MCN was utilized. Concurrent to the preparation of this document an electronic dataset was instituted (Microsoft Access) and is currently in use.

After the review of the cases (see below), the review team determined that a labeling change was necessary as the originally-approved label did not adequately convey the magnitude or the timing of the observed trovafloxacin-related hepatotoxicity. In an effort to determine the type of change needed (i.e. WARNING or not) as well as the mode of communication of the proposed change to practicing physicians (Dear Doctor letter), the MO compared the observed trovafloxacin AEs with the hepatic events associated with other approved quinolone antimicrobials within the first year after approval.

Comparison with Other Quinolone Antimicrobials:

Trovafloracin: approved 12/97

To date: 179 AEs reported: 9 serious liver and 21 non-serious liver

Total Liver: 30

Total Pancreatitis: 8 (1 with hepatitis serious, 2 serious and 5 NS)

274,000 oral prescriptions to date (IMS Health's NPA Database: prescriptions filled by retail and outpatient pharmacies)

Ciprofloxacin: Approved 10/87
1st yearly report: 375
Total liver: 21

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ON ORIGINAL**

Floxin: Approved 12/90
1st yearly: 388 total
Total liver: 9

Levofloxacin: approved 12/96:
1st yearly: 426
Total liver: 10
470,000 oral prescriptions

Sparfloxacin 12/96: to date 81 total reports, 1 liver
8000 oral prescriptions

**APPEARS THIS WAY
ON ORIGINAL**

Grepafloracin 11/97: 13 total, no liver
105,000 oral prescriptions

Temafloxacin: 1/92
1st year: 1621
Total liver (including hemolytic anemia) 212

All AEs/liver/2nd Quarter after approval and 1st Year cumulative

Drug	2 nd Quarter ALL	2 nd Quarter liver	1 st Year ALL	1 st year liver	# oral prescriptions
Trovafloracin (12/97)	181	34	-	-	274,000 (to date)
Ciprofloxacin 10/87	114	9	375	21	Not available
Ofloxacin 12/90	91	5	388	9	Not available
Levofloxacin 12/96	182	3	426	10	470,000 (first 6 months)
Sparfloxacin 12/96	32	0	81	1	8000 (first 6 months)
Grepafloracin 11/97	23	0	-	-	105,000 (first 6 months)
Temafloxacin 1/92	255	47 (26)*	1621	212 (76)*	Not available

* # in parentheses represents cases of hemolytic anemia.

Comment: From the above table and text it became apparent that trovafloracin had the most reported liver-associated AEs within the first 6 months after approval of any of the approved and on the market quinolone antimicrobial agents. Only temafloxacin (withdrawn in 6/92) had a larger number of reported events. The comparative incidence of hepatic events reported in the first year after approval could not be

events. The comparative incidence of hepatic events reported in the first year after approval could not be assessed for trovafloracin. With regard to the denominator, that is the number of prescriptions filled at the time this data was collected, the information provided by _____ is limited in that it refers only to the oral formulation and not to the IV. However, the limited data from levofloxacin, grepafloxacin and sparfloracin (34 reports of trovafloracin-related liver toxicity in the face of a denominator of at 274,000 as compared to levofloxacin with only 3 reports of liver toxicity despite its higher usage as expressed by a denominator of 405,000) serve to illustrate the magnitude of the trovafloracin-related hepatotoxicity as compared to other approved quinolones.

APPEARS THIS WAY
ON ORIGINAL

Temofloxacin experience

During the IND and pre-NDA phases of trovafloracin drug development concerns were raised by the preclinical and clinical reviewers over the similarities in chemical structure between the temofloxacin and trovafloracin molecules (see attached). The only difference in chemical structure was the substitution of an aza-bicyclo-hexyl ring at the 7th position of the trovafloracin molecule as compared to the temofloxacin molecule where a piperazine ring could be found at the 7th position.

This similarity was of concern because shortly after the temofloxacin approval in January 1992 and during the 2nd quarter of 1992, an increased incidence of AERs were noted with hemolytic uremic syndrome. The evaluation and description of these cases led to the negotiated withdrawal of temofloxacin.

Patients typically presented with fever, chills, and jaundice between 5 –7 days after starting therapy with temofloxacin. Renal failure, DIC and hemolysis were noted with accompanying decreases in hemoglobin, hematocrit and platelet counts. Renal dysfunction necessitating dialysis was found in 63% of the cases described. Concomitant LFT abnormalities were noted usually expressed as an increase in AST and total bilirubin. An immunologic mechanism was postulated because of a strong association found between prior use of a quinolone and development of the syndrome.

Despite the structural similarity between trovafloracin and temofloxacin, there were notable differences in the presentation of patients with the presumed trovafloracin-generated hepatitis as compared to the more complex multisystem illness seen in patients who had received temofloxacin including deaths attributed to temofloxacin-associated hemolytic anemia/rhabdomyolysis as well as the increased number of hospitalizations and dialysis required by the patients.

Described below are the 11 serious reports followed by the 27 non-serious. Presentation is in order of receipt.

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ON ORIGINAL

Serious Case Reports (N = 11):

- 9805098 and 9809955: Reported 2/28/98: 44 YO F on trovafloracin for pneumonia for 10 days. Discontinued for 2 days and then took another 2 days (received a total of 12 days). Finished R/x by 2/4 or 2/10. The patient then developed RUQ pain and elevated LFTs. A CT revealed liver enlargement and a very edematous gallbladder and LFTs continued to increase. A GI consultant saw the patient on 2/14/98 and performed an emergency cholecystectomy on 2/17. A liver biopsy revealed changes possibly consistent with recent antibiotic use (*eosinophilic infiltration and Kupffer cell hyperplasia*). As per the reporter, this patient did not have an elevated alkaline phosphatase or bilirubin. The ALT reached the 600 range and there was a previous history of prior (lifetime) quinolone usage (levofloxacin for chronic sinusitis). This patient had no history of liver disease, ETOH usage or use of other medications.

MO Comment: *This case was the most typical. The patient, a healthy female developed evidence of an eosinophilic hepatitis with no other obvious etiology. Notable is the different histopathology from that seen in the preclinical dog studies.*

- 9809892: reported 4/16/98: A female patient received trovafloxacin for 2 weeks for chronic sinusitis. She was hospitalized (3 weeks post-R/x) on 4/6 for a viral syndrome with fever, elevated LFTs and was diagnosed with pancreatitis. CT revealed pancreatic enlargement accompanied by mesenteric infiltration. Amylase and lipase remained within normal limits. Transaminases . Also had a transient rash. Trovafloxacin was discontinued on 4/6 and she improved. No further information was provided other than that there was no history of ETOH usage.

MO Comment: *This is the only case of pancreatitis with concomitant hepatitis. As opposed to the other pancreatitis cases, this patient developed disease 3 weeks after the conclusion of therapy.*

- 9808576: 74 YO F with LLL pn/nia received trovafloxacin for 10 days (2/13 – 2/23/98). Presented 3 weeks later (3/11/98) with elevated LFTs and fever and was admitted to the hospital. Specifically had temp watery diarrhea and an AST ALT The reporting MD stated that her alkaline phosphatase and bilirubin were within normal limits. CBC revealed an *eosinophilia* (not available). A work-up for viral hepatitis was negative (A, B and C). The patient improved spontaneously with regards to fever and diarrhea and has had a progressive decrease in her LFTs. A repeat test is pending. This patient had no history of liver disease, ETOH usage or use of other medications. *Clostridium difficile* workup was negative.

MO Comment: *The etiology of the patient's clinical picture is uncertain. The presence of fever and diarrhea suggest an infectious etiology, however, the presence of eosinophilia is of concern.*

- 9810538: 38 YO diabetic F with a diabetic foot ulcer and sepsis received trovafloxacin 300 mg IV qd from 4/10 – 4/12/98. Patient also received Diflucan® for an unspecified period and dose. Other R/X included Timentin®, Synthroid®, IN, Pepcid®, Lasix, Elavil, Zosyn®, Vancomycin, and Darvocet. There were no LFTs performed prior to 4/12/98. On that date the patients became jaundiced and lethargic and a chemistry profile revealed normal transaminases (ALT AST , a bilirubin and an alkaline phosphatase The patient was moved to the ICU where she recovered over the next few days. Final values were bilirubin) and Alk. Phos: Final LFTs not provided. The past medical history was notable for IDDM, CHF, CRF, CVA, hypothyroidism, and diabetic neuropathy. There was no history of Tylenol (other than Darvocet) or ETOH usage.

MO Comment: *Clinical picture inconsistent with rest of cases. Multiple medical problems lead to difficulty in attribution to trovafloxacin.*

- 98010252: 50 YO Female with a history of pneumonia with hospitalization for pancreatitis after 1 - 2 days of trovafloxacin. Positive history for diabetes. Trovafloxacin 200 mg PO qd was started on the day of hospitalization.

MO Comment: *The MO determined that this case was unlikely to be related to trovafloxacin as the patient developed pancreatitis on the first day of therapy.*

- 9810885: 56 YO male with hospitalization for pancreatitis after 2 days of trovafloxacin at a dose of 300 mg PO qd started on 4/13. Also had unspecified history of cancer.
- 7927: purpura: 32 YO DM F received 7 days of trovafloxacin 200 mg PO qd from 2/26. The patient developed increased Alk. Phos , ALT and AST as well as a "purple nose" Patient has a history of vasculitis. .

MO Comment: *Underlying vasculitis could cause this clinical picture.*

- 9811689: 29 YO F on a Swiss trovafloxacin pneumonia study on 12/31/97. Received 200 mg PO qd through Jan 18, 1998. (19 days r/x). The patient developed empyema and required transfer to ICU on January 4, 1998 where she was found to have elevated LFTs. Report mentions nonspecific history of

liver disease. Concomitant medications included paracetamol, tramadol, nadroparin, salbutamol, and ipratropiumbromid. LFTs on 12/31: LDH: , AST ALT Alk Phos Labs from 2/98 were wnl.

- 9809169 (83447) 49 YO male received trovafloxacin from 3/9 through 3/18. (NOTE only 7 doses taken). Patients had a history of sinusitis and allergic rhinitis. The patient also received ceftriaxone from 3/22 – 3/25. On 3/19 and prior to alternative antimicrobials, the patient developed cholecystitis which led to a cholecystectomy and hepatitis. Pleural and pericardial effusions as well as bullous skin lesions and a peripheral *eosinophilia* were also present, thus suggesting an allergic process. LFTs: A Phos: AST: ALT Bili: Hep A and C Patient had a HepBSAb (vaccine).
- 83816: 38 YO male received 200 mg trovafloxacin PO qd for 10 days. Also received Entex and Tylenol for sinusitis. After 2 – 3 days patient improved clinically and finished his course. 3 days post-therapy, patient presented complaining of fatigue. On 5/4 had a temp to 101. Saw original MD again, 10 days after stopping trovafloxacin. At that time he had dark urine, and RUQ tenderness. Physical exam revealed abdominal distention consistent with the presence of ascites. Lab: AST ALT: T Bili: Bili: CMV IgG elevated, hepatitis workup negative, peripheral eosinophilia present CT: ascites and increased liver size. There was no significant PMH and the patient drank approximately 3 beers a week. No baseline LFTs available. Latest LFTs: AST ALT Alk Phos Bili
- 9815470: 38 YO male ER nurse received trovafloxacin for 10 days for recurrent sinusitis. Previously received clarithromycin without relief. Approximately 6 days post-therapy the patient had an elevated temperature associated with an achy feeling. He also stated that he felt disoriented. The patient continued to have increasing weakness and 2 – 3 days later developed nausea and vomiting. 1 day later he had to leave work because of high fever, burning and nausea. In the ER the patient was found to have a tender liver and elevated LFTs and increased bilirubin INR. A CT scan was performed, no GB disease was found and he was discharged with a preliminary diagnosis of hepatitis. The next day he was unable to care for himself and was admitted for confusion. A liver biopsy was performed and then the patient was transferred to a tertiary care center where acute liver failure was diagnosed. The patient had evidence of edema and ascites. Biopsies from both institutions were similar and revealed zone 3 liver necrosis, no cirrhosis, eosinophilic infiltration, evidence of veno-occlusive disease and disseminated venulitis. The patient had evidence of portal hypertension with occlusion of the middle hepatic artery as well as hepatofugal flow (elevated R arterial pressure. versus normal Right lobe of liver). Assuming the need for transplantation he received steroids and diuretics and improved to the point of discharge. Transient renal dysfunction developed due to dye studies. Transplantation on hold at present. Previous history of quinolone use not known. LFTs improved. The patient had a remote history of exposure to paint stripper and a tractor accident. Additionally, he had been receiving Motrin. Follow-up obtained from MD (Chief GI), patients, and pharmacist. Further information is pending.

MO Comment: This case is the most severe of those reported to date. At this point further information is not available with regards to previous quinolone usage. This case and the first case are similar in that eosinophilic infiltration was seen in the biopsy material from both patients. Based on the available information, an immunologic mechanism (hypersensitivity reaction) can be postulated.

MO Comment: Of the 11 serious reports listed above, 8 were reported to the agency and to Pfizer and 3 only to the agency. 3/11 (27.2%) had evidence of pancreatitis and 8/11 (72.8%) of the patients had evidence of hepatitis. Outcome appears to have been resolution in most cases where information has been provided.

Non-serious Case Reports (N = 27)

- 9804918: Hospitalized patient received trovafloxacin 200 mg IV qd for surgical prophylaxis for a cholecystectomy. After 2 days patient was found to have an elevated bilirubin and therapy was discontinued.
- 9805225: 60 YO female received trovafloxacin 300 mg IV qd for pneumonia. Approximately 7 days after the start of therapy, the patient had a total bilirubin reported as doubled as well as an Alk. Phos. AST and gGT. Patient was also receiving TPN.
- 9805226: Unknown demographics and dosage. Reported that a patient developed pancreatitis after 2 days of trovafloxacin.
- 9805396: Unknown demographics and dosage. Reported that a patient developed pancreatitis after 2 days of trovafloxacin.
- 9805497: 51 YO female received trovafloxacin 200 mg PO qd. After 4 days of therapy, the patient developed a rash. In addition and at an unknown timepoint, the patient was noted to have abnormal LFTs. An ultrasound was negative for gallstones and the reporter suspected hepatitis secondary to trovafloxacin.
- 9806570: 69 YO male received trovafloxacin 200 mg PO qd for gangrene (3/4/98). 4 days after the start of therapy (3/8/98), the patient developed an increase in creatinine which peaked day 7 (3/10/98). On 3/9/98 the patient received an IV dose of alatrofloxacin. 6 days after the start of therapy the patient was also found to have increased LFTs with ALT and AST. LDH was Bili. Relevant PMH included liver disease, ETOH abuse, and diabetes.
- 9807737: Hospitalized female received alatrofloxacin 300 mg IV qd for an unknown indication. After 2–3 doses, she developed elevated LFTs with subsequent improvement after discontinuation.
- 9808005 (also reported as 9807717): 63 YO male received alatrofloxacin 200 mg daily for pneumonia. After 4 days of therapy, the patient developed elevated LFTs and therapy was discontinued on day 10. The patient subsequently improved.
- 9808037 (also reported as 9807718): An elderly female received intravenous alatrofloxacin (200 mg) followed by oral trovafloxacin at a dose of 200 mg qd for unspecified periods. Underlying diagnosis was bilateral pneumonia. The patient developed a gGT to three times normal. There was a PMH of diabetes controlled by diet and no further follow-up.
- 9808955: 80 YO male received trovafloxacin 200 mg PO qd for a RT infection as of 3/28. On 3/30 he was found to have an elevated creatinine and BUN. On 3/31 the reporter also stated that the patient had an elevated LDH and SGOT. These were attributed to the patient's underlying disease, multiple myeloma. No further info was provided.
- 9809169 (83447): Unknown demographics: patient developed eosinophilia, elevated LFTs and cholangitis while on trovafloxacin.
- 9811665: Unknown patient developed elevated LFTs after 10 days of trovafloxacin therapy.
- 9811667: Unknown patient developed elevated LFTs after 10 days of trovafloxacin therapy.
- 9811958: 54 YO male received trovafloxacin 200 mg PO qd for prostatitis for 28 days. On day 30 he was found to have elevated LFTs: ALT, AST, Bili, A Phos and LDH.
- 9812385: 92 YO female with diverticulitis and no underlying liver disease received trovafloxacin 200 mg a day. She also received Tylenol. Patient developed jaundice and an ultrasound and hepatitis workup were negative. The GI consultant attributed the jaundice to therapy.

- 9813438: Unknown patient with unspecified LFT elevation.
- 9814273: Male received trovafloxacin 200 mg PO qd for prostatitis. Developed jaundice and weakness with hepatitis attributed to trovafloxacin.
- 9814453: A patient with sinusitis received trovafloxacin 200 mg qd and developed hepatitis.
- 9811020: 64 YO female started 200 mg trovafloxacin qd on 4/3. On 4/14, day 12 developed generalized muscle aches and joint pains associated with dry mouth and headache. Trovafloxacin discontinued on 4/16 (day 14). LFT increase noted on 5/5.
- 9815753: female received trovafloxacin for 20 days for sinusitis. LFT increase noted post-therapy. Patient was symptomatic with weakness and malaise.
- 9815755: Male patient received trovafloxacin for 28 days for prostatitis. After completion had an SGOT
- 9815758: 66 YO male received alatrofloxacin IV. After 3 days was noted to have elevated BUN and creatinine as well as increased LFTs (bilirubin, LDH and SGOT). Dose decreased.
- 9815975: 62 YO male IDDM developed pancreatitis 9 days after starting alatrofloxacin 300 mg IV QD after a CABG. The patient developed fever accompanied by an amylase, and a lipase. There was gradual resolution of the pancreatitis over the next 3 weeks with a final amylase. The patient was receiving multiple concomitant medications including furosemide, famotidine, midazolam, dopamine and fentanyl.
- 9815973: 59 YO male developed pancreatitis 9 days after starting IV alatrofloxacin 300 QD as empiric Gram (+) coverage after small bowel resection. Concurrent medications included vancomycin, furosemide, famotidine, digoxin, diltiazem and clonidine. The initial amylase and lipase. The enzyme elevations were accompanied by fever and gradually resolved over a week.
- 9816101: unknown patient developed elevated LFTs after IV alatrofloxacin.
- 9817642: unknown patient developed elevated LFTs in less than a week on trovafloxacin.
- 9818538: (84288): Tremors and confusion developed in a patient after 7 days of IV alatrofloxacin 300 mg qd. The patient also received 1 PO 200 mg dose. LFTs were elevated with an AST and an Alk Phos. No eosinophilia was noted and the patient had a history of no quinolone usage in the last 4 years.

Comment: Of the 27 additional cases provided 4 were of pancreatitis bringing the total to 7. 2 of the additional pancreatitis cases were similar to the 2 of the 3 serious pancreatitis cases in that the pathology appeared to develop within 2 days of the start of therapy. In the remaining 2 cases, pancreatic disease with amylase and lipase elevations accompanied by fever developed 9 – 10 days into a course of alatrofloxacin therapy.

Based on the above, the MO performed cumulative statistics (see below) in an attempt to describe the epidemiology of the trovafloxacin-related hepatic and pancreatic events. Unfortunately and a common pitfall of this method of AE reporting was the scanty information provided as well as the difficulties encountered in contacting the individual reporters.

Cumulative Statistics:

Pancreatitis (N = 7):

Demographics:**Gender:** 2/7 female, 2/7 male and 3/7 unknown**Underlying diabetes:** 3/7 diabetes present, 2/7 unknown, and 2/7 (28.5%) non-diabetic**Age:** 3/7 age unknown, 4/7 years of age**Dosage:**

3/7 unknown dosage, 1/7 200 mg qd and 3/7 300 mg qd

Duration of Therapy prior to development of AE:

4/7 developed disease within 2 days of starting therapy, 1/7 after 3 weeks and 2/7 after 9 days.

Conclusion with regard to pancreatitis: Very little information was provided with regard to the clinical picture. It appeared as if inflammation of the pancreas developed most commonly within the first 2 days of therapy although the duration ranged from 2 days to 3 weeks. Most affected were patients in the age range, although information was not provided on approximately 40% of the patients. There appeared to be an equal distribution between genders and the presence or absence of underlying diabetes mellitus. Information with regard to the degree of inflammation was not provided on any patient. Overall it became evident that a labeling change was necessary in order to add pancreatitis to the AEs associated with trovafloxacin usage as no cases had been seen previously, however a description of the disease process could not be provided.

Hepatitis Total (N = 31)**APPEARS THIS WAY
ON ORIGINAL****Demographics:****Gender:** 14/31 (45.2%) female, 9/31 (29%) male, and 8/31 (26%) not reported**Age:** 8/31 (32%) > 60 years of age, 9/31 (29%) < 60, 13/31 (42%) not reported

Mean 54.25.

Underlying diabetes: 4/31 (13%) diabetic (3 women)**Dosage:** 200-300 mg PO or IV qd (predominantly 200)**Duration of therapy prior to the development of hepatotoxicity:** non-specific ranging from 2 days to 4 weeks (the majority 23/30 (77%) within first 10 days: Average 11)**Clinical Picture:** variable, all patients complained of fatigue.**Symptomatic Hepatitis (fatigue, fever, abdominal or RUQ pain, jaundice):** 8**APPEARS THIS WAY
ON ORIGINAL****Laboratory:****Eosinophilia (peripheral or localized to liver):** 5/31 (16.1%)**Transaminitis:** 13/31 (42%) reported elevated normal 17/31 (55%) not reported and 1/31 (3.2%) within normal limits**Alkaline Phosphatase:** 7/31 (22.6%) increased to > 3 x normal - > 10 x normal**Bilirubin:** 9/31 (29%) elevated 22/31 (71%) not reported**Hepatitis and Cholestasis:** 5/31 (16.1%)**Cholestasis:** 8**Cholestasis alone:** 3**APPEARS THIS WAY
ON ORIGINAL****Determination of Relatedness: N = 24:**

Definite: 4

Probable: 9

Possible: 11

From the above, it became apparent that the trovafloxacin-related hepatotoxicity was equally distributed between males and females, that it most commonly appeared in patients aged > 55. Average duration of therapy prior to the development of symptoms or LFT abnormalities was 11 days, much less than that described in the NDA review (4 weeks). Patients appeared to develop either mild symptomatic disease (as

described above) to overt liver failure or to develop a chemical hepatitis alone (LFT elevations without symptoms). Cholestasis also developed in some patients. The clinical and hepatic abnormalities resolved in all patients listed, usually over the course of 6 – 8 weeks. The MO determined that 24 of the cases listed were related to trovafloxacin usage.

Subsequent to the receipt and review of the above, the DSPIDPs requested that Pfizer provide a proposal with regard to a labeling change (June 1998). Pfizer submitted a proposal (see below).

Revised Label as per the sponsor:

Add to Adverse Reactions Section:

Post-Marketing Experience: adverse events reported with trovafloxacin during the post-marketing period for which a causal relationship is uncertain include: anaphylaxis, hepatitis, liver failure (including acute hepatic necrosis with findings of eosinophilic infiltrates), Stevens-Johnson syndrome.

The MO determined that the suggested by the sponsor labeling revision was inadequate and did not provide enough information to adequately guide prescribing MDs with regard to the development of LFT abnormalities and their degree. Additionally, the issue of the development of pancreatitis was not addressed.

Negotiations ensued and on July 9, 1998 a teleconference was held between the FDA and Pfizer and labeling changes were agreed upon. Final changes can be found at the conclusion of this document (page 13). Please refer to the current label (page 3) as needed.

Recommended Regulatory Action:

It is recommended that the TROVAN® label be revised as follows:

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Regina Alivisatos, MD
DSPIDPs, HFD-590

Cc:

Orig. NDA 20-759

Orig. NDA 20-760

HFD-590

HFD-590/DivDir/MGoldberger **/S/**

HFD-590/DepDivDir/RAlbrecht

HFD-590/MTL/BLeissa

HFD-590/Biopharm/FCIangel **/S/**

HFD-590/Micro/Dionne

HFD-590/Chem/Holbert

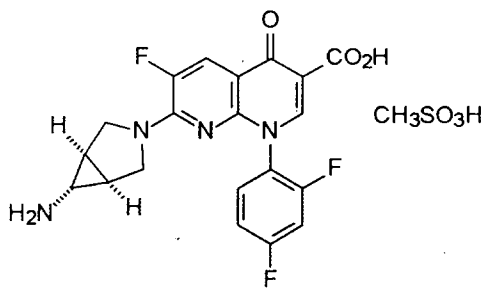
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HFD-590/CSO/RAnderson

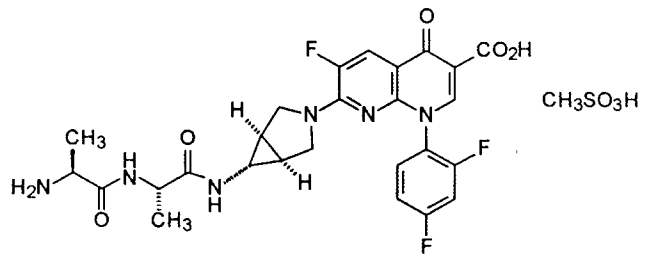
HFD-725/Biostat/Chakravarty

9/30/98

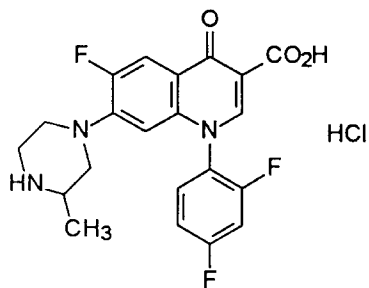
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ON ORIGINAL**



trovafloxacin mesylate



alatrofloxacin mesylate



temafloxacin hydrochloride

**APPEARS THIS WAY
ON ORIGINAL**

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ON ORIGINAL**

NDA 20-759/20-760; Study 154-144 "Acute Pelvic Infections"

Medical Officer's Review of NDA

OCT 20 1998

NDA 20-759/20-760

INDICATION: TREATMENT OF ACUTE PELVIC INFECTIONS

DRAFT LABELING EXCERPT:

Abbreviations used in this MOR:

AE = adverse event
AB = antibiotic
BV = bacterial vaginosis
CI = confidence intervals
C/sec = cesarean section
CRF = case report form
DAIDP = Division of Anti-Infective Drug Products
EOS = end of study
EOT = end of treatment
GC = gonococcal **OR** gonorrhea
IV = intravenous
MO = medical officer
MOR = medical officer review
PID = pelvic inflammatory disease **OR** patient identification number
po = by mouth, oral
PPE = postpartum endometritis or endomyometritis

APPEARS THIS WAY
ON ORIGINAL

PTC = Points to Consider document
 ROM = rupture of (amniotic) membranes
 Rx = therapy or treatment
 RX = prescription
 Sn = sign
 STD = sexually transmitted disease
 Sx = symptom
 TOA = tubo-ovarian abscess
 UTI = urinary tract infection

Materials and Literature Reviewed for this Indication:

E-sub from December 1996
 Various fax material from the sponsor
 E-mails from the sponsor
 Large packet of clinical tables mailed 10/30/97

Mandell, Douglas and Dolin, Principles and Practice of INFECTIOUS DISEASES, 4th Edition, 1995.

Sweet, R.L. and Gibbs, R.S., Infectious Diseases of the Female Genital Tract, 3rd Edition, 1995.

Weisenfeld, H.C. and Sweet, R.L., Gynecologic and Obstetric Infections, Chapter 14, 1996.

Casey, B.M. and Cox, S.M., chapter on endometritis, p. 203-22, Infectious Disease Clinics of North America, guest editors Tuomala and Cox, March 1997.

Clinical Background:

Acute pelvic infections constitute a diverse group of both community- and hospital-acquired infections. They are conveniently considered in three categories: infections related to pregnancy; infections following gynecologic surgery; and sexually-transmitted pelvic inflammatory disease (PID). This study included only infections related to postpartum pregnancy, postabortal pregnancy, and gynecological surgery. PID, cervicitis, and certain other specific pelvic infections were excluded per protocol.

It is important to note that **bacteria classically considered pathogenic may be part of the normal vaginal flora**, so there is debate concerning exactly which bacteria are pelvic pathogens. The normal vaginal flora consists of lactobacilli, various species of streptococci, *Gardnerella vaginalis*, strains of Enterobacteriaceae, and anaerobes. Anaerobes predominate in numbers, with a ratio of 10:1. *Bacteroides fragilis* may be cultured from the normal vagina in approximately 10% of patients, enterococci in 25%, *Clostridium perfringens* in 10%, group B streptococci in , *Gardnerella vaginalis* in , and *Prevotella* spp. (formerly *Bacteroides* spp.) in 25%. In a 11/7/97 talk at NIH, microbiologist Sharon Hillier stated that during pregnancy cultures were positive for enterococci in 33% of asymptomatic women, group B streptococci in 16%, *Gardnerella vaginalis* in 58%, and *Prevotella* spp. in 61%.

Wiesenfeld and Sweet state that **post partum endometritis (PPE)** rarely exceeds 3% of patients post vaginal delivery, but rates post Cesarean section range depending on many different well-established risk factors such as prolonged rupture of membranes, prolonged labor, number of internal exams, socioeconomic data, anemia or the concomitant presence of bacterial vaginosis (BV). There are different clinical diagnoses that are included within the general category of PPE; these include **endomyometritis, parametritis, endoparametritis, and puerperal infection**. PPE is most often a **mixed (polymicrobial) infection of aerobic and anaerobic bacteria**. of PPE cultures grow aerobic *Gardnerella vaginalis*, *Escherichia coli* & streptococci; grow group B & D streptococci; anaerobic growth is with *Bacteroides* spp., *Prevotella* spp., and *Peptostreptococcus* spp. as the most common. Chlamydia is associated with a late form of PPE, occurring 2 days to 6 weeks after vaginal delivery. Wiesenfeld and Sweet

recommend blood cultures in all patients as _____ will have bacteremia, with group B streptococci and *Gardnerella vaginalis* the most common isolates.

Because these infections are polymicrobial with aerobic and anaerobic organisms, broad spectrum antimicrobial coverage is recommended. Options for more severely ill patients include double or triple antibiotic combinations such as clindamycin or metronidazole + gentamycin +/- ampicillin, or a cephalosporin/penicillin combination such as cefoxitin or cefotetan + ampicillin or amoxicillin. A single agent like cefoxitin, cefotetan, Unasyn®, or Timentin® is appropriate in patients with milder disease or clearly established susceptible microorganisms. Treatment should be continued until the patient is afebrile for 48 hours. If IV therapy is successful, further treatment with oral agents may be unnecessary (Dinsmoor et al., *Obstet. Gynecol.* 77:60-2, 1991).

Failure of antimicrobial therapy usually results from either enterococcal superinfection or inadequate coverage of a multiresistant anaerobe. If fever persists despite apparently appropriate antimicrobial therapy, the differential diagnosis includes a wound or pelvic abscess, ovarian vein thrombosis, septic pelvic thrombophlebitis, or noninfectious fever (e.g., drug fever or breast engorgement).

Postabortion infection is an ascending process and occurs more often in the presence of retained products of conception or operative trauma (induced abortion). The infection typically has its onset within four days of the procedure or spontaneous miscarriage, and is most often caused by an unsuspected sexually transmitted pathogen, or a polymicrobial mixture of anaerobic and aerobic bacteria like those in PPE. Persistent bleeding, sonographic evidence of retained tissue, or persistent infection require curettage in addition to antimicrobial treatment. Many patients are given prophylactic antibiotic coverage at the time of an induced abortion, so a careful history is important when treating these patients.

Postoperative gynecologic infection includes pelvic cellulitis, parametritis, cuff cellulitis, and abscess; these infections are also not well understood in terms of the exact pathophysiology. An endogenous route of infection is most probable with the exception of *Fusobacteria* and *Bacteroides fragilis*, both infrequent members of the normal vaginal flora.

Many factors alter the vaginal flora and may indirectly predispose to postoperative infection. Hospitalization appears to exert a profound effect on the vaginal flora, regardless of surgery or antibiotic prophylaxis, and this change tends to be in the direction of more virulent organisms such as enterococci, *Bacteroides fragilis*, and resistant Enterobacteriaceae. Other common predisposing factors include the use of non-oxynol-9-containing vaginal contraceptives, oral contraceptive hormones, douching, use of the female condom, and the phase of the menstrual cycle. The significance of these factors in relation to infection after gynecologic surgery is unknown.

Many external risk factors for infection after hysterectomy (or any major operative procedure) have been identified such as poor nutrition, lower socioeconomic status, diabetes, anemia, old age, obesity and prolonged surgery. These factors were partially addressed in this clinical trial, and further comments are made later.

The most common infection after hysterectomy is **pelvic cellulitis**. The value of obtaining a culture from the vaginal cuff is controversial in cases of pelvic cellulitis because the infection is within the lower abdominal (pelvic) cavity. Some experts believe that cultures can identify the responsible pathogens, especially when an infection has not responded to the initial antimicrobial therapy. Others argue that contamination with the normal vaginal flora makes such cultures uninterpretable. Pelvic cellulitis usually responds to single-agent parenteral antibiotic therapy. Hager et al. (*Obstet. Gynecol.* 73:326-9, 1989) have shown that oral outpatient antibiotic therapy after successful parenteral therapy for pelvic cellulitis is unnecessary.

Cuff cellulitis is the normal inflammatory process at the margins of the vaginal cuff incision following a hysterectomy; a small percentage of cases will require antibiotics, often as outpatients. **Cuff and pelvic abscess** are the least common of postoperative gynecologic infections; any purulent material recovered should be cultured for aerobic and anaerobic pathogens. Identification of an abscess does not mandate immediate

surgical drainage, as antibiotic therapy alone is often successful in the treatment of this complication. Parenteral antibiotics should be given until the patient is afebrile for at least 24-36 hours.

Regulatory Background:

As noted above in the PDR™ listing of antimicrobial drugs for the general category of gynecological infections, **no quinolones are currently approved specifically for postpartum and postoperative pelvic infections.** Many of the drugs listed are specific for beta-lactamase producing microorganisms, or for *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*, or for only *Escherichia coli* (Ceptaz®, Fortaz®, Tazicef®, Zosyn®). Several are broad spectrum antimicrobials and cover a much wider range of bacteria, and therefore are approved for a variety of acute pelvic infections as noted above. Study 155-144 was submitted in order to attain approval for acute pelvic infections discussed above in the clinical background section.

The Division of Anti-Infective Drug Products (DAIDP) Points-to-Consider (PTC) document discusses gynecologic infections excluding STDs and acute PID. The PTC recommends that "one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product is needed. At least 50% of the clinically evaluable patients should also be microbiologically evaluable." If there is not a "reasonable mix of various gynecologic infections, such should be noted in the approved labeling by restricting the wording of the Indications and Usage section to just those types of infections actually studied." Furthermore, the PTC document guidelines allow data from a gynecological infections study and a complicated intra-abdominal infection study (such as 155-124) to be used jointly to support an approval for the study drug against specific species of bacteria as long as the extrapolation makes sense clinically and pharmacologically.

MO Comment: Data from both this acute pelvic infections study (154-144) and from the complicated intra-abdominal infections study (155-124) were used in this MOR to draw final conclusions concerning the specific bacteria to be included in the label. The PTC guidelines were closely followed.

Current IDSA/FDA Guidelines (Nov. 1992) devotes an entire section (S41- S52) to "Evaluation of New Anti-Infective Drugs for the Treatment of Acute Pelvic Infections in Hospitalized Women." The following are the recommended evaluability guidelines:

1. the protocol must be followed to assure the potential evaluability of each patient
2. must not miss 2 consecutive doses of antibiotic
3. have clinical categories of failure, improvement, presumptive cure and cure, but improvement is only an interim assessment
4. in the final evaluation, clinical criteria are "much more important than" micro findings, and final evaluation is failure, cure or non-evaluable (indeterminate)
5. patient should be reevaluated 14-28 days after completion of therapy for final (EOS) clinical evaluation
6. pelvic cultures during the last visit are not necessary if patient is clinically cured

The IDSA/FDA document further states that the expected cure rate of acute pelvic infections is ~90% at the EOS visit. Duration of therapy for an evaluable cure should be no less than 4 days and no more than 10 days. Parenteral therapy is recommended for at least the initial four days of therapy, but no specific statement is made about minimal parenteral therapy prior to switching to oral therapy. Use of another antibiotic for the treatment of a pelvic infection because of lack of clinical response is considered a failure.

MO Comment: The study protocol allowed 4 to 14 days of therapy and a minimum of one day of parenteral therapy before changing to oral therapy. After careful review of the literature, the IDSA guidelines, the general mild severity of illness in the majority of patients, and the high percentage of prior antibiotic use (as a confounding factor), **the MO elected to use 4 to 10 days of therapy as the evaluable range for cure.** Those patients who received 11 to 14 days of therapy were considered non-evaluable, rather than failures,

because the original protocol did allow up to 14 days of treatment. Patients receiving more than 14 days of the study or control arm antibiotic were considered failures in order to be consistent with the study protocol, as well as IDSA and MO criteria.

APPEARS THIS WAY
ON ORIGINAL

Microbiology and Chemistry: copied and modified from page 13 of study report.

Trovafoxacin is a fluoronaphthyridone derivative related to well-known fluoroquinolone antimicrobial drugs such as ciprofloxacin, norfloxacin, and ofloxacin. It has been formulated for human use as the mesylate salt. Trovafoxacin has shown a number of desirable characteristics in preclinical *in vitro* and *in vivo* animal testing. Its mechanism of action is the same as that of the quinolones which act by inhibiting the normal function of the A subunit of DNA gyrase, a bacterial DNA topoisomerase II. Trovafoxacin is selective for bacterial DNA gyrase, and does not significantly affect eukaryotic topoisomerase II.

Trovafoxacin has a broad spectrum of *in vitro* activity, particularly against the common pathogens involved in acute pelvic infections.

MO Comment: The MIC₉₀s of trovafoxacin for some of the pathogens involved in acute pelvic infections are listed in the following MO table with the MIC₉₀ data from Sousan Altaie, FDA microbiologist.

Pathogen	MIC ₉₀ (µg/mL)	
	Range	Median
<i>Bacteroides fragilis</i>		0.5
<i>Enterococcus faecalis</i> (VRE)		8
<i>Enterococcus faecalis</i> (VSE)		2
<i>Escherichia coli</i>		0.06
<i>Gardnerella vaginalis</i>		2
<i>Streptococcus agalactiae</i>		0.25
<i>Streptococcus anginosus</i>		None given
<i>Peptostreptococci</i> spp.		1
<i>Prevotella</i> spp.		1

APPEARS THIS WAY
ON ORIGINAL

Pharmacokinetics: modified from the study report.

Trovafoxacin mesylate salt was well-absorbed with an absolute bioavailability in man of approximately 90%. Single and multiple-dose pharmacokinetic studies indicate that systemic exposure increases in a dose-related manner. The peak blood level (C_{max}) of trovafoxacin at the 300 mg intravenous dose occurred at the end of the recommended 60 minute infusion; in acute pelvic infection subjects it measured ~4.4 µg/mL with a half-life of 10.8 hours. For the oral trovafoxacin, C_{max} was between 1-2 hours, with a range of 30 minutes to 4 hours.

MO Comment: The decreased absorption of trovafoxacin associated with antacid use, especially Bicitra in the surgical prophylaxis study, was determined by Pfizer. The use of antacids did not, however, seem to impact on the results of this gynecologic infections study.

It was also of note that C_{max} levels in general, for a given dose of oral trovafoxacin, were inversely proportional to body weight, irrespective of gender. All subjects in this study were obviously female, but due to their lower weights compared to men, their average peak blood levels were higher than that seen in other studies. This did not, however, impact on the incidence of dizziness or the efficacy of trovafoxacin in this study.

APPEARS THIS WAY
ON ORIGINAL

Study No. 154-144**A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL ASSESSING THE SAFETY AND EFFICACY OF INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN COMPARED WITH INTRAVENOUS CEFOXITIN FOLLOWED BY ORAL AMOXICILLIN/CLAVULANIC ACID FOR THE TREATMENT OF ACUTE PELVIC INFECTIONS.****OBJECTIVES:** copied from the study report.

To compare the safety and toleration and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin with the combination of intravenous cefoxitin followed by oral amoxicillin/clavulanic acid in the treatment of subjects with acute pelvic infections.

PRINCIPAL INVESTIGATORS (55)

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5017	John Gezon, MD
	5221	Ashwin Chatwani, MD
	5238	Subir Roy, MD
	5529	Vinod Dhawan, MD
	5601	James McGregor, MD
	5602	Stanley Gajl, MD
	5749	Gregory Fossum, MD
	5750	David Hemsell, MD
	5751	Abner Korn, MD
	5759	Richard Sweet, MD
	5768	Peter Marsh, MD
	5864	Melisa Holmes, MD
	5865	Andrew Kaunitz, MD
	5866	William Koltun, MD
	5867	Robert Nordland, MD
	5868	George Maroulis, MD
	5870	Mary O'Sullivan, MD
	5874	Dale Sundwall, MD
	5875	Michael Valley, MD
	5898	Pamela Berens, MD
	5899	Michael Campion, MD
	5900	Richard Dittrich, DO
	5901	Thomas Garite, MD
	5902	Bruce Mabine, MD
	5906	Dean Coonrod, MD
	5911	Dominic Muzsnai, MD
	5912	Gregory Parker, MD
	5913	Jeffrey Peipert, MD
	5917	Gerardo Carlos, MD
	5922	Daryl Gildenblatt, MD
5968	Denis Mee-Lee, MD	
5969	Thomas Stovall, MD	
5971	Robert Messer, MD	
5988	Ronald Pruitt, MD	
5994	Richard Hedrick, Jr., MD	
6077	Blane Crandall, MD	
Canada	6108	Gilles Murray, MD
	6109	Mark Martens, MD
	6120	Robert Kessler, MD
	6121	Marie Beall, MD

APPROVED THIS WAY
BY ORIGINAL

APPROVED THIS WAY
BY ORIGINAL

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	6124	Richard Hansell, MD
	6125	John McGee, MD
	6126	Todd Vanheest MD
	6144	Xavier Pombar, DO
		Howard Strassner, MD
	6148	Lloyd Lewis, MD
	6149	Hugh Miller, MD
	6154	Felix Oyola, MD
	6169	Lamar Ekbladh, MD
	6344	William O'Riordan, MD
	6346	George Harper, MD
	6347	Anthony Smith, MD
	6367	Del Dehart, MD
	6378	Edward Zelnick, MD
Canada	6385	Wendy Wolfman, MD
	6542	Jeanna Piper, MD

DESIGN: copied from the protocol.

Study 154-144 was a randomized, double-blind, double-dummy, multicenter comparative trial conducted at 35 centers from 21 June 1995 to 3 May 1996.

The Phase 3 Protocol stated: Subjects with suspected acute pelvic infections were randomized in a double-blind fashion to receive either a regimen of intravenous CP-116,517 (300 mg/day) and oral CP-99,219 (200 mg/day) or a combined regimen of cefoxitin (2 grams intravenously every 6 hours) followed by amoxicillin/clavulanic acid (500 mg orally every 8 hours) for a maximum of 14 days. Switching from parenteral to oral medication was determined by the investigator when oral intake had been re-established. Double-blind therapy was continued for a minimum of 4 days and terminated after a maximum duration of 14 days, independent of clinical response.

MO Comment: The use of parenteral cefoxitin followed by oral amoxicillin/clavulanic acid was an acceptable comparator for this study. It is an antibiotic regimen that is well-established, commonly used, and recommended by experts in the field of infectious diseases. The dosing used in the comparator arm of this study was the most commonly recommended regimen.

The goal was to obtain at least 300 hospitalized subjects, aged 18 or more, with a medical history and clinical findings consistent with an acute pelvic infection, either post-operative, postpartum, or post-abortion.

Efficacy was evaluated through clinical assessment of signs and symptoms of acute pelvic infections. Safety was assessed throughout the study by recording concomitant medication, vital signs, study drug dosing, adverse events, and laboratory evaluations.

MO Comment: Having a single trial was consistent with the DAIDP PTC document's recommendation that only one trial is required in patients with acute pelvic infections, NOT including sexually transmitted diseases or pelvic inflammatory disease. As noted earlier, the sponsor also conducted a separate clinical trial (study 154-124 to establish the efficacy of trovafloxacin in the treatment of complicated intra-abdominal infections) in order to support this acute pelvic infections trial, as recommended in the PTC document.

PROTOCOL OVERVIEW

Population, visits and procedures:

Copied from the electronic submission, page 30 of the study protocol, is the sponsor's schedule of visits and procedures seen below. Inpatient females who were at least 18 years of age with a preliminary diagnosis of an acute pelvic infection (other than acute PID or another sexually transmitted infection) were eligible for participation in the study.

APPENDIX
CONTINUED

SCHEDULE OF STUDY VISITS AND PROCEDURES

Study day	Day 1	Day 3	Day 5 ^e	Day 14 ^a	Day 30
Allowable Window:	-48 hours	Day 2-4	Day 5-7	Day 5-14	Day 28-42
Treatment Period	Day 1 to Day 14 ^a				
Follow-up period	Day 15 to Day 42				
Informed consent	X				
Demographic information	X				
Maximum body temperature ^b	X-----X				
Targeted physical exam	X	X	X	X	X
Vital signs	X	X		X	X
Clinical signs & symptoms	X	X	X	X	X
Concomitant medication	X-----X				
Dosing record	X-----X				
Microbiology culture & sensitivity ^c					
• pelvic areas	X	X ^d		X ^d	X ^d
• blood	X	X ^d		X ^d	X ^d
• urine	X	X ^d		X ^d	X ^d
Safety laboratory tests					
• hematology	X	X		X	abn
• biochemistry	X	X		X	abn
• urinalysis	X	X		X	abn
Adverse events	X-----X				X
Investigator's assessment of clinical response ^c		X		X	X
Health care resource utilization	X-----X				X

^aor end of double-blind therapy if sooner

^bperformed daily during the hospitalization period

^cand to be done at the time of discontinuation, if applicable

^donly if clinically indicated (e.g., time of discontinuation, previously positive culture, or time of the determination of drug failure)

abn = to be done only if abnormal at previous visit or if subject experiences a clinically-significant adverse event

^e only if subject remains hospitalized (June 29, 1995 Amendment)

The study consisted of a minimum of 4 subject evaluation visits, with clinically evaluable subjects having clinical and laboratory assessments at Day 1 (baseline), Day 3 (after 48 hours of therapy, allowable window days 2-4), Day 14 or earlier (end of double-blind therapy, designated EOT), and Day 30 (the final assessment, day 28 to 42, designated EOS). Targeted physical examinations and signs and symptoms (assessed during the baseline visit) were also assessed at Day 5 (allowable window days 5-7) only if the subject was still hospitalized (June 29, 1995 Amendment) after initiation of double-blind therapy.

MO Comment: Only 11 Trovan® and 11 control arm patients remained hospitalized on Day 5 and therefore potentially received clinical and laboratory assessments during the 5-7 day window. Also a large number did not have EOT assessments. This was acceptable to the MO because the test of cure (TOC) was based on the findings at the EOS visit. The MO also accepted a larger allowable window of up to day 52 for the "Day 30 final assessment" (EOS) evaluation.

The study consisted of inpatient followed by outpatient therapy for a minimum of 4 days to a maximum of 14 days. All subjects were randomized to receive intravenous medication initially, regardless of their ability to take oral medications. Thus, subjects were assigned single intravenous infusions of Alatrofloxacin or cefoxitin as the first treatment regimen in a double-blind fashion. NO subject was allowed to receive oral double-blind medication initially. Thereafter, based upon clinical impressions, the investigator could switch the subject from intravenous to oral medication. Each subject received two oral tablets once daily (morning dose) and 10 ml of oral suspension 3 times daily, every 8 hours (morning, afternoon, and evening), for a maximum total double-blind double-dummy treatment period of 14 days. A switch back to intravenous therapy was allowed at the investigator's discretion. Also, subjects could remain on intravenous therapy for the entire 14-day study period.

MO Comment: It is of note that of the 160 treated subjects in the trovafloxacin arm, 46 received only 1 day IV therapy and 52 received only 2 days IV therapy (this totals 61% (98/160) of the trovafloxacin arm). Of the 156 treated subjects in the cefoxitin arm, 18 received only 1 day IV therapy and 56 received only 2 days IV treatment (74/156 = 47% of the control arm). Therefore, the majority of the entire study population (172/316 = 54%) received only 1 or 2 days of IV therapy.

Day 1 (baseline) Visit- within 48 hours prior to the start of therapy (copied from page 17 of the protocol).

"The baseline assessment included collection of demographic information, concurrent diseases, antibiotic therapy within the last 7 days, concomitant medication use, vital signs (pulse, respiration, blood pressure, and body temperature), and a targeted physical examination. Signs and symptoms consistent with the diagnosis of an acute pelvic infection (e.g., fever [body temperature ≥ 38 °C], leukocytosis [WBC $\geq 12,500$ cells/mm³]) should be documented on the subject's Case Report Form.

Diagnosis of cuff cellulitis, pelvic cellulitis, or pelvic abscess, where applicable, should be noted on the subject's Case Report Form. In the event that the acute pelvic infection was secondary to incomplete abortion, the nature of the abortion (spontaneous, elective, or self-induced) should be noted on the subject's Case Report Form.

Blood and urine samples for laboratory safety testing should be obtained. Sites of infection were cultured for both aerobic and anaerobic bacteria; samples were obtained within 48 hours prior to initiation of therapy. Each probable pathogen will be identified to the species level."

MO Comment: The protocol did not clarify that testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be performed in all cases of septic abortion and possible

PID; a positive result would render the subject non-evaluable because this study excluded subjects with either pathogen.

The protocol did state that each probable pathogen should be identified to the species level, although this was not done consistently by the individual study sites.

"For subjects with the diagnosis of *endometritis*, *endomyometritis*, or *septic abortion*, a sample from the endometrial cavity will be obtained with a protected culture device. For subjects with *pelvic cellulitis* or *cuff cellulitis*, a sample will be obtained from the supravaginal space using a protected sterile swab. For subjects with *pelvic abscesses*, a sample will be obtained from the supravaginal space (abscess cavity) with a protected sterile swab or by suction (needle or syringe, computed tomography-directed drainage, or surgical drainage). Blood cultures (more than 1) for both aerobic and anaerobic cultures were obtained in all subjects. Isolates from blood cultures were sent to the central laboratory for testing.

A urine sample should be obtained by either the clean-catch method or by catheterization for culture in all subjects."

MO Comment: Upon MO request, the sponsor clarified the use of "a protected culture device;" a specific commercial device was recommended and used in order to minimize the chances of contaminating endometrial samples with "normal vaginal flora." This was an important requirement in the protocol because contamination of endometrial samples has been a common problem in accurately diagnosing the pathogens in pelvic infections.

Although important to rule out a primary or concomitant UTI in these subjects, the value of a "clean-catch" urine sample for culture in a postpartum patient was debatable in light of contamination due to the recent delivery or surgery, the heavy discharge, and normal post-op or postpartum bleeding.

Days 1 to 14 (Double-blind therapy)- copied from page 19 of the study protocol.

"Clinical response to therapy will be assessed by the investigator after 48 hours (day 3, allowable window: days 2-4) of double-blind therapy.

MO Comment: As Day 1 was the first day of treatment in this study, assessment of clinical response after 48 hours was an appropriate time for an early evaluation, but this would not have included Day 2. However, many patients were discharged from the hospital on days 1, 2, and 3; therefore, the MO accepted a window of days 2-4 for this second potential assessment.

The daily maximum body temperature will be recorded on the subject's Case Report Form. Targeted physical examinations and signs and symptoms (assessed during the baseline visit) will be assessed 48 hours (day 3, allowable window: days 2-4) and 120 hours (day 5, allowable window: days 5-7 *if still hospitalized*) after initiation of double-blind therapy. The battery of blood and urine safety tests and vital signs (respiration, blood pressure, and pulse) performed at baseline will also be repeated 48 hours after initiation of double-blind therapy, or if at any time the subject is experiencing a clinically significant event.

Other procedures to be performed throughout the hospitalization period are recording of concomitant medications, study drug dosing, and adverse events volunteered by the subject or observed by the investigator.

The decision to stop double-blind therapy will be made by the investigator based upon his/her assessment of a successful outcome. Typically, drug therapy continues until the subject is afebrile for a period of 24 to 48 hours. However, the determination to discontinue double-blind therapy either

based upon the determination of a successful outcome, because of an adverse experience, or due to the determination of failed drug therapy will be based upon the clinical assessment of the investigator. Under no circumstances will the subject remain on double-blind therapy after 14 days.

Blood and/or urine cultures are to be repeated at 48 hours after initiation of double-blind therapy only if the baseline blood and/or urine cultures were positive. If available and clinically-indicated, pelvic cultures should be obtained at 48 hours after initiation of double-blind therapy."

Day 14 or Earlier (End of double-blind therapy, also designated EOT)- page 20 of printed protocol.

"A targeted physical examination will be performed at the end of double-blind therapy. Vital signs, including body temperature, will be recorded at the end of double-blind therapy. Signs and symptoms assessed during the baseline visit will be re-evaluated at the EOT.

The battery of blood and urine safety tests performed at baseline will be repeated at the end of double-blind therapy, or if the subject is experiencing a clinically significant event.

Other procedures to be performed at the end of double-blind therapy are recording of concomitant medications, study drug dosing, and adverse events volunteered by the subject or observed by the investigator. Also, the investigator is to provide an evaluation of clinical response, as described in Section 8.1 of the protocol.

Blood and/or urine cultures are to be repeated only if the previous blood and/or urine cultures were positive. If available and clinically-indicated, pelvic cultures should be obtained at the EOT."

Day 30 (day 28 to 42- the final assessment)

All signs and symptoms identified at all the previous evaluations, as well as new signs or symptoms since the last visit, should be assessed.

Other procedures to be performed at the day 30 evaluation are recording of vital signs (including body temperature), concomitant medication, and adverse events volunteered by the subject or observed by the investigator. The battery of blood and urine safety tests performed at baseline needs to be repeated only if an abnormality was present at the end of double-blind therapy, or if the subject is experiencing a clinically-significant adverse event.

At this visit the investigator is to provide a final evaluation of clinical response.

MO COMMENT: There were very limited requirements to obtain follow-up pelvic cultures. As per protocol, pelvic cultures should be done only "if available and clinically-indicated." Follow up cultures were not strictly required in all subjects because the most important parameter for a cure in acute gynecologic infections was the clinical evaluation at end of study (EOS). The MO agreed with this approach.

Protocol Deviations: copied from the study report page 34.

Deviations from protocol were noted for 27 subjects, four of whom had more than one deviation, during the study. These deviations were categorized as follows:

1. Inclusion criteria deviations included subjects who: did not have an infection (endomyometritis/endometritis/myometritis, parametritis, phlegmon, and/or abscess, pelvic infection following hysterectomy, or septic incomplete abortion) requiring anti-infective therapy (4 subjects), were <18 years of age (10 subjects), were not permanently sterilized or were not using an accepted clinical means of contraception (2 subjects), did not sign an updated informed

consent to include nursing mothers (2 subjects), did not sign the informed consent (1 subject), and did not have physical examination findings consistent with an acute pelvic infection (1 subject).

2. Exclusion criteria deviations included subjects who had: a history of seizures or epilepsy (5 subjects), evidence of drug or alcohol abuse or dependence (4 subjects), received chronic treatment with known immunosuppressive drugs (2 subjects), and a known or suspected hypersensitivity or intolerance to any quinolone, penicillin, or β -lactam antibiotic (1 subject).

None of the five subjects (2 Trovan® and 3 control arm) who had a history of seizure or epilepsy prior to enrollment in the study had seizure activity or neurological adverse events at any time during the study. With the exception of the four subjects (2 Trovan® and 2 control arm) with inappropriate baseline diagnoses who were not evaluable, none of the subjects was considered to be nonevaluable due to protocol deviations.

MO Comment: The MO agreed with the sponsor's analysis.

Compliance:

This study was conducted in compliance with local and central Institutional Review Board (IRB) and informed consent regulations.

Protocol Amendments: copied from page 17 of study report.

The protocol was amended on June 29, 1995, as detailed below:

1. The minimum age for enrollment was changed from 18 to 16 years.
2. Signs and symptoms and targeted physical examinations were to be performed at Day 5 *only* if the subject was still hospitalized.
3. Outpatient women requiring intravenous antibiotic therapy were eligible for enrollment.
4. Procedures for collection of breast milk were specified.

The protocol was amended on August 18, 1995, as detailed below:

1. Discontinuation from study procedures were modified to specifically address subjects discontinued from study therapy because of clinical failure and adverse events.
2. Clinical failure criteria were modified to exclude subjects who stopped double-blind therapy due to the onset of a significant adverse experience.

The protocol was amended on December 1, 1995, as detailed below:

1. The minimum age for enrollment was changed from 16 to 18 years.
2. Statistical Methods section was updated.
3. Outpatient subjects who initially require IV therapy may be enrolled in the study.

MO Comment: The June 29, 1995 Amendment changed the minimum age of enrollment to 16: 10 patients in the study were < age 18, and 2 were age 14 or 15. Obstetrical patients under the age 18 are common and in fact are at risk for at least three of the indications in this study: septic abortion, Cesarean section delivery and postpartum endometritis. The

December 1, 1995 Amendment changed this back to age ≥ 18 years. Additionally, outpatients who required intravenous antibiotic therapy were also made potentially eligible. The December amendment did not clarify why the enrollment age changed back to ≥ 18 ; according to the sponsor, however, this was because the FDA expressed safety concerns about the use of quinolones in patients under 18 ("pediatric" population). All patients < 18 years old who were already enrolled were still included as potentially evaluable for safety and efficacy. The MO agreed with these above amendments.

The December 1995 amendment allowing outpatient subjects was an acceptable change in light of today's managed care and continuing pressure on the healthcare industry for increased outpatient treatments and procedures.

Concomitant Medications: modified from the study report.

The investigator documented all concomitant medications and any therapeutic interventions at each visit. Other antimicrobials were allowed if it was felt that they would not impact in any way on the pelvic infection. In such cases, however, in order to ensure that the subject remained evaluable, final efficacy assessments were to be performed prior to starting new antibiotic treatment. If another microbial was used that might influence the outcome of the pelvic infection, then the patient was classified as a treatment failure.

The concomitant use of no more than 10 mg/day prednisone or equivalent was allowed. The use of any other investigational drug or immunosuppressive therapy was prohibited. Mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, or magnesium-based antacids were not to be taken within (before or after) two hours of dosing.

MO Comment: Not allowing the concomitant use of certain minerals, vitamins, and antacids was important as it was demonstrated that they would adversely affect the absorption of oral doses of trovafloxacin, and potentially affect its efficacy.

Discontinuation of Therapy: copied and modified from page 17 of study report.

The investigator was to discontinue study therapy in the event of a serious or severe AE, limiting side effects or significant lab abnormalities. The reasons for discontinuation were to be recorded on the CRF, and all severe AEs were to be reported to the Pfizer monitor immediately.

Precautions:

Subjects were instructed not to donate blood during the study or for 6 weeks after the end of the study.

Inclusion/Exclusion Criteria of Note:

Inclusion: copied from page 11 of protocol.

Inpatient or outpatient women requiring intravenous antibiotic therapy. Subjects must not become pregnant both during the study and for a one month period after the end of the study.

Subjects who were found to have one of the infections listed below requiring anti-infective therapy. Subjects had to have physical examination findings consistent with an acute pelvic infection (e.g., new onset of lower abdominal, pelvic, back, and/or leg pain) as well as systemic evidence of inflammation (e.g., fever [body temperature ≥ 38 °C], elevated white blood cell count). Where appropriate, imaging studies could support signs and symptoms of an acute pelvic infection.

The following diagnoses were acceptable:

1. endomyometritis. Subjects must have had a recent cesarean or vaginal delivery, symptoms of pelvic pain and uterine tenderness, and at least one oral temperature of ≥ 38 °C.
2. parametritis, phlegmon, and/or abscess. The criterion for abscess inclusion was a palpable mass located laterally in a parametrial area, anteriorly under the bladder flap, or in the posterior pelvis. Where possible, identification should be confirmed by sonography or other noninvasive testing. This diagnosis could be associated with a delivery, abortion, or hysterectomy.

MO Comment: There were 23 subjects with a diagnosis of parametritis; the MO requested further information concerning additional diagnoses in this group of patients. The parametritis was related to 1 abortion, 1 salpingo-oophorectomy, 8 vaginal deliveries, 7 Cesareans, and 6 unspecified diagnoses.

There were only 3 sponsor-evaluable (1 MO evaluable) subjects with a pelvic abscess in the entire study.

3. pelvic infection (cuff cellulitis or pelvic cellulitis) following hysterectomy. Subjects must have symptoms of pelvic, abdominal, and/or back pain with tenderness in the lower abdomen and the vaginal cuff, parametria, and/or adnexa within 1 to 3 days after the procedure. A recurrent elevation in body temperature (≥ 38 °C oral or equivalent) should have persisted for approximately 24 hours after the procedure.
4. septic incomplete abortion (spontaneous or induced). This infection was diagnosed in a patient with amenorrhea or abnormal uterine bleeding who had a positive pregnancy test, a temperature of ≥ 38 °C (oral or equivalent) on two consecutive occasions, and lower abdominal and/or pelvic pain and uterine cramping associated with a tender uterus (and parametrium). The internal cervical os was usually open. The nature of the abortion (elective, spontaneous, or self-induced) will be noted on the subject's Case Report Form.

MO Comment: There were a total of 5 Trovan® and 8 control arm subjects with a septic abortion. It was not clear how many of these patients received a D&C in addition to the study antibiotic as part of their therapy during the study. This information was important because a D&C for retained tissue with a septic abortion would often be indicated. A D&C would render the subject non-evaluable by the MO because it would be a confounding factor in determining efficacy (was the cure due to the D&C, the antibiotic therapy, or both?).

Duration of the treatment of the acute pelvic infection is anticipated to be at least 4 days ("72 hours of continuous therapy").

MO Comment: The above statement was clear for the Trovan® arm of the study because of the q 24 hour IV dosing: it meant at least 4 IV doses or therapy over 72 hours. It was much more confusing for the control arm because of the q 6 hour IV dosing changing to q 8 hour po dosing. For example, a subject who received a 10PM dose on Day 1, 4 doses on Day 2 and 3, and 1 or 2 doses on Day 4 would have received insufficient (< 72 hours of) continuous control arm therapy over the course of 4 different study days, but enough of the Trovan® drug (4 doses on 4 different days).

Exclusion: copied from pages 12-13 of the protocol.

Pregnant women (determined by history of the subject by the principal investigator) or nursing mothers.

Known or suspected hypersensitivity or intolerance to any quinolone, penicillin, or β -lactam.

Subjects with any of the following disease states:

1. abdominal incision infection after cesarean section or hysterectomy
2. vulvar abscess
3. Bartholin gland abscess
4. pyometra
5. pelvic inflammatory disease
6. cervicitis
7. infection with *Chlamydia trachomatis* which requires treatment.

MO COMMENT: The exclusion criteria were standard and acceptable to the MO. It is of note that two of the excluded infections (PID and Chlamydia infections) were covered by separate Trovan® studies for additional specific indications in this NDA.

Subjects previously enrolled in this protocol.

Subjects with any infections that require treatment with an anti-infective agent other than the study drugs.

Subjects with any of the following conditions:

1. known acquired immunodeficiency syndrome (AIDS)
2. neutropenia, defined as a total white blood cell count $< 2,500$ leukocytes/mm³ or an absolute neutrophil count < 1000 neutrophils/mm³
3. immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including treatment with greater than 10 mg/day prednisone or equivalent)
4. prior history of seizures or epilepsy
5. terminal illness, defined as subjects who are expected to expire within 48 hours
6. severe renal failure (creatinine clearance < 10 mL/minute/1.73 m² defined by the Cockcroft-Gault equation)

Treatment with another investigational drug within 4 weeks prior to the baseline visit, or requiring investigational drug therapy throughout the study period.

Treatment with any systemic antibiotic for 24 hours or longer within 2 weeks prior to entry into the study, unless there is documented evidence of clinical failure. Single dose or standard regimen antibiotics administered for prior surgical prophylaxis are allowed.

MO Comment: Sponsor Table 7 "Listing of Prior Antibiotics Taken at Study Entry", found in Appendix V, listed 157 patients (157/317 represented 49.5% of the entire study subjects). Overall the MO agreed with the sponsor's listing of the clinical evaluability status of these subjects. More than 90% of the prior antibiotics were for prior surgical prophylaxis, which was allowed by protocol, but which was certainly a confounding factor.

Nowhere in the protocol or study report was it clear to the MO exactly what was an acceptable regimen for "prior surgical prophylaxis," and in fact many different antibiotics were used. Close review by the MO of the different prophylactic antibiotic combinations showed, however, that they were commonly-used (acceptable) regimens.

Table 2.4 "Listing of Concomitant Antibiotics Taken During Study" (Appendix I) listed 139 subjects. Closer analysis shows that there was duplication between this Concomitant Antibiotic list and the Prior Antibiotic list, and that at least 47/139 (34%) of these subjects received the antibiotic(s) as surgical prophylaxis. These 47 patients were considered evaluable by the MO if there was evidence that the "concomitant antibiotics" had failed to prevent or treat the patient's infection.

Evidence of recent drug or alcohol abuse or dependence.

Evaluability Criteria

Patients were considered **clinically evaluable by the sponsor** if the following general conditions were met (modified and bolding by MO, from pages 24-5 of study report):

1. they met the inclusion and exclusion criteria;
2. completed between 4-14 days of the therapy;
3. no other systemic anti-infective medications were taken at any time from Day 1 to EOS;
4. completed the study visits and were compliant according to the protocol.

MO Comment: Patients were considered **clinically evaluable by the MO** if the above sponsor criteria were used, except as noted below:

1. patient completed at least 4 days or 72 hours of continuous Rx, and no more than 10 days of Rx;
2. patient could be reevaluated 14 - 52 days after completion of therapy for final clinical evaluation;
3. eliminated patients that could also have had acute PID (from the CRF the MO could not tell if most of the parametritis patients were post op or postpartum or neither); upon request, the sponsor provided further information by email on 11/4/97 on the 23 patients diagnosed with "parametritis". The sponsor provided data on underlying causes, chlamydia and gonorrhea cultures, and prior antibiotic treatment or prophylaxis. MO analysis showed that 17 "parametritis" patients clearly had acceptable associated diagnoses such as PPE or septic abortion; 6 had unspecified diagnoses.
4. allowed 20% of clinically evaluable patients to be evaluated by follow up phone contact, as opposed to an actual visit, under extenuating circumstances (transportation, child care or social problems);
5. required that all patients must have had at least one post-baseline clinical assessment, unless considered a clinical failure or given another antibiotic for insufficient response or unknown reason (after Day 1) at any time during the study; and
6. patient had no intercurrent illness to confound the clinical evaluation.

Patients were considered **clinically non-evaluable by the sponsor** if any of the following were present at the end of study (modified from pages 24-5 of study report):

1. **Insufficient Therapy:** A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before completing 3 days of active double-blind therapy (IV and/or oral) was not evaluable.
2. **Prior Antibiotic Usage:** A subject who took an antibiotic for 1 or more calendar days within 14 calendar days before Day 1 and the baseline pathogens were susceptible to the prior antibiotic were not evaluable unless there was documented evidence of clinical failure or unless the subject had a pelvic abscess and/or phlegmon at baseline. This excluded any antibiotic which began on Day 1 and any prophylaxis before start of the study. If a prior antibiotic started and stopped on Day 1 prior to administration of study medication, that antibiotic was not considered concomitant.
3. **Concomitant Antibiotics Given for Intercurrent Illness:** A subject who was prescribed a concomitant antibiotic during the course of active treatment for indications other than the primary diagnosis was not evaluable. Additional antibiotics given after the end of active double-blind treatment did not render the subject not evaluable for efficacy assessment unless the antibiotic was given before the End of Study assessment for longer than 1 day. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication or unknown reason was not a reason for exclusion from the Clinically Evaluable Subjects subset. A prior antibiotic use that ended on Day 1 was not considered concomitant.
4. **Intercurrent Illness:** A subject who developed an intercurrent illness whose clinical course confounded the clinical evaluation of the subject's clinical response was not evaluable. The sponsor determined intercurrent illnesses that caused a subject to be not evaluable for this reason.
5. **No Post-Baseline Clinical Assessments:** A subject with no post-baseline investigator clinical assessments was not evaluable unless given an antibiotic for insufficient response or discontinued due to inadequate response any time during the study, up to and including the last day of the End of Study analysis window.

MO Comment: Patients with the following were considered non-evaluable as per the MO.

1. Received 11 to 14 days of double-blind therapy (7 Trovan® and 11 control arm patients);
2. Received less than 4 days or 72 hours of the study double-blind therapy and were not a clinical failure;
3. Discontinued the study antibiotic because of side effects;
4. Non-compliance with the study protocol;
5. Had an uncertain baseline diagnosis (e.g., possible PID, UTI, ruptured cyst, appendicitis);
6. Had an additional infection and/or antibiotic that would interfere with the study evaluation; or
7. Had a concomitant medical or surgical condition that would interfere with the study evaluation (e.g., one subject had acute cholecystitis and another had TTP during the study time).

Endpoints

Primary efficacy endpoint- from page 31 of Phase 3 Protocol.

"The primary efficacy endpoint will be *sponsor defined* (December 1, 1995 Amendment) clinical response at follow-up (day 30). Clinical response will be determined by the sponsor and evaluated after 48 hours of double-blind therapy, at the end of double-blind therapy, and at the end of the follow-up period (day 30). Clinical response will be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. The investigator will classify the clinical presentation of the subject at the evaluation time point (without regard to factors that may have influenced the presentation) using the criteria that follow:

Cure

"The investigator defined complete resolution of all signs and symptoms as cure. The final assessment of cure was made at follow-up (day 30) by the investigator.

Typically, cure was characterised by resolution of:

1. signs and symptoms of an inflammatory response (e.g., fever [body temperature ≥ 38.5 °C], elevated white blood cell count [WBC $\geq 12,500$ cells/mm³]),
2. signs and symptoms of acute pelvic distress. Therapy is typically continued for at least 24 hours after body temperature falls below 37.8 °C in those subjects with relatively uncomplicated acute pelvic infections. In subjects who develop phlegmon or abscess, therapy often continues for 48 hours after temperature returns to normal.

Regardless of which parameters were used, the opinion of the investigator determined cure of the acute pelvic infection in each subject.

Improvement

"Improvement was defined as partial resolution of fever, abdominal pain, and/or other signs and symptoms of acute pelvic infection that were identified during the baseline period prior to initiation of double-blind therapy and no requirement for additional antibiotic.

Failure

"Failure was defined by one or all of the following conditions:

1. lack of resolution of any signs and symptoms of an acute pelvic infection as defined above and a need for additional antibiotic.
2. the need for greater than 14 days of double-blind therapy.
3. the need for surgical intervention. An exception is allowed when the initial diagnosis is made at the time of a surgical procedure.
4. death of the subject as a result of the infectious process.

The occurrence of any of the following conditions will supersede the evaluation of response as cure, improvement, or failure and will result in the reassignment of outcome by the sponsor as follows:

1. for subjects who were previously assessed as failures, the outcome will always be failure at subsequent time points.
2. for subjects who were given a concomitant systemic antibiotic prior to an evaluation time point, response will be classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.
3. for subjects who stopped double-blind therapy because of no apparent response, response will be classified as failure (August 18, 1995 Amendment).

MO Comment: The MO agreed with these 3 definitions of clinical response.

Bacteriological Response- from page 33 of the protocol.

"Bacteriological response was determined by the sponsor and evaluated (if applicable) after 48 hours of double-blind therapy (day 3), at the end of double-blind therapy, at the end of follow-up (day 30), and at the time of discontinuation due to lack of clinical response.

Definition of bacteriological response was as follows:

Bacteriologic evaluable patient subgroup: from page 33-4 of the protocol.

All subjects with positive pelvic and/or blood cultures at baseline were considered for bacteriologic evaluability.

The following subjects were considered as having **indeterminate outcomes** and excluded from bacteriologic evaluability:

1. relevant post-baseline cultures are not obtained, unless it is a result of the absence of adequate purulent culture material or concomitant antibiotic use due to bacteriologic persistence
2. the subject was not considered clinically evaluable.

The occurrence of any of the above conditions will preclude the evaluation of response as being any of those found below:

Eradication: Elimination of the original causative organism(s) from the same site (e.g., pelvic dead space, abscess, or blood) during or upon completion of therapy.

Presumed Eradication: Absence of adequate culture material (i.e., tissue or abscess) for evaluation because the subject was clinically improved and there was no need to collect any further samples.

Persistence: Failure to eradicate the original causative organism at completion of therapy from sites previously cultured, whether signs of infection are present or not. Also included are the subjects given concomitant antibiotics for bacteriologic persistence at a prior time point.

Superinfection: Emergence of new pathogens during therapy or within 3 days after treatment had been completed, either at the original site of infection or at a distant site.

Presumed Microbiological Persistence: Use of concomitant antibiotic therapy due to continued clinical symptoms of the infection at study entry in the absence of microbiological data.

MO COMMENT: The MO agreed with the above.

Statistical Considerations

The primary efficacy endpoints were clinical response at Day 30 and bacteriological response if it was evaluable. Clinical response was based on the percent of patients showing a clinical response of cure or improvement at or about day 30 after the first day of antibiotic therapy. The bacterial response was based on the percent of patients showing a bacterial response of "eradication" or "presumed eradication".

The objective of this study was to demonstrate that trovafloxacin was as effective as standard therapy (intravenous cefoxitin and oral amoxicillin/clavulanic acid) in the treatment of acute pelvic infections in women.

The definition of equivalence was that the lower 95 % confidence limit for the difference in response rates is greater than -10% when the true satisfactory response rate of the reference drug is 90 % or better.

A computer-generated, blinded randomization list was provided by the sponsor to the investigators in the study. The treatment groups were randomly assigned with each center and are balanced in a ratio of 1:1.

MO COMMENT: The MO agreed with the above, except to note that a continuity correction factor (CCF) was used by the MO or FDA statistician in calculating each 95% confidence interval (CI). Furthermore, the allowable delta (δ) used in the 95% CI calculation varied with the higher percentage rate of the two treatment groups being compared. The two treatments were considered statistically similar if the lower limit of the 95% CI for the difference in the overall success rates (trovafloxacin minus comparator arm) exceeded a specified value (δ). The specified value was $\delta = -10\%$ if the larger of the two overall success rates was equal to or exceeded 90%; $\delta = 15\%$ if the larger of the two overall success rates was between 80% and 89% (inclusive).

Evaluability: modified from the study report.

As per the sponsor, there were 320 randomized subjects with a signed consent, of which 3 were withdrawn because of an inappropriate baseline diagnosis, leaving 317 treated subjects (see Table below). One other subject was withdrawn, leaving 316 in the clinical ITT group. Of the 317 randomized subjects, 160 received Trovan® and 157 the control arm regimen. 113 Trovan® subjects and 128 control arm subjects completed treatment, and 141 Trovan® subjects and 139 control arm subjects completed study. 66% (107/161) of the Trovan® and 75% of the control arm subjects were clinically evaluable. 55% (88/161) of the Trovan® and 58% (93/159) of the control arm subjects were bacteriologically evaluable. 100% of all treated subjects were evaluated for adverse events, and 146/160 (91%) of Trovan® and 152/157 (97%) of control arm patients were assessed for safety by laboratory testing.

MO Comment: The above percent of bacteriologically evaluable patients met the PTC criteria of at least 50%. The primary efficacy variable, however, was the clinically evaluable population at the end of study (EOS).

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The Sponsor's Table A. of Summary of Subject Disposition: from the study report page 31:

Table A. Summary of Subject Disposition per Applicant				
	Alatrofloxacin ↓ Trovafoxacin		Cefoxitin ↓ Amoxicillin/Clavulanic Acid	
	Number and Percentage (%) of Subjects			
Randomized Subjects	161		159	
Randomized, Not Treated ^a	1		2	
ALL TREATED SUBJECTS	160	(100%)	157	(100%)
Withdrawn from Treatment^b	47	(29%)	29	(18%)
Completed Treatment	113	(71%)	128	(82%)
Withdrawn from Study	20	(13%)	18	(11%)
Withdrawn during Treatment	17	(11%)	10	(6%)
Withdrawn during Follow-Up	3	(2%)	8	(5%)
Completed Study	141	(88%)	139	(89%)
Completed Treatment and Study	110	(69%)	120	(76%)
EVALUATED FOR EFFICACY				
Clinical Intent-to-Treat	159	(99%)	157	(99%)
Clinically Evaluable	107	(66%)	119	(75%)
Bacteriologically Intent-to-Treat	132	(82%)	122	(77%)
Bacteriologically Evaluable	88	(55%)	93	(58%)
Assessed for Safety				
Adverse Events	160	(100%)	157	(100%)
Laboratory Tests	146	(91%)	152	(97%)
a	One randomized, not treated subject (Subject 5221-0474) in the alatrofloxacin/trovafoxacin group received one dose of placebo and completed study.			
b	Of the 47 alatrofloxacin/trovafoxacin subjects who were withdrawn from treatment, 30 completed study; of the 29 cefoxitin/amoxicillin/clavulanic acid subjects who were withdrawn from treatment, 19 completed study.			
Ref.: Tables 1.1 and 1.2				

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MO Comment: The two arms were comparable with respect to the numbers of treated subjects who were bacteriologically evaluable and assessed for safety. They differed, however, in terms of the number of subjects who were clinically evaluable, withdrew from treatment, and completed treatment. The difference was primarily due to the 43/161 Trovan® subjects (27%) who withdrew from the treatment after only 1 to 3 days of therapy for reasons other than failure of the treatment (40 of these subjects received only IV therapy) and became clinically non-evaluable. In the control arm there were 33/159 subjects (20.7%) who withdrew after 1 to 3 days of therapy for reasons other than failure of the treatment. See study discontinuation section for further analysis of the subjects who withdrew early in the study.

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Evaluability by Center: Table 144.1 below was created by the MO from study report data.

Table 144.1
By Center Evaluability, as per the Applicant

			Trovafloxacin Arm			Control Arm		
		Total Rx'd	Treated # N	Eval. # n	% Eval. = n/N	Treated # N	Eval. # n	% Eval. = n/N
Sponsor Totals →		317 (% of total)	160	107	67%	157	119	76%
Center	Location							
5221	Philadelphia, PA	23 (7.3%)	12	6	50%	11	10	91%
5238	Los Angeles, CA	100 (31.5%)	51	39	76%	49	42	86%
5529	Los Angeles, CA	3 (0.9%)	1	1	100%	2	2	100%
5601	Denver, CO	3 (0.9%)	1	0	0%	2	2	100%
5602	Louisville, KY	4 (0.3%)	2	1	50%	2	1	50%
5750	Dallas, TX	7 (2.2%)	4	3	75%	3	3	100%
5751	San Francisco, CA	1 (0.3%)	0	0	0%	1	1	100%
5759	Pittsburgh, PA	3 (0.9%)	1	1	100%	2	2	100%
5768	Tacoma, WA	1 (0.3%)	1	1	100%	0	0	0%
5864	Charleston, SC	12 (3.8%)	6	5	83%	6	4	67%
5865	Jacksonville, FL	20 (6.3%)	11	4	36%	9	5	56%
5866	San Diego, CA	29 (9.1%)	14	12	86%	15	12	81%
5870	Miami, FL	2 (0.6%)	1	0	0%	1	1	100%
5875	Oklahoma Cty, OK	6 (1.9%)	3	1	33%	3	1	33%
5898	Houston, TX	7 (2.2%)	3	1	33%	4	2	50%
5899	Philadelphia, PA	2 (0.6%)	1	1	100%	1	1	100%
5900	Philadelphia, PA	15 (4.7%)	7	5	71%	8	5	63%
5901	Orange, CA	3 (0.9%)	2	1	50%	1	1	100%
5902	Philadelphia, PA	6 (1.9%)	3	2	67%	3	3	100%
5911	Sylmar, CA	6 (1.9%)	3	1	33%	3	1	33%
5912	Charlotte, NC	1 (0.3%)	0	0	0%	1	1	100%
5968	Honolulu, HI	5 (1.6%)	2	2	100%	3	2	67%
5988	Nashville, TN	1 (0.3%)	1	0	0%	0	0	0%
6077	Naples, FL	1 (0.3%)	1	0	0%	0	0	0%
6108	Quebec, Canada	1 (0.3%)	1	0	0%	0	0	0%
6109	Minneapolis, MN	26 (8.2%)	13	7	54%	13	9	69%
6125	New Orleans, LA	1 (0.3%)	1	1	100%	0	0	0%
6126	Detroit, MI	9 (2.8%)	4	2	50%	5	3	60%
6144	Chicago, IL	4 (1.3%)	2	0	0%	2	2	100%
6148	Tampa, FL	1 (0.3%)	1	1	100%	0	0	0%
6154	Fort Meyers, FL	5 (1.6%)	3	2	67%	2	0	0%
6344	San Diego, CA	1 (0.3%)	0	0	0%	1	1	100%
6347	Philadelphia, PA	3 (0.9%)	2	2	100%	1	0	0%
6385	Toronto, Ontario	1 (0.3%)	0	0	0%	1	1	100%
6542	San Antonio, TX	4 (1.3%)	2	2	100%	2	1	50%
35 Centers	Applicant TOTALS	317	160	107	67%	157	119	76%
	MO TOTALS**	317	160	96	60%	157	107	68%

** MO totals are listed here for comparison, but discussed later in the MOR.

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MO Comment: There were 55 centers of which 35 enrolled patients for this study. The distribution of subjects was uneven with center #5238 in Los Angeles enrolling 100/317 patients (31.5%). Next, in descending order, there were 7 centers collectively with 134/317, or 42.3% of the subjects: 29 (9.1%), 26 (8.2%), 23 (7.3%), 20 (6.3%), 15 (4.7%), 12 (3.8%), and 9 (2.8%) patients. 20 of the centers enrolled a total of 41 patients (1 to 4 subjects per center), and the 20 centers that enrolled 0 patients are not listed above.
TOTAL: 317 patients treated.

The MO's 203 evaluable patients totaled 23 less than the sponsor's number of 226. The distribution of these 23 patients was relatively equally split with 11 from the trovafloxacin arm and 12 from the control arm. The listing of the MO changes in evaluable patients can be found in Tables 144.2 and 144.3 shown later in the MOR.

Exclusions from Evaluation: modified from the study report.

Of the 161 Trovan® randomized subjects and 159 control arm subjects, 2 and 1 respectively had an inappropriate baseline diagnosis and were excluded from all analyses. In addition, one subject in the control arm had a perforated appendix and was excluded. This left 159 Trovan® and 157 control arm subjects. 52 in the Trovan® group and 38 in the control group were not clinically evaluable. Therefore 107 and 119 subjects were evaluable. The most common reason for exclusion was concomitant antibiotic therapy for intercurrent illness in 33/161 Trovan® (20%) subjects and 12/159 control arm (8%) subjects. Other reasons were lack of follow-up assessments, insufficient therapy, and antibiotic use for > 24 hours within 2 weeks prior to study entry.

Table 2.1.1 copied below from the E-sub presented demographic characteristics of all patients enrolled in both arms of the study. There were obviously no males, only 2 subjects < 16 years old, 7 "older" subjects age 45 to 64, and one age > 64. Per the applicant, "the two treatment groups were generally comparable with respect to age, race and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects."

Table 2.1.1
Demographic Characteristics
Treated Subjects according to Applicant
Trovafloracin Protocol 144

	Alatrofloxacin 300 mg -> Trovafloracin 200 mg			Cefoxitin 2000mg q6h -> Amoxicillin/Clavulanic acid 500		
	Male	Female	Total	Male	Female	Total
mg t.i.d.						
Number of Subjects		160	160		157	157
Age (yr)						
14-15	0	2 (1%)	2 (1%)	0	0	0
16-44	0	154 (96%)	154 (96%)	0	153 (97%)	153 (97%)
45-64	0	3 (2%)	3 (2%)	0	4 (3%)	4 (3%)
>=65	0	1 (<1%)	1 (<1%)	0	0	0
Mean		27.8	27.8		27.4	27.4
Minimum						
Maximum						
Race						
ARABIC	0	1 (<1%)	1 (<1%)	0	0	0
ASIAN	0	6 (4%)	6 (4%)	0	7 (4%)	7 (4%)
ASIAN INDIAN	0	1 (<1%)	1 (<1%)	0	0	0
BLACK	0	53 (33%)	53 (33%)	0	62 (39%)	62 (39%)
HAWAIIAN	0	1 (<1%)	1 (<1%)	0	2 (1%)	2 (1%)
HISPANIC	0	72 (45%)	72 (45%)	0	69 (44%)	69 (44%)
NATIVE AMERICAN	0	0	0	0	2 (1%)	2 (1%)
WHITE	0	26 (16%)	26 (16%)	0	15 (10%)	15 (10%)
Weight (kg)						
Mean		76.9			78.0	
Minimum						
Maximum						
Missing		3			6	

Percentages may not add to 100 due to rounding.

Source Data: APPENDIX V TABLE 3 Data Extract: 09/09/96 14:45 Table Generation: 09/09/96 14:52

MO COMMENT: It was of note that 96 and 97% of the 160 and 157 treated patients were age 16 to 44, and 97 and 98% of the 107 and 119 clinically evaluable patients in the two study arms (Trovan® and control arm, respectively) were age 16 to 44. Obviously this is the age category for post-partum and post-abortion women, but not necessarily for post-operative gynecological surgery patients. Furthermore, there is discussion in the literature about differences in the vaginal/pelvic flora in pre- and post-menopausal women, as well as differences in the risk of infection in these two groups. This study had only 8/317 subjects (2.5%) over the age of 44.

The MO also noted that the ethnic distribution between the two arms was very similar, with the Trovan® treated arm having a 4% Asian, 16% White, 33% Black, and 45% Hispanic ethnic distribution, and the comparable control arm having a distribution of 4% Asian, 10% White, 39% Black, and 44% Hispanic.

Risk Factors Associated with Acute Pelvic Infection: modified from page 32 of the study report.

Among clinically evaluable subjects, the distribution of types of infection was similar between the two treatment groups. The majority of subjects in the alatrofloxacin/trovafloxacin group and the cefoxitin/amoxicillin/clavulanic acid group had endomyometritis (76% and 80%, respectively) present at baseline. In addition, the mean body mass index (30 kg/m²) was the same for both treatment groups.

Of the clinically evaluable subjects, 50 in the alatrofloxacin/trovafloxacin group (47%) and 58 in the cefoxitin/amoxicillin/clavulanic acid group (49%) had at least one risk factor associated with treatment failure present at baseline. Subjects in the alatrofloxacin/trovafloxacin and cefoxitin/amoxicillin / clavulanic acid groups were comparable with respect to the incidence of risk factors, which included presence of diabetes, no health insurance, and delivery by cesarean section. Similar results were noted for clinically intent-to-treat subjects.

A summary of type of infection and risk factors associated with treatment failure for clinically evaluable subjects is presented by treatment group in the following applicant table, copied from page 33 of the study report.

Table C. Summary of Type of Infection and Risk Factors Associated With Treatment Failure				
Clinically Evaluable Subjects according to Applicant				
	Alatrofloxacin ⇒ Trovafoxacin		Cefoxitin ⇒ Amoxicillin/Clavulanic Acid	
	Number and Percentage (%) of Subjects			
Type of Infection	(N=107)	(100%)	(N=119)	(100%)
Endomyometritis	81	(76%)	95	(80%)
Parametritis	13	(12%)	10	(8%)
Phlegmon	1	(<1%)	0	
Pelvic Abscess	1	(<1%)	1	(<1%)
Post-Hysterectomy Pelvic Infection	5	(5%)	6	(5%)
Cuff Cellulitis	4	(4%)	5	(4%)
Septic Incomplete Abortion ^a	5	(5%)	8	(7%)
Other	7	(7%)	4	(3%)
Risk Factors For Treatment Failure^b				
Number of Subjects with At Least One Risk Factor	50	(47%)	58	(49%)
Diabetes				
Present	6	(6%)	7	(6%)
Health Insurance				
None	8	(7%)	11	(9%)
Type of Delivery				
Cesarean	47	(44%)	48	(40%)
a Septic incomplete abortion combines spontaneous, elective, and self-induced abortions.				Ref.: Table 2.3.1
b Counts may not add to number of subjects because subjects may fall into more than one category.				

MO Comment: Sponsor Table C. was labeled as factors associated with treatment failure. Diabetes, (lack of) health insurance, and type of delivery are predisposing factors for developing an infection, as well as for treatment failure. The distribution of these risk factors was numerically equal between the two arms of the study.

Several major risk factors (such as prolonged ROM, prolonged labor, number of internal exams, anemia, time in surgery, and emergent Cesarean as opposed to elective scheduled Cesarean), that are also associated with both developing an infection and treatment failure were not included in the study report, because they were not part of the study protocol.

Concomitant Medications, including Antimicrobials: modified from page 34 of study report.

99% of patients in both groups received concomitant medications during study therapy. Most commonly used were analgesics, vitamins, electrolyte and water replacement, laxatives, iron-replacement, and drugs prescribed for gout and rheumatic diseases. During the study, 79 subjects in the trovafloxacin group and 60 subjects in the control arm received antibiotics other than the study antibiotics for the following reasons:

1. inadequate response (i.e., clinical failure): 10/160 (6.3%) Trovan® and 17/157 (10.8%) control arm
2. early discontinuation due to side effects: 20/160 (12.5%) Trovan® and 3/157 (1.9%) control arm
3. other infections or other reasons: 49/160 (30.6%) Trovan® and 40/157 (25.5%) control arm

MO Comment: All patients with inadequate response were carried forward as failures.

Study Discontinuations

Of the 160 Trovan® and 157 control arm subjects, 47 (29.4%) and 29 (18.5%), respectively, were prematurely discontinued from treatment as summarized in the following table copied from the study report:

Table B. Summary of Premature Discontinuations From Treatment (All-Treated Subjects per Sponsor)				
	Alatrofloxacin ↓ Trovafloxacin (N=160)		Cefoxitin ↓ Amoxicillin/Clavulanic Acid (N=157)	
	Number and Percentage (%) of Subjects			
Total Discontinued	47	(29%)	29	(18%)
Discontinuations Related to Study Drug:	28	(18%)	16	(10%)
Adverse Event*	21	(13%)	1	(<1%)
Insufficient Response*	7	(4%)	15	(10%)
Discontinuations Unrelated to Study Drug:	19	(12%)	13	(8%)
Adverse Event	6	(4%)	4	(3%)
Did Not Meet Randomization Criteria	0		1	(<1%)
Lost to Follow-Up	4	(3%)	3	(2%)
Other	6	(4%)	0	
Protocol Violation	1	(<1%)	0	
Withdrawn Consent	2	(1%)	5	(3%)
Ref.: Table 4.1				

***Bolded by MO**

MO Comment: Most notable from Sponsor Table B. was the high percentage of Trovan® subjects (29%) who discontinued treatment as compared to those in the control arm (18%). There was a striking difference in the adverse event category (21 Trovan® versus 1 control arm). The next most notable difference was with the insufficient response in 15 control arm subjects versus 7 Trovan® subjects.

Further analysis of the 21 Trovan® patients who were discontinued prematurely related to an adverse event due to the study drug is found on page 42 of this report.

Evaluability Changes by MO: See Tables 144.2 and 144.3 below created by MO analysis and data.

Table 144.2
EVALUABILITY Changes[™] by Patient, as per the MO

PID	Sponsor Status	MO Change	MO Reason	MO COMMENT
52380566	Evaluable	to Non	Cannot clearly tell UTI from PPE symptoms.	Postpartum; very mild Sx/Sn; mixed urine and endometrial cultures.
56010003	Evaluable	to Non	Insufficient Rx.	Received < 3 days Rx.
57500279	Evaluable	to Non	Insufficient Rx.	Received only 9 doses of control drug.
57500283	Evaluable	to Non	Insufficient Rx & concomitant Rx.	PPE, C-sec: study antibiotics on days 1-3 only.
Trovan Arm 52380250, 58990025*, 59000397, 59020239, 59020241, 59110296, 63470599	Evaluable	to Non per MO criteria	The protocol allowed Rx for 4-14 days, but IDSA and MO criteria allow only 10 days .	Change from cure to Non-evaluable, because of > 10 days Rx. * One patient (58990025) would remain a failure because of > 14 days treatment.*
Control Arm 55290090, 55290091, 56010001, 58650161, 58990026, 59000079, 59020238*, 59020240, 59020242, 59110295, 61260725, 63850605	Evaluable	to Non per MO criteria	The protocol allowed Rx for 4-14 days, but IDSA and MO criteria allow only 10 days .	Change from cure to Non-evaluable, because of > 10 days Rx. * One patient (59020238) would remain a failure because of > 14 days treatment.*
59000401	Evaluable	to Non	Insufficient Rx.	Inadequate Rx (48 hr), and inappropriate Dx (?PID or UTI?).
59000402	Evaluable	to Non	Uncertain baseline Dx endometritis and parametritis	No fever; home day 1.
60770145	Evaluable	to Non	Uncertain Dx of phlegmon.	Day 5 laparoscopy saw no infection: home next day on no Rx
63470598	Evaluable	to Non	Prior antibiotic usage.	Prior Amp/ Unasyn x 2+ days. Home on study day 2.

MO Change from EVALUABLE to NON-Evaluable status: 25 patients + 2 failures

Table 144.3
MO Change from NON-Evaluable to EVALUABLE (EVAL) Status

PID	Sponsor Status	MO Change	Sponsor Reason for Status	MO COMMENT
58980269	Non-Eval	to EVAL	Other	Evaluable + FAILURE
58980271	Non	to EVAL	Concomitant antibiotics	Evaluable + FAILURE
61090557	Non	to EVAL	Prior antibiotic usage	Had Doxy x 6 days with a clinical failure; then entered the study. Eval + CURE.
61090511	Non	to EVAL	> 24 hr prior antibiotic therapy	Clinical failure on Amp, Clinda and Genta. Had study Rx x 4 days. Eval + CURE.
61540364	Non	to EVAL	Prior antibiotic usage	Clinical failure on Ancef & Genta x 2 days; study Rx x 8 days. Eval+ CURE.

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MO Comment: The 30 patients (listed in the 2 tables above) with a change in evaluability status by the MO came from 15 different centers. 13 of these centers had only 1 or 2 patients' status changed by the MO. The 2 remaining centers, 5900 and 5902 (both in Philadelphia, PA), had 4 and 5 patients, respectively, with changes by the MO in their evaluability status. 7 of these 9 patients were determined to be non-evaluable due to prolonged duration of therapy (> 10 days), which was allowed by protocol, but not by the MO's criteria for evaluability.

Sponsor's Efficacy Analysis:

Sponsor-Defined Clinical Response:

Sponsor-defined clinical response rates at the end of treatment and at the end of study are shown for clinically evaluable subjects in Table D. Sponsor-defined clinical success rates (cure + improvement) were comparable between the Trovan® and control treatment groups at the end of treatment (89% and 84%, respectively) and at the end of study (90% and 86%, respectively). Comparisons (95% confidence intervals) of the difference between the two treatment groups in sponsor-defined clinical success rates at the end of study supported equivalence of the two treatment regimens (Trovan®, 90%; control, 86% [Sponsor CI: -4.5%, 12.5%]).

A summary of sponsor-defined clinical response rates for clinically evaluable subjects at the end of treatment and at the end of study was presented by treatment group in the following table copied and modified from page 38 of the study report.

Table F. Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study (Sponsor Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloxacin (N=107)		Cefoxitin ↓ Amoxicillin/ Clavulanic Acid (N=119)		Sponsor 95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	93	(100%)	104	(100%)	
Success (Cure + Improvement)	83	(89%)	87	(84%)	(-3.9%, 15.1%)
Distribution of Clinical Response:					
Cure	73	(78%)	77	(74%)	
Improvement	10	(11%)	10	(10%)	
Failure	10	(11%)	17	(16%)	
End of Study:^a					
Number of Subjects Assessed	107	(100%)	119	(100%)	
Success (Cure + Improvement)	96	(90%)	102	(86%)	(-4.5%, 12.5%)
Distribution of Clinical Response:					
Cure	94	(88%)	100	(84%)	
Improvement	2	(2%)	2	(2%)	
Failure	11	(10%)	17	(14%)	
CI = Confidence Interval					
^a Sponsor-defined subject clinical response at end of study is the primary endpoint.					
Ref.: Table S.1.1					

For a detailed description of clinically evaluable subjects with sponsor-defined clinical failure, see Section 8.3.5 of the study report.

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MO Comment: The MO applied a 95% CI with CCF ($\Delta=10$) to the EOS results (TOC). The results were (-5.4%, 13.4%). Therefore trovafloxacin was equivalent to the approved comparator for the primary efficacy variable of clinical response.

Table 144.4
Clinical Response Rates at EOT and EOS, Clinically Evaluable Subjects as per the MO

	Alatrofloxacin ↓ Trovafoxacin (N=96)		Cefoxitin ↓ Amoxicillin/ Clavulanic Acid (N=107)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	84	(100%)	91	(100%)	(-5.9%, 17.3%) ^c
Success (Cure + Improvement)	74	(88.1%)	75	(82.4%)	
Distribution of Clinical Response:					
Cure	74	(88.1%)	75	(82.4%)	
Failure	10	(11.9%)	16	(17.6%)	
End of Study:^a					
Number of Subjects Assessed	96	(100%)	107	(100%)	(-5.2%, 15.9%) ^c
Success (Cure)	85	(88.5%)	89	(83.2%)	
Distribution of Clinical Response:					
Cure	85	(88.5%)	89	(83.2%)	
Failure	11	(11.5%)	18	(16.8%)	
CI = Confidence Interval					
^a MO-defined subject clinical response at end of study is the primary endpoint; MO did not request data for EOT because this was not a primary endpoint.					
^c per MO calculation with continuity correction factor (CCF).					

MO Comment: When comparing the success (cure) rates at the primary endpoint (EOS) and at the EOT, the 95% CI with CCF ($\Delta = 15$) showed that Trovan was equivalent to the approved comparator for the FDA evaluable population at both timepoints.

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Sponsor-Defined Types of Pelvic Infections: table created by MO from sponsor provided data.

Table 144.5
Clinical Response at EOT and EOS by Type of Infection, as per the Sponsor

Sponsor Evaluable Population	Alatrofloxacin ⇒ Trovafoxacin (N=107)		Cefoxitin ⇒ Amoxicillin/Clavulanic Acid (N=119)		95% CI (Δ = 10)
	Number and Percentage (%) of Subjects				
Overall TOTALS at EOS	114*	(100%)	128*	(100%)	
Success (Cure + Improvement)	103	(90.3%)	110	(85.9%)	
ENDOMYOMETRITIS (EOT)					(-3.9%, 17.1%) ^a
Number of Subjects Assessed	68	(100%)	80	(100%)	
Success (Cure + Improvement)	64	(94%)	70	(87.5%)	
ENDOMYOMETRITIS (EOS)^a					(-4.9%, 13.6%) ^a
Number of Subjects Assessed	81	(100%)	95	(100%)	
Success (Cure + Improvement)	76	(93.8%)	85	(89.5%)	
PARAMETRITIS (EOT)					
Number of Subjects Assessed	11	(100%)	8	(100%)	
Success (Cure + Improvement)	10	(90.9%)	6	(75%)	
PARAMETRITIS (EOS)					
Number of Subjects Assessed	13	(100%)	10	(100%)	
Success (Cure + Improvement)	12	(92.3%)	8	(80%)	
POST-HYST INFECTION (EOT)					
Number of Subjects Assessed	6	(100%)	10	(100%)	
Success (Cure + Improvement)	2	(33.3%)	7	(70%)	
POST-HYST INFECTION (EOS)					
Number of Subjects Assessed	6	(100%)	10	(100%)	
Success (Cure + Improvement)	2	(33.3%)	7	(70%)	
PHLEGMON/ABSCESS (EOT)					
Number of Subjects Assessed	2	(100%)	1	(100%)	
Success (Cure + Improvement)	2	(100%)	0	(0%)	
PHLEGMON/ABSCESS (EOS)					
Number of Subjects Assessed	2	(100%)	1	(100%)	
Success (Cure + Improvement)	2	(100%)	0	(0%)	
SEPTIC ABORTION (EOT)					
Number of Subjects Assessed	5	(100%)	8	(100%)	
Success (Cure + Improvement)	5	(100%)	8	(100%)	
SEPTIC ABORTION (EOS)					
Number of Subjects Assessed	5	(100%)	8	(100%)	
Success (Cure + Improvement)	5	(100%)	8	(100%)	
"OTHER" INFECTION (EOT)					
Number of Subjects Assessed	7	(100%)	4	(100%)	
Success (Cure + Improvement)	6	(85.7)	2	(50%)	
"OTHER" INFECTION (EOS)					
Number of Subjects Assessed	7	(100%)	4	(100%)	
Success (Cure + Improvement)	6	(85.7)	2	(50%)	

*the numbers total to > the number of assessable subjects because some subjects had > 1 infection listed.

^a per MO calculation with continuity correction factor (CCF).

MO Comment: The number trovafoxacin-treated subjects in each of the last five categories listed above was too small (from 2 to 13) to draw statistically meaningful conclusions. Therefore, only general comments were made about these categories. The 33.3% cure rate in the post-hysterectomy infections (2/6 subjects) was numerically inferior in the trovafoxacin group compared to the 62.5% (5/8) in the control arm. The Trovan® arm appeared numerically equal to the comparator for septic

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abortion, and numerically superior for "parametritis" and "other" infections. No conclusions could be drawn for the category of phlegmon/abscess because of the small (3 subject) sample size.

In the control arm there are 14 more assessable subjects and each infection category had at least 8 subjects, except for abscess with 1 subject and "other" with 4 subjects. The "test of cure" visit was at the end of study (EOS), so this data was bolded by the MO.

The predominant infection in this study was postpartum endomyometritis, totaling 176/242 (72.7%) of the sponsor evaluable infections. Likewise, 15/23 patients diagnosed with parametritis and 3/11 patients with "other" infections had postpartum infections. Therefore 176+18= 194/242 (80.2%) of the evaluable patients had postpartum endomyometritis. Adding in the 8+5= 13 septic abortion subjects brings the total to 194+13= 207/242 (85.5%) of all the infections were directly related to pregnancy. Valid conclusions can be drawn only for pregnancy-related pelvic infections including endomyometritis, parametritis and septic abortion.

Table 144.6
Clinical Response at EOT and EOS by Type of Infection, as per the MO

MO Evaluable Population	Atatrofloxacin ⇒ Trovafoxacin (N=96)		Cefoxitin ⇒ Amox/Clavulanic (N=107)		FDA 95% CI
	Number and Percentage (%) of Subjects				
Overall TOTALS at EOS	101*	(100%)	113*	(100%)	
Success (Cure + Improvement)	90	(89.1%)	95	(84.1%)	
ENDOMYOMETRITIS (EOT)					(-4.1%, 19.0%)
Number of Subjects Assessed	62	(100%)	72	(100%)	
Success (Cure + Improvement)	58	(93.5%)	62	(86.1%)	
ENDOMYOMETRITIS (EOS)					(-3.7%, 17.3%)
Number of Subjects Assessed	73	(100%)	88	(100%)	
Success (Cure + Improvement)	68	(93.2%)	76	(86.4%)	
PARAMETRITIS (EOT)					
Number of Subjects Assessed	10	(100%)	7	(100%)	
Success (Cure + Improvement)	9	(90%)	6	(85.7%)	
PARAMETRITIS (EOS)					
Number of Subjects Assessed	11	(100%)	8	(100%)	
Success (Cure + Improvement)	10	(90.9%)	7	(87.5%)	
POST-HYST INFECTION (EOS)					
Number of Subjects Assessed	6	(100%)	8	(100%)	
Success (Cure + Improvement)	2	(33.3%)	5	(62.5%)	
PHLEGMON/ABSCCESS (EOS)					
Number of Subjects Assessed	0	(100%)	1	(100%)	
Success (Cure + Improvement)	0	(0%)	0	(0%)	
SEPTIC ABORTION (EOS)					
Number of Subjects Assessed	5	(100%)	6	(100%)	
Success (Cure + Improvement)	5	(100%)	6	(100%)	
"OTHER" INFECTION (EOS)					
Number of Subjects Assessed	6	(100%)	2	(100%)	
Success (Cure + Improvement)	5	(83.3%)	1	(50%)	

*the numbers total to > the number of assessable subjects because some subjects had > 1 infection listed.

MO Comment: The MO evaluable population had 28 fewer infections (242 - 214 = 28) than did the sponsor. Some subjects had > 1 infection listed, so the total number of infections was greater than the total number of assessable subjects. End of therapy (EOT) results were not provided by the sponsor for the last four categories of infection, because of the small number of infections and because the test of cure was at the EOS visit. The

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interpretation of the data and the comments are the same for this Table 144.6 as for the previous Table 144.5; see MO Comments following Table 144.5 above.

Sponsor-Defined Clinical Response Versus Investigator-Defined Clinical Response: from study report.

At Day 3, clinical responses differed between the investigator and the sponsor for four subjects in the alatrofloxacin/trovafoxacin group and no subjects in the cefoxitin/amoxicillin/clavulanic acid group. At the end of treatment, clinical responses differed between the investigator and the sponsor for six subjects in the Trovan® group and for 14 subjects in the control group. At the end of study, clinical responses differed between the investigator and the sponsor for nine subjects in the Trovan® group and 12 subjects in the control group. A summary table of the differences between the investigator-defined and sponsor-defined clinical response was presented for clinically evaluable subjects in table G on page 39 of the study report.

MO Comment: The summary table included a total of 19 Trovan® patients and 26 control patients. In all 45 cases the investigator assessment was a non-failure category (improvement, cure, or not assessed) and the sponsor assessment was failure. The reason for the sponsor assessment of failure was 5 cases of treatment for > 14 days, 1 case of failure at Day 3, and 39 cases of concomitant antibiotics due to inadequate response. The MO agreed with this data and agreed to accept the sponsor-defined clinical response.

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Clinically and Bacteriologically Evaluable Subjects

Sponsor-defined clinical response rates at Day 3, at the end of treatment, and at the end of study were analyzed for clinically and bacteriologically evaluable subjects. Sponsor-defined clinical success rates (cure + improvement) were comparable between the Trovan® and control treatment groups at Day 3 (92% and 87%, respectively), at the end of treatment (90% and 84%, respectively), and at the end of study (91% and 86%, respectively). See Table 5.1.3 below from the electronic submission list of tables.

Summary of Sponsor-Defined Clinical Response Rates Day 3, at the End of Treatment, and at the End of Study (Clinically and Bacteriologically Evaluable Subjects per Sponsor)					
Sponsor Evaluable Population	Alatrofloxacin ↓ Trovfloxacin (N=88)		Cefoxitin ↓ Amoxicillin/Clavulanic (N=93)		95% CI # p-value*
	Number and Percentage (%) of Subjects				
Day 3:					
Number of Subjects Assessed	84	(100%)	89	(100%)	(-4.1%, 14.4%)
Success (Cure + Improvement)	77	(92%)	77	(87%)	0.187 *
Distribution of Clinical Response:					
Cure	26	(31%)	23	(26%)	0.298 *
Improvement	51	(61%)	54	(61%)	
Failure	7	(8%)	12	(13%)	
End of Treatment:					
Number of Subjects Assessed	77	(100%)	83	(100%)	(-5.1, 15.6)
Success (Cure + Improvement)	69	(90%)	70	(84%)	0.239 *
Distribution of Clinical Response:					
Cure	61	(79%)	62	(75%)	0.410 *
Improvement	8	(10%)	8	(10%)	
Failure	8	(10%)	13	(16%)	
End of Study:^a					
Number of Subjects Assessed	88	(100%)	93	(100%)	(-4.4, 14.1)
Success (Cure + Improvement)	80	(91%)	80	(86%)	0.234 *
Distribution of Clinical Response:					
Cure	78	(89%)	78	(84%)	0.404 *
Improvement	2	(2%)	2	(2%)	
Failure	8	(9%)	13	(14%)	
95% CI # = Confidence interval based on normal approximation. p-value* = Cochran-Mantel-Haenszel Test includes adjusting for center effect. ^a Sponsor-defined subject clinical response at end of study is the primary endpoint. Ref.: Table 5.1.3					

MO Comment: The MO agreed with this analysis. For the sponsor's clinically and bacteriologically evaluable subjects, trovafloxacin was shown to be statistically-similar to the approved comparator regimen.

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Table 144.7
Clinical Response at EOS
Clinically and Bacteriologically Evaluable Subjects, as per the MO

	Alatrofloxacin ↓ Trova floxacin (N=78)	Cefoxitin ↓ Amoxicillin/Clavulanic (N=87)	95% CI #
Number and Percentage (%) of Subjects			
End of Study:^a			
Number of Subjects Assessed	78 (100%)	87 (100%)	
Success (Cure + Improvement)	70 (89.7%)	72 (82.8%)	(-4.6%, 18.6%)
Distribution of Clinical Response:			
Cure	70 (89.7%)	72 (82.8%)	
Failure	8 (10.3%)	15 (17.2%)	
95% CI # = per MO calculation with continuity correction factor (CCF).			
^a MO-defined subject clinical response at end of study was the primary endpoint.			
Ref.: Table RA:xx- version 05DEC97 from sponsor.			

MO Comment: When comparing the success (cure) rates at the primary endpoint (end of study), the 95% CI with CCF ($\delta = 15$) indicated that Trovan was statistically-similar to the approved comparator for the FDA clinically and bacteriologically evaluable population..

Clinical Response by Baseline Pathogen

Modified from page 41 of the study report: sponsor-defined clinical response rates by all baseline pathogens are presented for clinically evaluable subjects in the following table 144.8. Among clinically evaluable subjects, sponsor-defined clinical success rates were higher in subjects in the Trovan® group with baseline isolates of 26/26 *Enterococcus* sp. (100% cure) and 18/19 *Streptococcus agalactiae* (95% cure) compared to the respective cure rates of 81% and 67% in subjects with these two isolates in the control group at EOS.

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Sponsor defined clinical success rates were comparable between the two treatment groups for all other baseline isolates.

Table 144.8
Clinical Response by Baseline Pathogen at EOS
(Clinically Evaluable Population as per the Sponsor)

All Baseline Bacterial Isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N #	Success Rate		N #	Success Rate	
		n	n/N = %		n	Percent
<i>Acinetobacter calcoaceticus</i>	1	1	100	1	1	100
<i>Acinetobacter calcoaceticus v. Anitratus</i>	2	2	100	1	1	100
<i>Acinetobacter calcoaceticus v. Lwoffii</i>	1	1	100	0	0	--
<i>Actinomyces meyeri</i>	3	3	100	1	1	100
<i>Aerococcus viridans</i>	1	1	100	1	0	0
Alpha hemolytic streptococcus	2	2	100	6	4	67
Anaerobic gram positive coccus	1	1	100	0	0	--
Anaerobic gram positive rods	2	2	100	1	1	100
<i>Bacteroides distasonis</i>	1	1	100	1	1	100
<i>Bacteroides fragilis</i>	3	3	100	1	1	100
<i>Bacteroides gracilis</i>	0	0	--	1	1	100
<i>Bacteroides melaninogenicus</i>	2	2	100	0	0	--
<i>Bacteroides ovatus</i>	2	2	100	0	0	--
<i>Bacteroides spp.</i>	2	3	67	1	2	50
<i>Bacteroides thetaiotaomicron</i>	4	4	100	0	0	--
<i>Bacteroides uniformis</i>	2	1	50	0	0	--
<i>Bacteroides ureolyticus</i>	1	0	0	2	2	100
<i>Bacteroides vulgatus</i>	1	1	100	1	1	100
Beta hemolytic streptococcus	1	1	100	1	0	0
Beta hemolytic streptococcus group B	0	0	--	1	1	100
Beta streptococcus group A	0	0	--	1	1	100
Beta streptococcus group F	0	0	--	1	1	100
<i>Citrobacter diversus</i>	2	1	50	3	3	100
<i>Citrobacter freundii</i>	0	0	--	3	3	100
<i>Citrobacter koseri</i>	0	0	--	1	1	100
<i>Citrobacter spp.</i>	0	1	0	1	1	100
<i>Clostridium spp.</i>	1	1	100	0	0	--
Coagulase negative <i>Staphylococcus</i>	10	10	100	7	6	86
<i>Corynebacterium jeikeium</i>	1	1	100	2	1	50
<i>Corynebacterium spp.</i>	23	20	87	16	12	75
<i>Coryneform organism</i>	3	4	75	1	1	100
<i>Eikenella corrodens</i>	1	1	100	0	0	--
<i>Enterobacter aerogenes</i>	1	1	100	0	0	--
<i>Enterobacter cloacae</i>	2	2	100	2	0	0-
<i>Enterococcus faecalis</i>	29	28	97	32	29	91
<i>Enterococcus faecium</i>	1	0	0	0	0	--
<i>Enterococcus spp.</i>	26	26	100	27	22	81
<i>Escherichia coli</i>	12	10	83	16	16	100
<i>Eubacterium lentum</i>	0	0	--	1	1	100
<i>Ewingella spp.</i>	1	1	100	0	0	--
<i>Fusobacterium necrophorum</i>	3	3	100	0	0	--
<i>Fusobacterium nucleatum</i>	1	1	100	0	0	--
<i>Fusobacterium spp.</i>	4	3	75	0	0	--
<i>Gamma hemolytic streptococcus</i>	1	1	100	1	0	0
<i>Gardnerella vaginalis</i>	11	10	91	13	13	100
<i>Gemella spp.</i>	2	2	100	1	1	100
Gram negative anaerobic rods	3	3	100	2	2	100

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All Baseline Bacterial Isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N #	Success Rate		N #	Success Rate	
		n	n/N = %		n	Percent
Gram negative bacilli	1	1	100	1	1	100
Gram negative coccobacilli	1	1	100	0	0	--
Gram negative rods	3	3	100	2	0	0
Gram positive bacilli	0	0	--	1	1	100
Gram positive cocci	1	1	100	2	1	50
Gram positive rods	1	1	100	1	0	0
Group G beta streptococcus	0	0	--	1	0	0
Haemophilus parainfluenzae	0	0	--	1	0	0
Klebsiella pneumoniae	4	3	75	5	5	100
Lactobacillus acidophilus	1	1	100	0	0	--
Lactobacillus spp.	11	8	73	15	14	93
Micrococcus spp.	1	0	00	0	0	--
Mobiluneus spp.	2	2	100	0	0	--
Moraxella lacunata	0	0	--	1	1	100
Morganella morganii	1	1	100	0	0	---
Peptostreptococcus magnus	4	3	75	4	4	100
Peptostreptococcus prevotii	3	3	100	2	2	100
Peptostreptococcus spp.	16	14	88	19	18	95
Prevotella intermedia	3	3	100	0	0	--
Prevotella spp.	18	17	94	15	14	93
Propionibacterium acnes	2	1	50	0	0	---
Proteus mirabilis	3	2	67	7	6	86
Pseudomonas aeruginosa	0	0	--	3	3	100
Pseudomonas spp.	1	1	100	0	0	--
Staphylococcus aureus	5	4	80	13	10	77
Staphylococcus epidermidis	16	14	88	12	10	83
Staphylococcus haemolyticus	4	2	50	2	1	50
Staphylococcus hominis	2	2	100	4	4	100
Staphylococcus spp.	3	2	67	9	7	78
Streptococcus acidominus	1	1	100	0	0	--
Streptococcus agalactiae	19	18	95	12	8	67
Streptococcus anginosus	12	12	100	6	6	100
Streptococcus bovis	1	1	100	0	0	--
Streptococcus group D (non-enterococcus)	3	3	100	2	2	100
Streptococcus intermedius	1	1	100	2	2	100
Streptococcus milleri	1	1	100	0	0	--
Streptococcus mitis	1	1	100	3	2	67
Streptococcus pyogenes	1	0	0	1	1	100
Streptococcus salivarius	0	0	--	1	1	100
Streptococcus sanguis i	1	1	100	0	0	---
Streptococcus sanguis ii	4	4	100	3	3	100
Streptococcus spp.	13	13	100	13	12	92
Streptococcus viridans	5	5	100	2	2	100
Veillonella spp.	0	0	--	4	4	100

MO Comment: the long list above includes all the baseline bacteria from the study.

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Table 144.9
Clinical Response by Baseline Pathogen at EOS
(Clinically Evaluable Population as per the MO)

Baseline Bacteria isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N #	Success Rate		N #	Success Rate	
		n	n/N = %		n	n/N = %
<i>Acinetobacter calcoaceticus</i>	1	1	100	1	1	100
<i>Acinetobacter calcoaceticus v. Anitratus</i>	2	2	100	2	1	50
<i>Acinetobacter calcoaceticus v. Lwoffii</i>	1	1	100	0	0	--
<i>Actinomyces meyeri</i>	2	2	100	1	1	100
<i>Aerococcus viridans</i>	0	0	--	1	0	00
<i>Bacteroides distasonis</i>	0	0	--	1	1	100
<i>Bacteroides fragilis</i>	3	3	100	1	1	100
<i>Bacteroides gracilis</i>	0	0	--	1	1	100
<i>Bacteroides melaninogenicus</i>	2	2	100	0	0	--
<i>Bacteroides ovatus</i>	2	2	100	0	0	--
<i>Bacteroides thetaiotaomicron</i>	3	3	100	0	0	--
<i>Bacteroides uniformis</i>	2	1	50	0	0	--
<i>Bacteroides ureolyticus</i>	1	0	0	2	2	100
<i>Bacteroides vulgatus</i>	0	0	--	1	1	100
<i>Citrobacter diversus</i>	2	1	50	4	4	100
<i>Citrobacter freundii</i>	0	0	--	2	2	100
<i>Citrobacter koseri</i>	0	0	--	2	2	100
Coagulase negative <i>Staphylococcus</i>	9	9	100	6	5	83
<i>Corynebacterium jeikeium</i>	1	1	100	2	1	50
<i>Corynebacterium</i> spp.	20	17	85	15	9	60
<i>Eikenella corrodens</i>	1	1	100	0	0	--
<i>Enterobacter aerogenes</i>	1	1	100	0	0	--
<i>Enterobacter cloacae</i>	1	1	100	3	0	0
<i>Enterococcus faecalis</i>	26	25	96	30	26	87
<i>Enterococcus faecium</i>	1	0	0	0	0	--
<i>Escherichia coli</i>	12	10	83	15	14	93
<i>Eubacterium lentum</i>	0	0	--	1	1	100
<i>Fusobacterium necrophorum</i>	3	3	100	0	0	--
<i>Fusobacterium nucleatum</i>	1	1	100	0	0	--
<i>Gardnerella vaginalis</i>	9	8	89	10	10	100
<i>Haemophilus parainfluenzae</i>	0	0	--	1	0	0
<i>Klebsiella pneumoniae</i>	3	2	67	4	4	100
<i>Moraxella lacunata</i>	0	0	--	1	1	100
<i>Morganella morganii</i>	1	1	100	0	0	--
<i>Peptostreptococcus magnus</i>	4	3	75	3	3	100
<i>Peptostreptococcus prevotii</i>	3	3	100	2	2	100
* <i>Peptostreptococcus</i> spp.*	14	12	86	17	16	94
<i>Porphyromonas gingivalis</i>	0	0	--	1	1	100
<i>Prevotella intermedia</i>	3	3	100	0	0	--
* <i>Prevotella</i> spp.*	17	16	94	16	15	94
<i>Propionibacterium acnes</i>	2	1	50	0	0	--
<i>Proteus marabilis</i>	3	2	67	8	7	88
<i>Pseudomonas aeruginosa</i>	0	0	--	3	3	100
<i>Staphylococcus aureus</i>	4	3	75	12	9	75
<i>Staphylococcus epidermidis</i>	14	12	86	8	6	75

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Baseline Bacteria isolates	Alatro → Trova			Cefoxitin → Augmentin		
	N #	Success Rate		N #	Success Rate	
		n	n/N = %		n	n/N = %
<i>Staphylococcus haemolyticus</i>	4	2	50	2	1	50
<i>Staphylococcus hominis</i>	2	2	100	3	3	100
* <i>Staphylococcus spp.</i> *	3	2	67	8	4	50
<i>Streptococcus agalactiae</i>	14	13	93	13	9	69
<i>Streptococcus anginosus</i>	11	11	100	5	5	100
<i>Streptococcus bovis</i>	1	1	100	0	0	--
<i>Streptococcus group D (non-enterococcus)</i>	3	3	100	1	1	100
<i>Streptococcus intermedius</i>	1	1	100	2	2	100
<i>Streptococcus milleri</i>	1	1	100	0	0	--
<i>Streptococcus mitis</i>	1	1	100	3	2	67
<i>Streptococcus pyogenes</i>	1	0	0	1	1	100
<i>Streptococcus sanguis i</i>	1	1	100	0	0	--
<i>Streptococcus sanguis ii</i>	4	4	100	2	2	100
* <i>Streptococcus spp.</i> *	11	11	100	13	12	92
<i>Streptococcus viridans</i>	4	4	100	0	0	--

MO Comment: Table 144.9 includes all speciated bacteria and selected genera (e.g., *Staphylococcus spp.*) grown from the MO's clinically and bacteriologically evaluable subjects and analyzed at the primary endpoint (EOS). Similar results were noted at Day 3 and EOT, and among clinically intent-to-treat subjects, so those results were not listed in this table or elsewhere in this MO review.

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MO Comment: Based on the number of isolates, the clinical response at the end of study (EOS) as per the MO, and comparisons between the two arms of the study, the MO concluded that the following pathogens could be included in the Indications and Usage label:

1. *Enterococcus faecalis*- 25/26 (96%) success (cure) rate compared to 26/30 (87%) in the control arm.
2. *Escherichia coli*- 11/12 (92%) success rate compared to 14/15 (93%) in the control arm.
3. *Streptococcus agalactiae*- 13/14 (93%) success rate compared to 9/13 (69%) in the control arm.
4. *Streptococcus anginosus*- 11/11(100%) success rate compared to 5/5 (100%) in the control arm.

There were 3 other isolates that required further consideration:

1. *Gardnerella vaginalis*- This organism is commonly found in acute pelvic infections and considered by most experts to be a potential pathogen, although it is often found in the "normal" flora of the vagina. In the MO evaluable population, the cure rate in the trovafloxacin group was 8/9 (89%), compared to 10/10 in the control arm. Because there were only 9 isolates in the study group, this does not strictly meet the 1992 PTC document which stated that to include an organism in an indication, only those organisms which are generally considered pathogenic and represent at least 10% of the evaluable cases OR 10 total (whichever is higher) AND the organism's eradication rate must be clinically acceptable. The MO elected to include *Gardnerella vaginalis* because it is generally considered pathogenic or associated with pelvic infections, had a 89% eradication rate, and needed only one more isolate to meet both the 10% and 10 total isolate PTC guidance for being listed in the label.

2. *Prevotella* species- These anaerobes (former *Bacteroides* spp.) are also commonly found in the "normal" vaginal flora; they are definitely considered pathogenic and are commonly isolated from polymicrobial acute pelvic infections. In the MO evaluable population, there were 3 *Prevotella intermedia* and 17 *Prevotella* spp. isolates with a 19/20 (95%) cure rate. From the complicated intra-abdominal study 154-124, there were 16 *Prevotella* spp. isolates with a 12/16 (75%) cure rate. This combined data, plus the widely-accepted pathogenicity of *Prevotella* spp., warranted the inclusion of *Prevotella* spp. in the approved label.

3. *Peptostreptococcus* species- These organisms are considered pathogenic and are commonly isolated from mixed (polymicrobial) acute pelvic infections with anaerobic and aerobic bacteria. In the MO evaluable patients, there were 3 *Peptostreptococcus prevotii*, 4 *Peptostreptococcus magnus*, and 14 *Peptostreptococcus* spp. isolates with a 18/21 (86%) cure rate. From the complicated intra-abdominal study 154-124, there were 14 *Peptostreptococcus* spp. isolates with a 11/14 (79%) cure rate. This combined data, plus the widely-accepted pathogenicity of *Peptostreptococcus* spp., warranted the inclusion of *Peptostreptococcus* spp. in the approved label.

4. In addition to the above, the sponsor requested approval for the following: *Bacteroides fragilis*, *Streptococcus viridans*, *Bacteroides thetaiotaomicron*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterobacter* species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species, *Bacteroides* species. These organisms or species were not considered approvable because of the low number of isolates or because they were not speciated.

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Safety Results: copied from page 11 of the study report.

Number of Subjects with Adverse Events. The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events and clinically significant laboratory values are presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Alatrofloxacin ↓ Trova floxacin		Cefoxitin ↓ Amoxicillin/Clavulanic Acid	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	83/160	(52%)	56/157	(36%)
Treatment-Related Adverse Events	38/160	(24%)	10/157	(6%)
Discontinuations From Treatment Due to Adverse Events ^a	30/160	(19%)	9/157	(6%)
Clinically Significant Laboratory Values	103/146	(71%)	99/152	(65%)

^a Twenty-one (21) and one discontinuation(s) in the alatrofloxacin/trovafloxacin and cefoxitin/amoxicillin/clavulanic acid treatment groups, respectively, were treatment-related.

Ref.: Tables 1.2, 4.1, 4.2, 6.1, 6.3, 7.1, and Appendix I, Table 3.1

MO Comment: an additional reference is Appendix V, Table 10, "Listing of All Adverse Events" from the study report. There were 21 Trovan® subjects who were "prematurely" discontinued from the study due to an AE felt to be related to the drug (see Table C. Summary of Premature Discontinuations From Treatment on page 28 of this review). In contrast, only one control arm subject was listed in this category. Approximately half of the 21 Trovan® subjects had >1 AE, e.g., rash, pruritus, and dizziness; 7/21 (33%) had 3 or more AEs listed. Four of the reactions were considered by the investigator to be severe (2 allergic reactions, 1 IV site reaction, and 1 pseudo-membranous colitis), while all the remaining ones were either mild or moderate. A large majority of subjects (17/21= 81%) received only one day of IV alatrofloxacin; 2 received two days, and 2 received three days. None of the 21 discontinued subjects received po trovafloxacin.

Adverse Events in 21 Trovan® Subjects Prematurely Discontinued from Study*			
Adverse Event (AE)	17 Subjects with 1 Day IV Rx	2 Subjects with 2 Days IV Rx	2 Subjects with 3 Days IV Rx
Allergic reaction: severe	2		
Allergic reaction: mild/moderate	2		
Pruritus	5		
Rash	5		
Dizziness	6		
Nausea and/or vomiting	3		
CV: palpitations, flushing	5		
Neuro: headache, numbness	3		
IV site reaction	3	1	1
Leg symptoms	2		
Diarrhea	1		
Pseudo-membranous colitis		1	
Peri-orbital edema			1

*MO table created from data found in 83 page Table 10 in Appendix V.

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MO Comment: The above MO table lists the general types of reactions experienced by these 21 subjects. The total number of AEs is > 21 because of the fact that half the subjects had > 1 AE. As mentioned, all 21 subjects received only IV alatrofloxacin. The large majority of the AEs were judged to be mild by the site investigator, and the large majority were cleared in 24 to 48 hours. Thus, although there was a 21 Trovan® subjects "prematurely" (before 4 days of therapy) discontinued from the study, the MO did not ascertain any area or AE of particular concern.

A summary of the most commonly reported treatment-related adverse events is presented by body system in the following table copied from page 58 of study report.

Table D. Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafoxacin (N=160)		Cefoxitin ↓ Amoxicillin/Clavulanic Acid (N=157)	
Number and Percentage (%) of Subjects				
Number of Subjects With at Least One Adverse Event	38	(24%)	10	(6%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	6	(4%)	0	
Appl./Inj./Incision/Insertion Site Reaction	5	(3%)	0	
AUTONOMIC NERVOUS SYSTEM	5	(3%)	0	
Flushing	5	(3%)	0	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	14	(9%)	1	(<1%)
Dizziness	9	(6%)	1	(<1%)
Headache	4	(3%)	0	
GASTROINTESTINAL	11	(7%)	6	(4%)
Diarrhea	1	(<1%)	5	(3%)
Nausea	9	(6%)	2	(1%)
Vomiting	6	(4%)	1	(<1%)
SKIN/APPENDAGES	14	(9%)	3	(2%)
Pruritus	8	(5%)	2	(1%)
Rash	5	(3%)	2	(1%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site				
a ≥3 % of subjects in any treatment group.				
b Includes data up to 7 days after last dose of active study medication.				
Ref.: Tables 6.3 and 6.5				

MO Comment: The most commonly (>5%) reported treatment-related AEs in the trovafloxacin group were nausea and dizziness, and in the control group was diarrhea. The data from the sponsor's overall summary of safety report showed that females aged 16-44 had the highest incidence of nausea (189/1845=10%) and dizziness (304/1845=16%) compared to other age groups and to all male groups. The acute pelvic infection study showed a much lower incidence here (6% and 6%, respectively) for both these AEs, and there was no obvious explanation from the sponsor or the MO for this finding.

Serious Adverse Events/Deaths. No subjects in either treatment group died during this study. Fifteen (15) subjects in the alatrofloxacin/trovafoxacin group and 10 subjects in the cefoxitin/amoxicillin/clavulanic acid group had serious adverse events. Two subjects in the

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alatrofloxacin/trovafloxacin group had serious adverse events (acute anaphylactoid reaction and allergic reaction) that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, "other" reasons, or concomitant treatment.

No subjects in either treatment group were discontinued from treatment due to laboratory abnormalities. For liver function parameters, the percentage of subjects with clinically significant abnormalities in aspartate aminotransferase (SGOT) was 2 subjects (1%) in the trovan group and 7 subjects (5%) in the control arm group. The number of subjects with clinically significant alanine aminotransferase (SGPT) values was 4 subjects (3%) in the trovan group and 6 subjects (4%) in the control group. One subject (<1%) in the control group had clinically significant total bilirubin values.

No subjects in either treatment group had clinically significant creatinine values; and 15 subjects (10%) in the trovan group and 14 subjects (9%) in the control group had clinically significant decreases in hemoglobin values.

MO Comment: The MO agreed with the above statements and did not find any areas of concern in terms of the safety or adverse events with trovafloxacin. The issues of dizziness, lightheadedness, and abnormal hepatic function are discussed in a separate MOR.

Concentration of Trovafloxacin in Breast Milk. Trovafloxacin was found in measurable concentrations up to 2.1 µg/mL in a subset population of lactating subjects. 113 breast milk samples were obtained from 14 subjects randomized to the trovan group; of these, a total of 18 samples were analyzed from 3 subjects, and the average (range) measurable concentration was 0.8 µg/mL (

MO Comment: This data clearly shows that trovafloxacin is present in the breast milk of lactating women. Because the potential for serious adverse reactions has not been studied in nursing newborns and infants from mothers taking trovafloxacin, the sponsor and MO recommended that nursing women should either discontinue nursing or discontinue taking the antibiotic.

Resistance: modified from the study report and Table 5.6.

Two (2) superinfecting pathogens (one isolate each of *S. viridans* and *Corynebacterium* sp. from abscess fluid) were isolated from one subject (<1%) in the alatrofloxacin/trovafloxacin group and seven superinfecting pathogens (one isolate of *E. cloacae* from the endometrial cavity; one isolate each of *Enterococcus* sp. and *Lactobacillus* sp. from the supravaginal space; one isolate of *E. faecalis* from supra-vaginal swabs; one isolate each of *Corynebacterium* sp., coagulase-negative *Staphylococcus*, and Gram-negative *bacilli* from surgical wound discharge; and one isolate of *Enterococcus* sp. from vaginal washout) were isolated from four subjects (3%) in the cefoxitin/amoxicillin/clavulanic acid group.

Colonizing organisms were isolated from three subjects (2%) in each treatment group.

There was no evidence for resistance.

MO Comment: The MO reviewed the study report and Table 5.6 and agreed with the sponsor.

SUMMARY and CONCLUSIONS of SPONSOR: modified from page 63-4 of the study report.

One hundred sixty-one (161) subjects were randomized to treatment with alatrofloxacin/trovafloxacin (Trovan®) and 159 subjects were randomized to treatment with cefoxitin/amoxicillin/clavulanic acid (the "control group"). Of the randomized subjects, 160 subjects in the Trovan® group and 157 subjects

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in the control group received treatment; one and two enrolled subjects in the Trovan® and control groups, respectively, were randomized but did not receive active treatment. One hundred seven (107) subjects in the Trovan® group and 119 subjects in the control group were clinically evaluable; 88 subjects in the Trovan® group and 93 subjects in the control group were bacteriologically evaluable. All treated subjects were included in analysis of adverse events.

The two treatment groups were generally comparable with respect to characteristics at baseline, including diseases/syndromes at study entry and use of prior and concomitant medications.

Trovan® was statistically equivalent to the control antibiotics for sponsor-defined clinical success (cure + improvement) rates in clinically evaluable and intent-to-treat subjects with acute pelvic infections at the end of study. Sponsor-defined clinical success rates were comparable between the two treatment groups at Day 3 and at the end of treatment for both clinically evaluable and intent-to-treat subjects.

Success rates among clinically evaluable subjects in the Trovan® and control groups were 91% and 86%, respectively, at Day 3, 89% and 84%, respectively, at the end of treatment, and 90% and 86%, respectively, at the end of study. These findings were supported by marked decreases from baseline to Day 3, to the end of treatment, and to the end of study in the presence of clinical signs and symptoms of acute pelvic infections in both treatment groups.

Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates for *Enterococcus* spp. were higher in the Trovan® group compared to the control group at Day 3 (100% and 81%, respectively), at the end of treatment (100% and 80%, respectively), and at the end of study (100% and 81%, respectively). Sponsor-defined eradication rates for baseline pathogens of *Enterococcus faecalis*, *Peptostreptococcus* spp., *Prevotella* spp., and *Corynebacterium* spp. were comparable between the two treatment groups at all three evaluation timepoints. Similar results were observed among bacteriological intent-to-treat subjects.

Thirty subjects, (30/160, 19%) in the Trovan® group and nine subjects (9/157, 6%) in the control group were discontinued from treatment due to adverse events. Twenty-one (21) subjects in the Trovan® group and one subject in the control group were discontinued due to adverse events that were considered by the investigator to be study drug-related.

Ten (10) Trovan® subjects were discontinued due to rash and/or pruritus and eight subjects were discontinued due to headache, dizziness and/or hypoesthesia that were considered by the investigator to be treatment related. One subject in the control group was discontinued due to dizziness, nausea and vomiting that were considered by the investigator to be treatment related.

Thirty-eight (38) subjects (24%) in the Trovan® group and ten subjects (6%) in the control group reported treatment-related adverse events. The most commonly reported treatment-related adverse events were dizziness and nausea for subjects in the Trovan® group and diarrhea for subjects in the control group. Treatment-related injection site reactions were reported by 4% of subjects in the Trovan® group.

No subjects in either treatment group died during this study.

Fifteen (15) subjects in the Trovan® group and 10 in the control group had serious adverse events. With the exception of two subjects in the Trovan® group who had serious adverse events (acute anaphylactoid reaction and allergic reaction) that were considered by the investigator to be treatment related, all serious adverse events that occurred during this study were considered to be unrelated to study drug.

No subjects in either treatment group were discontinued from treatment due to laboratory abnormalities.

Clinically significant post-baseline laboratory abnormalities were observed for 71% (103/146) of subjects in the Trovan® group and 65% (99/152) of subjects in the control group. These abnormalities were observed at comparable incidence rates in both treatment groups.

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MO Comment: The MO agreed with the sponsor's overall summary and conclusions. The biggest difference in the overall analysis was the fact that the MO had fewer clinically and bacteriologically evaluable patients in each arm; see Table 144.12 below.

Table 144.12
Population Data, as per the Sponsor and the MO

POPULATION	SPONSOR DATA		MO DATA	
	Trovan® Arm	Control Arm	Trovan® Arm	Control Arm
Randomized Subjects	161	159	161	159
Treated Subjects	160	157	160	157
Clinically Evaluable	107	119	96	107
Bacteriologically Evaluable	88	93	78	87
Clinical Success at EOS	96/107 (90%)	102/119 (86%)	85/96 (88.5%)	89/107 (83%)

MO Comments continued: Of clinically evaluable subjects, the MO had 11 fewer in the Trovan® and 12 fewer in the control arm primarily because 17 subjects receiving 11 to 14 days therapy were changed to non-evaluable by the MO. The MO also changed the evaluability status of 13 additional subjects as listed in Tables 144.2 and 144.3. The decrease in clinically evaluable subjects automatically decreased the number of bacteriologically evaluable subjects, because this was a subset within the clinically evaluable group. The primary efficacy endpoint was, however, clinical success at EOS, and both the sponsor and the MO showed that Trovan® was statistically comparable to the approved comparator drug regimen.

Final MO Discussion and Recommendations:

Discussion: The severity of illness of the large majority of study patients was judged by the MO to be mild to moderate based on the parameters of temperature elevations, mild severity of signs and symptoms, rapid clearing of such, WBCs and differential counts, early switches to po therapy, and early hospital discharges (120/160=75% of Trovan subjects went home by day #3; 109/160=68% of control subjects went home by day #3). It was of note that the IDSA guidelines talk about a minimum of 4 days of parenteral therapy, when 71.5% of the ITT subjects in this study were home by day 3.

84.7% of all the infections were directly related to pregnancy. Valid conclusions from this study can be drawn only for pregnancy-related pelvic infections including endomyometritis, parametritis and septic abortion.

Following the IDSA/FDA guidelines, the 154-144 study data by itself showed that trovafloxacin was effective in the treatment of pregnancy-related infections and should be approved for the following pathogens:

Enterococcus faecalis
Escherichia coli
Gardnerella vaginalis
Streptococcus agalactiae
Streptococcus anginosus

APPROVED FOR
0-01-0001

The initial MO recommendation for the approved label, based solely on data from study 154-144, the MO's analysis, and IDSA/FDA guidelines, was the following:

Gynecologic and pelvic infections (mild to moderate), including endomyometritis, parametritis, septic abortion, and post-partum infections caused by *Enterococcus faecalis*, *Escherichia coli*, *Gardnerella vaginalis*, *Streptococcus agalactiae* and *Streptococcus anginosus*.

Because the subjects in study 154-124 (complicated intra-abdominal infections) were generally more severely ill, had mixed anaerobic and aerobic infections with identical pathogens, and also responded to comparable trovafloxacin dosing, the two reviewing MOs determined that the bacteriological data and clinical conclusions could be combined and extrapolated from the intra-abdominal study to this pelvic infection study. The accepted pathogenicity of *Prevotella* and *Peptostreptococcus* species and the 154-144 data by itself supported the clinical and bacteriological efficacy for approval of these two species. The additional 154-124 baseline pathogen data for *Prevotella* spp. (12/16 = 75% cure) and *Peptostreptococcus* spp. (11/14 = 79% cure) provided further support for the inclusion of these two species in the label. See Table 144.13 below for individual study and combined data.

Data from study 154-124 also supported the additional approval of *Bacteroides fragilis* and viridans group streptococci. Both are pathogens associated with acute pelvic infections, and the combined data from the two studies showed an overall cure rate of 92% (22/24) for viridans group streptococci and 85% (29/34) for *Bacteroides fragilis*. Because *Streptococcus anginosus* is a member of the viridans group, it need not be listed separately in the final label. See Table 144.13 below for the combined pathogen data.

Table 144.13
Summary of Clinical Success Rates at EOS
For the Most Frequently Isolated Baseline Pathogens (Clinically Evaluable Subjects)

PATHOGEN	Trovan® Arm GYN Study		Control Arm GYN Study		Trovan® Arm CIAI Study		COMBINED Trovan® Data	
	n/N	%	n/N	%	n/N	%	n/N	%
Gram Positive Aerobes								
Alpha-haemolytic streptococci	N.A.				8/12	67%	8/12	67%
✓ Beta-hemolytic streptococci, Gp. B (= <i>S. agalactiae</i>)	13/14	93%	9/13	69%	0/1	0%	13/15	87%
✓ Viridans group streptococci	4/4	100%	0	--	18/20	90%		
✓ <i>S. anginosus</i>	11/11	100%	5/5	100%	6/10	60%	17/21	81%
✓ <i>Streptococcus</i> sp.	11/11	100%	12/13	92%	26/30	87%	23/24	96%
<i>E. faecium</i>	0/1	0%	0	--	3/4	75%	3/5	60%
✓ <i>E. faecalis</i>	25/26	96%	26/30	87%	6/13	46%	31/39	79%
✓ <i>Enterococcus</i> sp. (sponsor population)	26/26	100%	22/27	81%	7/10	70%	33/36	92%
✓ <i>S. aureus</i>	3/4	75%	9/12	75%	8/11	73%	11/15	73%
Gram Negative Aerobes								
✓ <i>E. coli</i>	10/12	83%	14/15	93%	66/77	86%	76/89	85%
<i>E. aerogenes</i>	1/1	100%	0	--	3/3	100%	4/4	100%
<i>E. cloacae</i>	1/1	100%	0/3	0%	5/7	71%	6/8	75%
✓ <i>Enterobacter</i> sp.	0	--	0	--	2/3	67%	2/3	67%
✓ <i>K. pneumoniae</i>	2/3	67%	4/4	100%	10/15	67%	12/18	67%
✓ <i>P. aeruginosa</i>	0/0	--	3/3	100%	14/16	88%	14/16	67%
<i>Gardnerella vaginalis</i>	8/9	89%	10/10	100%	N.A.		8/9	89%
Gram Positive Anaerobes								
✓ <i>Peptostreptococcus</i> sp.	12/14	86%	16/17	94%	11/14	79%		
<i>Clostridium</i> sp.	1/1	100%	0	--	4/5	80%	5/6	83%
✓ <i>Corynebacterium</i> sp.	17/20	85%	9/15	60%	3/3	100%	20/23	87%
Gram Negative Anaerobes								
<i>Prevotella buccae</i>	0	--	0	--	1/2	50%		
<i>Prevotella intermedia</i>	3/3	100%	0	--	1/1	100%		
✓ <i>Prevotella</i> sp.	16/17	94%	15/16	94%	10/13	77%		
✓ <i>B. fragilis</i>	3/3	100%	1/1	100%	26/31	84%		
✓ <i>B. thetaiotaomicron</i>	3/3	100%	0	--	11/18	61%	14/21	67%
<i>B. uniformis</i>	1/2	50%	0	--	5/7	71%	6/9	67%
<i>B. vulgatus</i>	0	--	1/1	100%	5/7	71%	5/7	71%
✓ <i>Bacteroides</i> sp.	2/3	67%	1/2	50%	7/9	78%	9/12	75%
<i>Fusobacterium necrophorum</i>	3/3	100%	0	--	3/3	100%	6/6	100%
<i>Fusobacterium nucleatum</i>	1/1	100%	0	--	1/2	50%	2/3	67%
✓ <i>Fusobacterium</i> sp. (sponsor population)	3/4	75%	0	--	6/7	86%	9/11	82%

✓ = "pathogen" requested in labeling

*Combined data sufficient to add pathogen to approved GYN list of pathogens in the final label.

APPROVED FOR LABELING
 07/04/2004

During labeling negotiations with the applicant, further discussions centered on the MO's initial recommendation that the label included the qualifying words (mild to moderate) concerning the pelvic infections. Although it was true that the majority of subjects in the 154-144 study had mild to moderate pelvic infections, the severity of infection in the 154-124 CIAI study was very different. The subjects were more seriously ill with more complicated infections, had longer IV therapy, longer hospital stays, and more deaths (11 of 201 treated in the Trovan® arm in CIAI, compared to 0 of 160 treated in the Trovan® arm of the pelvic study). Hence, there was a much sicker baseline population in the complicated intra-abdominal study. As noted above, the infections in both studies were often mixed polymicrobial and involved many of the same pathogens, except *Gardnerella vaginalis*. Extrapolation of the overall CIAI clinical and bacteriological data strongly supported omitting any qualifying words from the final approved label, and the MO agreed with this after discussions with the sponsor.

FINAL MO RECOMMENDED INDICATION AND USAGE Label for Study 154-144:

TROVAN® is indicated for the treatment of Gynecological and pelvic infections, including endomyometritis, parametritis, septic abortion and postpartum infections caused by: *Escherichia coli*, *Bacteroides fragilis*, viridans group streptococci, *Enterococcus faecalis*, *Streptococcus agalactiae*, *Peptostreptococcus* species, *Prevotella* species, or *Gardnerella vaginalis*.

MO Discussion on Dosage and Administration:

The requested dosage and administration was 300 mg IV followed by 200 mg oral when the patient can tolerate po meds. The total duration of treatment requested was 7-14 days. As explained in this MOR, patients with 11-14 days of therapy were rendered non-evaluable by the MO. Six patients (6/107 = 5.6%) in the sponsor evaluable Trovan® arm received 11-14 days of therapy with a 6/6 (100%) cure rate. These 6 subjects tolerated the longer duration of therapy, did not have any significant AEs, and achieved an excellent (100%) cure rate. For this reason, the MO concluded that the safety and efficacy of Trovan® was adequately demonstrated for a total duration of treatment of 7-14 days.

FINAL MO RECOMMENDED DOSAGE AND ADMINISTRATION for Study 154-144:

The recommended dosage for Trovan® Tablets or Trovan® IV for the treatment of infections is 300 mg IV followed by 200 mg oral when the patient can tolerate po meds. Doses of Trovan® are administered once daily. Patients whose therapy is started with Trovan® IV may be switched to Trovan® Tablets when clinically indicated at the discretion of the physician. The total duration of treatment is 7-14 days.

/s/
Daniel Davis, MD, MPH
Medical Officer, HFD-590

cc:

Orig. NDA #20-759
Orig. NDA #20-760
HFD-590 Division Files
HFD-590/Dep. Dir./RALbrecht
HFD-590/MO/RAlivisatos
HFD-590/Pharm/AEllis
HFD-590/Biopharm/PColangelo
HFD-590/Biostat/Silliman
HFD-590/CSO/RAnderson
HFD-590/LEISSA

/s/
Concurrence: HFD-590/Div. Dir./MGoldberger
HFD-590/MTL/BLeissa */s/*

OCT 20 1998

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATIONS
NDA's 20-759 and 20-760

Applicant Name and Address: Pfizer Central Research, Medical Research Laboratory
Eastern Point Road
Groton, Connecticut 06340

Date of Submission: 27 December 1996

CDER Stamp Date: 30 December 1996

Date Submissions Received by Reviewer: 4 June 1997

Date Review Begun: 1 July 1997

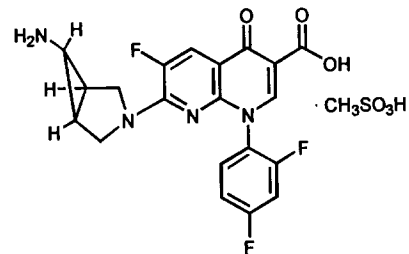
Date Review Completed: 11 December 1997

Generic Name: Trovafloxacin mesylate (tablets)
Alatrovafloxacin mesylate (solution for injection)

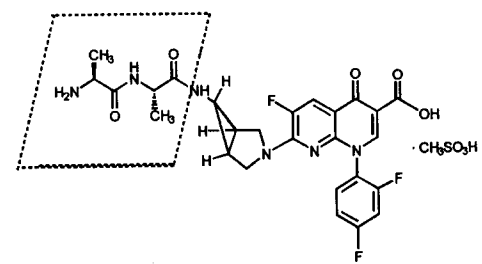
Proposed Trade Name: Trovan

Chemical Name: Tablet: 100 mg, 200 mg
(1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate.

Chemical Structure:



Solution: 5 mg/ml
(1 α , 5 α , 6 α)-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate.



Molecular Formula: C₂₀H₁₅F₃N₄O₃ • CH₃SO₃H

Molecular Weight: 512.46

Pharmacologic Category: Fluoronaphthyridone

Dosage Forms: Tablets (NDA 20-759)
Solution (NDA 20-760)

Routes of Administration: Oral (NDA 20-759)
Parenteral (NDA 20-760)

Molecular Formula: C₂₆H₂₅F₃N₆O₅ • CH₃SO₃H

Molecular Weight: 654.62

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A. General Information

1. Proposed Indication

(Verbatim from proposed labeling by applicant)

The following is the proposed indication, with regards to skin and skin structure infections, as it appears in the proposed label:

"SKIN AND SKIN STRUCTURE INFECTIONS (uncomplicated and complicated, including diabetic foot infections) caused by *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, *Proteus mirabilis*, *Corynebacterium* species, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Streptococcus equisimilis*, *Enterobacter cloacae*, *Staphylococcus simulans*, *Staphylococcus hominis*, or *Peptostreptococcus* species."

2. Proposed Dosage and Administration

(Verbatim from proposed labeling by applicant)

Skin and Skin Structure Infections, Complicated, including diabetic foot infections
200 mg oral or 200 mg I.V. followed by 200 mg oral for 10-14 days duration

Skin and Skin Structure Infections, Uncomplicated
100 mg oral for 7-10 days duration

3. Approved agents

The following agents have been approved for treatment of skin and skin structure infections:

Skin and Skin Structures

Amoxicillin/clavulanate potassium (Augmentin™)

caused by beta-lactamase-producing strains of *S. aureus*, *E. coli*, and *Klebsiella* spp.

Cefamandole: *S. aureus* (penicillinase- and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, *E. coli*, *Enterobacter* sp, and *P. mirabilis*.

Ceftazidime: *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Cefuroxime:

Zinacef™ *S. aureus* (penicillinase- and non-penicillinase-producing strains), *S. pyogenes*, *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

Kefurox™ *S. aureus* (penicillinase- and non-penicillinase-producing strains), *S. pyogenes*, *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

Cephalexin:

Keflex™ *Staphylococci* and/or *streptococci*.

Keftab™ *S. aureus* and/or beta-hemolytic *streptococci*.

Cefpodoxime: *S. aureus* (including penicillinase-producing strains) or *S. pyogenes*.

Imipenem

Intramuscular preparation: including abscesses, cellulitis, infected skin ulcers and wound infections caused by *Staphylococcus aureus* including penicillinase-producing strains; *Streptococcus pyogenes**; Group D streptococcus including *Enterococcus faecalis*; *Acinetobacter* species* including *A. calcoaceticus**; *Citrobacter* species*; *Escherichia coli*; *Enterobacter cloacae*; *Klebsiella pneumoniae**; *Pseudomonas aeruginosa** and *Bacteroides* species* including *B. fragilis**.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Intravenous preparation: *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri**, *Pseudomonas aeruginosa*, *Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species*.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Piperacillin: It is approved for treatment of skin infections due to the following organisms (however, there is no specification as to whether the infections are to be complicated or uncomplicated): *E. coli*, *Klebsiella* sp, *Serratia* sp, *Acinetobacter* sp, *Enterobacter* sp, *Pseudomonas aeruginosa*, indole-positive *Proteus* sp, *Proteus mirabilis*, *Bacteroides* sp, including *B. fragilis*, anaerobic cocci, and enterococci.

Uncomplicated

Azithromycin: *S. aureus*, *S. pyogenes*, or *S. agalactiae*.

Clarithromycin: *S. aureus*, and *S. pyogenes*.

Dirithromycin: *S. aureus* (methicillin-susceptible strains).

Cefaclor: *S. aureus* (methicillin-susceptible strains).

Cefepime: *S. aureus* (methicillin-susceptible strains only) or *S. pyogenes*.

Cefprozil: *S. aureus* (including penicillinase-producing strains) and *S. pyogenes*.

Cefuroxime:
Ceftin™ *S. aureus* (including beta-lactamase-producing strains), and *S. pyogenes*.

Loracarbef: *S. aureus* (including penicillinase-producing strains) or *S. pyogenes*.

Piperacillin/Tazobactam: Piperacillin resistant, beta-lactamase producing strains of *S. aureus*.

Levofloxacin: *S. aureus* or *S. pyogenes*.

Ciprofloxacin: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, (methicillin susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

(Note: Ciprofloxacin's label has a table listing dosages guidelines per indication and it has an entry under Skin and Skin Structure for "Severe/Complicated." It is believed that the use of the term "complicated" in this label is different than how it is presently intended in the Points to Consider document, as it precedes the existence of the document.)

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Ofloxacin: *S. aureus*, *S. pyogenes*, and *P. mirabilis*.

Complicated

Piperacillin/Tazobactam: piperacillin resistant, beta-lactamase producing strains of *Staphylococcus aureus*.

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4. Material Reviewed

This review was done utilizing an electronic submission provided by the applicant as a stand-alone network server. The application was on an electronic search and retrieval system which contained the results of the statistical analyses, case report forms, and submission documents (study reports, study protocols, safety reports, etc.). The documents were stored in Portable Document Format (PDF) files, as well as Microsoft Word word processing software format. The application supported full text search through a World Wide Web interface (Netscape Navigator).

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5. Regulatory Background

The original IND for the trovafloxacin mesylate tablets. The IND for the intravenous formulation, alatrovafloxacin mesylate.

There were several protocol amendments submitted for each of the studies. Please refer to the NDA submission for details.

There were no Phase II/III Clinical issues that were contested regarding the protocols for the indications addressed in this review. The protocols attempted to follow the guidelines suggested by the Division's Point to Consider Document with respect to these indications. In particular, that document, which became available in 1992, specifically mentioned the following points regarding trials design for study of skin and skin structure infections:

Uncomplicated Skin and Skin Structure Infections

1. One statistically adequate and well-controlled multicenter trial which establishes equivalency or superiority to an approved product.
2. In order for this general claim to be granted, there should be at least 20% each of the following: simple abscesses, impetiginous lesions, furuncles, and cellulitis.
3. Inclusions/exclusion criteria, evaluability criteria, and outcome definitions should be clearly stated in the protocol.
4. At least 50% of the clinically evaluable patients should be microbiologically evaluable. Of the microbiologically unevaluable, the majority should be patients with "cellulitis" as the diagnosis, where low pathogen recovery is expected. Growth of transient or resident skin flora should not be considered a microbiologically evaluable patient.
5. Analyses should include stratification by the presence or absence of therapeutic surgical interventions.
6. Analyses should establish a correlation between clinical cure and bacterial eradication. Further, the direction of the independent 95% confidence interval testing of the successful outcome rates between the overall clinically evaluable, and the clinically and bacteriologically evaluable subsets should be confirmatory.
7. Adequate microbiologic data and specific human pharmacokinetic/-dynamic data supportive of clinical effectiveness should be provided.

Complicated Skin and Skin Structure Infections

The recommendations were very similar to the points mentioned above, and only the differences will be noted below:

1. Diagnoses under this heading include infected ulcers, burns, and major abscesses or other skin structure infections that require significant surgical intervention in addition to antimicrobial therapy.
2. At least 70% of the clinically evaluable patients should be microbiologically evaluable.

In addition, the general discussion section of the document indicates that only those microorganisms considered to be an etiologic agent (pathogen) in at least 10%, or 10 total cases, whichever is higher, of the evaluable cases of the specific infection should be included in the INDICATIONS AND USAGE section of the product labeling. These cases should meet both the clinical and microbiological evaluability criteria. Furthermore, the eradication rate of the pathogen accomplished by the investigative agent should be clinically acceptable.

However, it may be possible to include other organisms in this section of the label, even if they number of cases do not meet the numerical threshold described above. The following criteria, reproduced from the Points to Consider document, should be met:

- "(1) generally accepted as pathogens at the site of infection under investigations (however in numbers less than 10%) and the number of such infections studied in the clinical trials is consistent with the percentage of such infection due to these pathogens in the general population,
- (2) for which in vitro activity is at least similar to that of other pathogens more substantially evaluated in the clinical trials,
 - (3) for which the mechanism(s) of resistance is similar to other pathogens more substantially evaluated in the clinical trials, and
 - (4) for which there are no scientific data suggesting any differences in the management of the infection due to these pathogens or in the prognosis of patients with the infection due to these pathogens."

6. Foreign Marketing Experience

These applications are the first marketing applications for alatrofloxacin and trovafloxacin. The applicant indicated that they were planning on submitting registration dossiers to the European Medicines Evaluation Agency in 1997, as well as to the Canadian Health Protection Branch.

7. Summary of Clinical Development Program

The following table is a summary of the clinical trials which support the indications cited in this review. For each indication, a pivotal study enrolling U.S. patients was performed.

Clinical Trials

Study	Countries	Pivotal vs. Supportive	Blinding	Evaluations	Controlled	Number of Patients
Complicated Skin and Skin Structure Infection						
154-131	United States	Pivotal	Blinded	Clinical/bacteriological	Yes	287
154-132	United States, Costa Rica, Canada	Supportive	Unblinded	Clinical/bacteriological	No	214
154-139	United Kingdom, Ireland, Italy, Spain, Belgium, United States, Germany	Supportive	Unblinded	Clinical/bacteriological	Yes	323
Uncomplicated Skin and Skin Structure Infection						
154-130	United States, Costa Rica	Pivotal	Blinded	Clinical/bacteriological	Yes	446
154-129	United Kingdom, Belgium, Ireland, Germany	Supportive	Blinded	Clinical	Yes	280

B. Evaluation of Efficacy and Safety by Indication and Study

1. Complicated Skin and Skin Structure Infection

1.1 Study 154-131

Title: A randomized, multicenter, investigator/subject-blind (double-blind) trial comparing intravenous alatrofloxacin (CP-116,517) followed by oral trovafloxacin (CP 99,219) and intravenous piperacillin sodium/tazobactam (Zosyn™) followed by oral cefpodoxime proxetil (Vantin™) for the treatment of complicated infections of the skin and skin structure.

Study Dates

27 June 1995 - 28 May 1996

1.1.1 Study Design and Objectives

A randomized, double-blind, double-dummy, comparative, multicenter trial. The duration of treatment was 10-14 days. The treatment groups were:

1. Alatrofloxacin, 200 mg/day, intravenously, for 2 to 7 days, followed by oral trovafloxacin, 200 mg/day, orally, for a maximum total treatment duration of 10 or 14 days.

2. Zosyn™, 3.375 g, intravenously qid, for 2 to 7 days, followed by oral Vantin™, 400 mg bid, orally, for a maximum total treatment duration of 10 or 14 days.

Medical Officer Comment

The choice of comparators were discussed with the applicant during the End of Phase II meeting, and were considered appropriate.

The safety and efficacy measurements were performed as per the schedule summarized in the table on the following page, which is adapted from Appendix A of the Study Protocol in the applicant's submission:

Visit number	1	2	3	4
Study day	Day 1	Day 4	End Rx Day + 1	Day 30
Allowable window	(~48 hours)	(Day 3-7)	(Day 11-16)	(Day 28-35)
Treatment period	Day 1 to Day 10 or Day 14			Day 11 or 15 to Day 35
Follow-up period				
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Bone X-ray of infected area	x ²			
Microbiology				
exudate (or other specimen)	x	x	x	x ³
culture & sensitivity				
blood culture	x	x ⁴	abn	
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test ¹	x			
Adverse events				
routine events		x	x	x
serious adverse events		x	x	x
Investigator's evaluation of clinical response ⁵		x	x	x

abn = abnormal at previous visitor clinically significant adverse event

¹ to be done by local site for women of childbearing potential

² to be done if the skin and skin structure infection is proximal to bone to rule out contiguous osteomyelitis

³ to be done if clinically indicated

⁴ to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure

⁵ to be done at time of discontinuation, if applicable

The objective of the study was to assess the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin compared to intravenous piperacillin sodium/tazobactam sodium (Zosyn™) followed by oral cefpodoxime proxetil (Vantin™), in the treatment of subjects with complicated infections of the skin and skin structure. The infections were to have been of such severity that the patient was to have been assessed as initially requiring inpatient intravenous antimicrobial therapy.

1.1.2 Eligibility Criteria

The following inclusion/exclusion criteria are reproduced from the applicant's submission.

Inclusion Criteria

1. Males and females age ≥ 18 at baseline.
2. Females of childbearing potential must have had a negative urine pregnancy test immediately prior to entry into the study, and were to have used adequate contraception during the study and for one month after the end of the study. Childbearing potential was defined as not surgically sterile and < 1 year post-menopausal.
3. A clinically documented infection of the skin or skin structure. The following were included:
 - a. infected ischemic ulcers
 - b. diabetic foot ulcers without underlying osteomyelitis
 - c. infected burns
 - d. major abscesses
 - e. other skin structure infections requiring significant surgical intervention along with antimicrobial therapy
 - f. infections of the deeper soft tissues, including post-operative surgical wound infections
4. Written informed consent

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Exclusion Criteria

1. Treatment with other antibiotics under the following conditions:
 - a. Treatment with any other systemic antibiotic for 24 hours or longer, within 72 hours prior to the baseline visit (unless there was documented evidence of clinical failure).
 - b. Treatment with a topical antibiotic within 24 hours prior to the baseline visit or during the study.
 - c. The need for treatment with an antibiotic other than the study drugs or treatment for longer than 14 days.
2. Necrotizing fasciitis, or infections of prosthetic material.
3. Infection of the skin or skin structure whose severity did not warrant initial intravenous therapy.
4. Significant gastrointestinal, or other condition that could affect study drug absorption.
5. Immunologic compromise (including neutropenia, ARCS/AIDS, non-skin cancers, or malignant melanoma).
6. History of epilepsy or seizures.
7. Evidence of current or recent drug or alcohol abuse/dependence that, in the opinion of the investigator, suggested an inability to complete the protocol requirements.

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Medical Officer Comment
 The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient ID No.	Treatment arm	Type of deviation	Analyses performed by applicant					
			Clinical			Bacteriological		
			ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
Inclusion criteria								
5880-0079	Zosyn to Vantin	Enrolled with osteomyelitis	N	N	NA	N	N	NA
5880-0157	Zosyn to Vantin	Enrolled with osteomyelitis	Y	Y	N	Y	Y	N
5881-0315	Zosyn to Vantin	Enrolled with osteomyelitis	Y	Y	Y	N	N	NA
5881-0372	Zosyn to Vantin	Enrolled with osteomyelitis	Y	Y	Y	Y	N	NA
Exclusion criteria								
5606-0133	Alatrofloxacin to trovafloxacin	Received > 24 hr. of IV tx before enrollment	Y	N	NA	Y	N	NA
5881-0320	Zosyn to Vantin	History of seizure disorder	Y	N	NA	Y	N	NA
6025-0172	Zosyn to Vantin	History of seizure disorder	Y	N	NA	Y	N	NA

All three patients that were deemed clinically evaluable at EOT by the applicant were in the Zosyn to Vantin treatment group. Their clinical response assessment were "improved" (5880-0157), "cured" (5881-0315), and "failed" (5881-0372). There was no explanation provided by the applicant as to why they were included in the clinically evaluable analyses, however, it is not believed that the inclusion of these three patients in the analysis had a significant impact on the results.

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1.1.3 Study Drugs and Randomization Method

A double-dummy technique was utilized in order to maintain blinding. Alatrofloxacin (equivalent to 200 mg of trovafloxacin) was provided for intravenous administration in vials of 5 mg/ml (100 mg/20 ml) to be reconstituted to 1 mg/ml concentration with 5% dextrose in water (D5W), for a total of 20 mg in 200 - 250 ml. Intravenous Zosyn or matching placebo was provided in 3.375 gram vials, reconstituted with 15 ml of D5W and diluted with D5W to 200 ml total volume.

All concomitant therapies were to be noted in the case report form. In particular, the protocol prohibited the use of any other investigational drug within 4 weeks prior to the baseline visit. Furthermore, if an antibiotic was taken for a different infection, the subject was to have a final efficacy assessment. Mineral supplements, calcium- or magnesium-based antacids were allowed, but not within two hours of dosing. Systemic corticosteroids were allowed for subjects receiving chronic low doses of oral steroids (defined as 10 mg of prednisone/day or less).

A computer generated blinded randomization list was provided to the investigators by the applicant. The treatment groups were balanced in a ratio of 1:1.

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1.1.4 Study Endpoints

The study protocol indicated that the clinical success rates would be utilized in the efficacy analyses, and that the primary efficacy endpoint would be the clinical response at the end of therapy. Bacteriological response at the end of therapy, and clinical and bacteriological response at the end of the study were to be secondary endpoints. The clinical evaluation would be assessed by the investigator at Visits # 3 and 4, and classified as either a cure, improvement or failure, based on the overall assessment of the clinical presentation compared to baseline. Bacteriological response was to be evaluated by the applicant, at the end of therapy (either Day 11 or 15) and at the end of follow-up (Day 30).

Medical Officer Comment

Although both timepoints were analyzed by the applicant, and both will be discussed in this review, the Division felt that the most important timepoint for clinical assessment would be the End of Study visit. The rationale was that the End of Treatment visit tended to be only about a day or so after treatment had terminated, allowing for the possibility that there might still be some residual drug levels. This would not have been a concern at the End of Study visit.

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Clinical outcome definitions

Clinical outcomes at the end of treatment were defined as follows (adapted from Appendix B of the Study Protocol):

1. **Cure** - Resolution of signs and symptoms, including the presence of a culturable exudate, warmth, erythema, induration, tenderness, pain, swelling, discoloration, fever, diaphoresis, and leukocytosis.
2. **Improvement** - Incomplete resolution of the signs and symptoms as described above, and no requirement for additional antibiotic.
3. **Failure** - Lack of resolution of any of the signs and symptoms as described above, and the need for additional antibiotics.

Clinical outcomes at the end of the study were to be categorized as follows:

1. **Success** - Cure or improvement with no relapse at the end of the study.
2. **Failure** - Failure at the end of therapy, as previously defined.
3. **Relapse** - Cure or improvement at the end of therapy, but requiring additional antibiotic therapy for their primary disease prior to the end of the study.

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The applicant also defined conditions under which the assessment would be defined "failure," superseding the investigator's assessment:

1. If the investigator-defined clinical response was failure at any visit.
2. If a subject was given a concomitant antibiotic for insufficient clinical response during any of the following: active therapy plus one day, anytime before the assessment plus one day, during an assessment window for which a subject did not have an assessment.
3. If a subject lacked a post-baseline assessment (in the Intent-to-treat analysis only).
4. If a subject required surgical treatment as adjunct or follow-up therapy due to failure of the study medication.

Further, the applicant would make an assessment of "relapse" if either of the following conditions occurred:

1. The subject was a clinical cure or improvement at the end of treatment but was assessed as a failure by the investigator at a subsequent visit.
2. The subject was a clinical cure or improvement at the end of treatment but required additional antibiotic for the primary disease before the end of the study.

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Bacteriological outcome definitions

The defined categories for bacteriological responses were as follows (also reproduced from Appendix B of the Study Protocol):

1. **Eradication** - Elimination of the original causative organism(s) from the same site during or upon completion of therapy.
2. **Presumed eradication** - Absence of adequate culture material for evaluation because the subject is clinically *cured* or improved.
3. **Persistence** - Failure to eradicate the original causative organism at all post-baseline time points from sites previously cultured, regardless of whether signs of infection are present or not. Includes subjects given concomitant antibiotics for bacteriologic persistence at a prior time point.
4. **Relapse** - Reappearance of the original causative organism from the original site of infection *after* a post-baseline culture has been negative.
5. **Superinfection** - Development of a new skin or skin structure infection during the study that is due to a new or resistant pathogen which was not recognized as the original causative organism.
6. **Colonization** - Positive culture (exudate, swab, or aspirate) yielding a bacterial strain other than the primary causative isolate, and not associated with fever or other signs and symptoms of a complicated skin or skin structure infection.
7. **Presumed Persistence** - Use of concomitant antibiotic therapy due to continued clinical symptoms of the infection at study entry in the absence of microbiologic data. Includes subjects lost to follow-up who had a persistent pathogen at a prior evaluation.
8. **Indeterminate** - This designation was used if any of the following occur prior to the evaluation time point:
 - a. no baseline causative pathogen is isolated or was done more than 48 hours before the first dose of study medication.
 - b. relevant post-baseline cultures were not obtained (unless it was due to the absence of adequate culture material due to investigator determined clinical cure or improvement).
 - c. the subject was not considered to be clinically evaluable.

In addition, subjects would be excluded from the evaluable end of treatment and/or end of study analysis for any of the following reasons:

- a. Received less than 5 days of dosing - unless the subject had been considered a treatment failure.
- b. Inapplicable diagnosis (the patient did not meet entry criteria for a complicated skin or skin structure infection).
- c. The subject took an antibiotic for more than 24 hours within 72 hours of study initiation, without any evidence of clinical failure.
- d. The subject received concomitant systemic antibiotic for intercurrent illness.
- e. The subject had an intercurrent illness that confounded the efficacy evaluation.
- f. The subject missed a visit at the evaluation (unless the subject had previously been designated a treatment failure).

1.1.5 Termination and Follow-up

Visit # 3 constituted the visit at the end of treatment, at which time safety and efficacy evaluations were performed, and the investigator was to provide an evaluation of the clinical response. Patients were to be followed until Day 30 (Visit # 4), which was considered the end of the study. Safety and efficacy evaluations were again performed, and the investigator provided a final evaluation of clinical response. Any patient that had clinically significant laboratory abnormalities at Visit # 3 was to have them re-assessed at this time.

Medical Officer Comment

The number of patients that were lost to follow-up were minimal and comparable between the two treatment groups (1 in the alatrofloxacin/trovafloracin arm, and 2 in the Zosyn™/Vantin™ arm).

1.1.6 Sample Size and Statistical Plan

The applicant determined 95% confidence intervals for the difference seen in the success rates between the two treatment arms. As indicated above, the applicant defined clinical success as cure or improvement. An analysis controlling for center effect was also done with the Cochran - Mantel-Haenzel test.

The definition of equivalence that was used required that the 95% confidence interval for the difference in response rates between two arms must be within 15% when the satisfactory response rate for the reference treatment is 80%. Their calculations for sample size indicated that in order to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy between the two arms not exceed 15%, then 112 subjects would need to be clinically evaluable, for it was assumed that the response rate of the reference drug was 80%. The applicant assumed that 10% of patients would be clinically non-evaluable, therefore, they would need to enroll at least 124 patients per treatment group.

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1.1.7 Study Results

1.1.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 287 patients were randomized to therapy - 145 to the alatrofloxacin/trovafloroxacin arm, and 142 to the Zosyn™/Vantin™ treatment group. One patient in the in alatrofloxacin/trovafloroxacin treatment group did not receive therapy. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

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Demographic characteristics of treated Subjects

	Alatrofloxacin 200 mg IV to Trovafloroxacin 200 mg PO			Zosyn 3.375 mg IV q 6 hr to Vantin 400 mg PO bid		
	Male	Female	Total	Male	Female	Total
Number of Subjects	87	57	144*	85	57	142
Age (yr)						
16-44	30 (34%)	14 (25%)	44 (31%)	23 (27%)	16 (28%)	39 (27%)
45-64	32 (37%)	17 (30%)	49 (34%)	36 (42%)	29 (51%)	65 (46%)
>=65	25 (29%)	26 (46%)	51 (35%)	26 (31%)	12 (21%)	38 (27%)
Mean	52.4	57.6	54.5	54.9	54.7	54.8
Minimum						
Maximum						
Race						
White	64 (74%)	30 (53%)	94 (65%)	56 (66%)	38 (67%)	94 (66%)
Black	16 (18%)	22 (39%)	38 (26%)	20 (24%)	16 (28%)	36 (25%)
Hispanic	6 (7%)	4 (7%)	10 (7%)	6 (7%)	3 (5%)	9 (6%)
Asian	1 (1%)	1 (2%)	2 (1%)	1 (1%)	0	1 (<1%)
Arabian	0	0	0	1 (1%)	0	1 (<1%)
Samoan	0	0	0	1 (1%)	0	1 (<1%)

*Includes a patient randomized who did not receive therapy.

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In addition, the type of skin infections present at baseline are summarized in the table below (Table B from the applicant's Study Report):

Table B. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects				
	Alatrofloxacin ↓ Trovafoxacin (N=143)		Zosyn ↓ Vantin™ (N=140)	
Type of Infection^a	Number and Percentage (%) of Subjects			
Diabetic Foot Ulcer Without Osteomyelitis	23	(16%)	19	(14%)
Other Ischemic Ulcer	11	(8%)	14	(10%)
Infected Burn	0		2	(1%)
Major Abscess	22	(15%)	23	(16%)
Other Skin Structure Infection Requiring Significant Surgical Intervention	13	(9%)	19	(14%)
Cellulitis	6	(4%)	5	(4%)
Post-operative Surgical Wound Infection	0		1	(<1%)
Abscess	3	(2%)	5	(4%)
Ulcer	1	(<1%)	2	(1%)
Hydrantitis	0		1	(<1%)
Erysipelas	0		0	
Other ^b	3	(2%)	5	(4%)
Other Deep Soft Tissue Infections (e.g., Post-Operative Surgical Wound Infection)	89	(62%)	82	(59%)
Cellulitis	67	(49%)	61	(44%)
Post-operative Surgical Wound Infection	13	(9%)	12	(9%)
Abscess	1	(<1%)	1	(<1%)
Ulcer	1	(<1%)	0	
Hydrantitis	2	(1%)	1	(<1%)
Erysipelas	3	(2%)	2	(1%)
Other ^c	3	(2%)	5	(4%)
Subjects Requiring Surgical Drainage Procedure^d	90	(62%)	88	(62%)
At Baseline	61	(42%)	47	(33%)
Post-Baseline	44	(30%)	53	(37%)
Before the EOT Assessment	36	(25%)	44	(31%)
After the EOT Assessment	18	(12%)	21	(15%)
EOT = End of Treatment ^a A subject may have had more than one type of infection. ^b Other types of skin structure infections requiring surgery pressure sores, flexor tenosynovitis, septic arthritis, necrotizing soft tissue infection, human bite, cat bite, right medial knee and bursae and embedded foreign object. ^c Other types of deep soft tissue infections included cellulitis, post-operative surgical wound infections, abscesses, erysipelas, hydrantitis, and others [a gun shot wound, bursitis, infected stump, IV infection, traumatic injury, right pretibial hallux and posterior medial malleolus on right leg and infected laceration]. One subject (5881-0081) in the alatrofloxacin/trovafoxacin group had both bursitis (classified as "other") and cellulitis listed as a deep soft tissue infection; neither was designated as the primary infection. ^d Subjects were counted in each timepoint that they had a surgical drainage procedure. Therefore, numbers do not add up to the total. Ref.: Tables 2.3 and 2.4 in the submission.				

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Medical Officer Comment

The demographic characteristics, baseline diagnoses and baseline medical histories were comparable between the two treatment arms. There were 60 patients (42%) in the

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alatrofloxacin/trovafoxacin arm and 71 patients (50%) in the Zosyn/Vantin™ with diabetes. It is noted that patients with infected burns were not enrolled in the trovafoxacin arm in this study.

It is also noted that the term “cellulitis” is used as a diagnostic category. This term is usually not used to designate a serious infection, and the Point to Consider Document lists this as an example of an “uncomplicated infection.” However, review of the case report forms of all the patients that had cellulitis as sole diagnosis revealed that the vast majority had complicated infections, either because of the extent of the infection, or concurrent medical conditions. Therefore, it is believed that the diagnostic classification of “cellulitis,” although less than optimal, represented patients with medical conditions suitable for this study.

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1.1.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

	Alatrofloxacin 200 mg IV to Trovafoxacin 200 mg PO	Zosyn™ 3.375 mg IV q 6 hr to Vantin™ 400 mg PO bid
Number of randomized subjects	145	142
Randomized not treated	1	0
Number of treated subjects	144	142
Withdrawn from treatment	50 (35%)	29 (20%)
Withdrawn from study when treatment stopped	14 (10%)	7 (5%)
Withdrawn from treatment but completed study	36 (25%)	22 (15%)
Completed treatment	94 (65%)	113 (80%)
Withdrawn from study during follow-up	13 (9%)	7 (5%)
Completed treatment and study	81 (56%)	106 (75%)

Of the patients that were discontinued while on treatment, a total of 50 patients (35%) were discontinued from the alatrofloxacin/trovafoxacin arm, and 29 (20%) discontinued from the Zosyn™/ Vantin™ arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table D of the Summary Report):

	Alatrofloxacin 200 mg IV to Trovafoxacin 200 mg PO	Zosyn 3.375 mg IV q 6 hr to Vantin 400 mg PO bid
Number of Treated Subjects	144	142
Discontinued Subjects	50 (35%)	29 (20%)
Related to Study Drug	24 (17%)	12 (8%)
Adverse event	12 (8%)	4 (3%)
Insufficient response	11 (8%)	8 (6%)
Laboratory abnormality	1 (<1%)	0
Not Related to Study Drug	26 (18%)	17 (12%)
Adverse event	8 (6%)	2 (1%)
Does not meet randomization criteria	0	1 (<1%)
Laboratory abnormality	0	1 (<1%)
Lost to follow-up	1 (<1%)	2 (1%)
Other	14 (10%)	7 (5%)
Protocol violation	1 (<1%)	2 (1%)
Withdrawn consent	2 (1%)	2 (1%)
Completed treatment	94 (65%)	113 (80%)

The applicant indicated that the most common reason listed under “other” that led to study drug discontinuation was the presence of methicillin-resistant *S. aureus*.

Medical Officer Comment

It is noted that approximately 50% more patients were discontinued from the alatrofloxacin/ trovafloxacin treatment group compared to the Zosyn™/Vantin™. In addition, three times as many patients discontinued due to an adverse event. This will be addressed in more detail in the safety assessment section (Section 1.5).

1.1.7.3 Primary Analyses

Utilizing the criteria identified above, in section 1.1.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

1. Clinical

In the alatrofloxacin/trovafloxacin treatment arm, 145 patients were randomized. Two had inappropriate baseline diagnosis, and were not included in the intent-to-treat and evaluable analyses. Of the remaining 143 patients, 40 were not clinically evaluable.

In the Zosyn™/Vantin™ treatment arm, 142 patients were randomized. As in the other treatment arm, two had inappropriate baseline diagnosis, and were not included in the intent-to-treat and evaluable analyses. Of the remaining 140 patients, 17 were not clinically evaluable.

Reasons for exclusion included concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical response in the evaluable window, no post-baseline clinical assessment, prior antibiotic usage, and randomized but not treated. The most common reason was insufficient therapy.

2. Bacteriological

Of the 143 clinical intent-to-treat patients in the alatrofloxacin/trovafloxacin arm, only 115 were included in the bacteriological intent-to-treat group, because 28 subjects had negative baseline cultures. It was noted that 23 of these were in the 103 clinically evaluable group, therefore, only 80 subjects were bacteriologically evaluable for purposes of the study.

In the Zosyn™/Vantin™ treatment arm, only 103 of the 140 clinical intent-to-treat were included in the bacteriological intent-to-treat group, because 37 had negative baseline culture. Thirty-four of these were in the 123 clinically evaluable group, therefore, only 89 were bacteriologically evaluable.

The following table summarizes the number of evaluable patients in each category for purposes of the primary analyses, for each treatment arm:

	Alatrofloxacin/ Trovafloxacin	Zosyn/ Vantin
Number Randomized	145	142
Not evaluable (inappropriate baseline diagnosis)	2 (1.3%)	2 (1.4%)
Treated and evaluable patients	143 (98.6%)	140 (98.6%)
Negative baseline cultures	28 (20%)	37 (26%)
Bacteriological Intent-to-Treat	115 (79%)	103 (73%)
Clinically Evaluable	103 (71%)	123 (87%)
Negative baseline cultures	23 (16%)	34 (24%)
Bacteriologically Evaluable	80 (55%)	89 (63%)

Efficacy Results

The applicant performed several analyses comparing the results of the investigator-defined response rates and the applicant defined response rates. This was done for both timepoints - at the end-of-treatment and at the end-of-study visits. In addition, the patient subgroups analyzed included the clinically intent-to-treat, clinically evaluable, and bacteriologically evaluable patients.

1. Clinically evaluable

In the clinically evaluable group of subjects, the applicant-defined clinical success rates (cure and improvement) were as follows: In the alatrofloxacin/trovafoxacin arm, of the 103 in the clinically evaluable group, 99 were assessed at the end of treatment, with a success rate of 81%. In the Zosyn™/Vantin™ arm, of the 123 in the clinically evaluable group, 117 were assessed at the end of treatment, with a success rate of 85% [95% CI around the difference: (-14.0, 6.3)].

The applicant's analysis at the end-of-study timepoint reported the following: In the alatrofloxacin/trovafoxacin arm, of the 103 in the clinically evaluable group, 85 were assessed, with a success rate of 73%. In the Zosyn™/Vantin™ arm, of the 123 in the clinically evaluable group, 105 were assessed at the end of study, with a success rate of 77% [95% CI around the difference: (-16.6, 8.2)].

The following table, adapted from Table E in the applicant's submission, summarizes the clinical response rates for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafoxacin (N=103)		Zosyn ↓ Vantin™ (N=123)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	99	(100%)	117	(100%)	
Success (Cure + Improvement)	80	(81%)	99	(85%)	(-14.0%, 6.3%)
Distribution of Clinical Response:					
Cure	41	(41%)	41	(35%)	
Improvement	39	(39%)	58	(50%)	
Failure	19	(19%)	18	(15%)	
End of Study:					
Number of Subjects Assessed	85	(100%)	105	(100%)	
Success (Cure + Improvement)	62	(73%)	81	(77%)	(-16.6%, 8.2%)
Distribution of Clinical Response:					
Cure	55	(65%)	58	(55%)	
Improvement	7	(8%)	23	(22%)	
Failure	21	(25%)	18	(17%)	
Relapse	2	(2%)	6	(6%)	
CI=confidence interval Ref.: Table 5.1.1 in the submission.					

2. Clinical intent-to-treat

The clinically intent-to-treat group analysis yielded similar results: At the end of treatment, the alatrofloxacin/trovafoxacin arm had a 73% success rate in 134 subjects assessed out of a possible 143; the Zosyn™/Vantin™ arm, 80% success rate in 133 subjects assessed out of a possible 140. The 95% confidence interval around the difference was (-16.7, 3.6).

At the end of study the alatrofloxacin/trovafoxacin arm had a 71% success rate in 143 subjects assessed out of a possible 143; the Zosyn™/Vantin™ arm, 76% success rate in 140 subjects assessed out of a possible 140. The 95% confidence interval around the difference was (-15.7, 5.1).

Medical Officer Comment

The analysis of the clinically evaluable and clinically intent-to-treat patient groups supports the applicant's claim of equivalent efficacy compared to the combination of Zosyn™ and Vantin™.

It was also noted that the assessment of the clinical response differed between the applicant and the investigator for several patients, both at the end of treatment and at the end of study:

	Alatrofloxacin/ trovafoxacin	Zosyn™/ Vantin™
Number of disagreements		
At the end of treatment	1	3
At the end of study	19	26

In each of these cases, the applicant assigned a more conservative assessment - trending towards the more negative result.

3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Streptococcus agalactiae*. In the clinically evaluable subjects, the response rate was comparable between the treatment arms. The following table is reproduced from the Study Report (Table G):

Most frequently isolated baseline pathogens^a

Pathogen	Alatrofloxacin to Trovafoxacin (N=103)		Zosyn™ to Vantin™ (N=123)		Alatrofloxacin to Trovafoxacin (N=103)		Zosyn™ to Vantin™ (N=123)	
	Number of Subjects							
	End of Treatment				End of Study			
<i>S. aureus</i>	32/38 (84%)	31/37 (84%)	26/34 (76%)	26/33 (79%)				
<i>S. epidermidis</i>	8/10 (80%)	10/15 (67%)	6/8 (75%)	11/16 (69%)				
<i>Enterococcus faecalis</i>	9/11	9/13	7/10	7/11				
<i>S. Agalactiae</i>	7/11	6/7	4/9	7/8				

^a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15 at least once for a given pathogen.
A subject could have had more than one pathogen isolated at baseline.
Ref.: Table 5.3.1

Medical Officer Comment

This study supports the use of alatrofloxacin, 200 mg intravenously, followed by oral trovafoxacin, 200 mg, for a total of 10-14 days of therapy for the treatment of complicated skin/skin structure infections due to the following organisms: *Staphylococcus aureus*, *Enterococcus faecalis*, and *Streptococcus agalactiae*.

The applicant had also listed *Staphylococcus epidermidis* as a baseline pathogen, however, review of the case report forms revealed that only three patients had pure cultures, and of

these, only one was bacteriologically evaluable. Therefore, it is believed that not enough patients with *Staphylococcus epidermidis* were studied in this trial to adequately assess the effectiveness of the therapeutic regimen against this potential pathogen.

1.1.7.4 Additional Analyses

The applicant also performed the following analyses:

1. Clinical response stratified by type of infection at baseline
2. Clinical response stratified by timing of surgical intervention
3. Presence and severity of clinical signs/symptoms at baseline, end-of-treatment, and end-of-study.

Medical Officer Comment

For the three analyses, the results were comparable between the treatment groups. Due to the limited number of patients with diabetic foot ulcers who ended up requiring amputation, it was not possible to make any definitive conclusions regarding any difference between the two treatment arms with respect to the study drug's ability to reduce the need for surgical amputations in this patient population.

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1.2 Study 154-132

Title: An open-label, non-comparative, multicenter trial on the use of oral trovafloxacin (CP-99,219) for the treatment of diabetic foot infections.

Study Dates

7 June 1995 - 16 May 1996

1.2.1 Study Design and Objectives

Open label, non-comparative, multicenter trial. All patients received trovafloxacin, orally, 200 mg/day in a single dose (2 x 100 mg tablets). The duration of treatment was 10 - 14 days.

The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3	4
Study day	Day 1	Day 4	End Rx Day + 1	Day 30
Allowable window	(~48 hours)	(Day 3-7)	(Day 11-16)	(Day 28-35)
Treatment period	Day 1 to Day 10 or Day 14			
Follow-up period			Day 11 or 15 to Day 35	
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Bone X-ray of infected area	x ²			
Microbiology				
exudate (or other specimen) culture & sensitivity	x	x	x	x ³
blood culture	x	x ⁴	abn	
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test ¹	x			
Adverse events				
routine events		x	x	x
serious adverse events		x	x	x
Investigator's evaluation of clinical response ⁵		x	x	x

abn = abnormal at previous visitor clinically significant adverse event

¹ to be done by local site for women of childbearing potential

² to be done if the skin and skin structure infection is proximal to bone to rule out contiguous osteomyelitis

³ to be done if clinically indicated

⁴ to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure

⁵ to be done at time of discontinuation, if applicable

The objective of this study was to evaluate the safety and efficacy of trovafloxacin in the treatment of patients with diabetic foot infections, who required oral antibiotic therapy.

1.2.2 Eligibility Criteria

Inclusion Criteria

The inclusion criteria were the same as in Study 153-131, except for the explicit statement that culturable material (exudate, swab, or aspirate) was to be obtained.

Exclusion Criteria

The exclusion criteria were the same as in Study 154-131, except that the following exclusions were not specifically mentioned:

1. Necrotizing fasciitis, or infections of prosthetic material.
2. Significant gastrointestinal or other condition that could affect study drug absorption.
3. Evidence of current or recent drug or alcohol abuse/dependence that, in the opinion of the investigator, suggested an inability to complete the protocol requirements.

Medical Officer Comment

No deviations from inclusion criteria were reported.

The following protocol deviations from the exclusion criteria were reported :

Patient ID No.	Type of deviation	Analyses performed by applicant					
		Clinical			Bacteriological		
		ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
5177-0005	Enrolled with osteomyelitis	Y	Y	Y	Y	Y	Y
6053-0001	Enrolled with osteomyelitis	Y	Y	Y	N	N	NA
6536-0027	Had UTI at baseline; tx'd with Bactrim	Y	Y	Y	Y	Y	Y

All three patients were deemed clinically evaluable by the applicant. Their clinical response assessment at the end of treatment were "cure" (5177-0005), failure (6053-0001), and "improvement" (6536-0027). It is not believed that inclusion of these three patients in the clinically evaluable analysis had a significant impact on the results.

1.2.3 Study Drugs and Randomization Method

The trovafloxacin tablets were packaged in blister packs (28 tablets/pack), and the patients received a single daily dose of 200 mg (2 x 100 mg tablets).

This was a single arm, open label study, therefore there was no randomization. Patients were assigned a study number sequentially as they were determined to be eligible for the study.

1.2.4 Study Endpoints

The primary efficacy endpoint was applicant-defined clinical response at the end of treatment visit. This assessment was based primarily on the overall evaluation made by the investigator. Secondary efficacy endpoints were: pathogen eradication (at the end of treatment visit, and end of study visit), and investigator defined clinical response (at the end of treatment visit, and at the end of study visit).

The definitions for the clinical response and bacteriological response classification were the same as for Study 153-131, as were the definitions for establishing whether a subject was evaluable.

Medical Officer Comment

As with Study 154-131, the timepoint for clinical assessment preferred by the Division was End of Study.

1.2.5 Termination and Follow-up

If the patient discontinued prior to the prescribed end of treatment, a final evaluation was to be performed. If the discontinuation was due to clinical failure, then the final clinical and microbiological evaluations were to be performed. If the discontinuation was due to adverse events, then appropriate therapeutic measures would be taken and the patient would be followed through Visit 4 (Day 30), with performance of all clinical and microbiological evaluations.

1.2.6 Sample Size and Statistical Plan

Since this is a single arm, open-label trial, sample size calculations were not performed by the applicant. Descriptive statistics were used in the analysis of the study's results. The applicant performed subgroup analyses based on the presence or absence of surgical interventions.

1.2.7 Study Results

1.2.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 225 patients were treated. The demographic features of the treatment group are summarized in the table below:

	Trovafloracin 200 mg PO daily		
	Male	Female	Total
Number of Subjects	116	109	225
Age (yr)			
16-44	12 (10%)	7 (6%)	19 (8%)
45-64	46 (40%)	52 (48%)	98 (44%)
>=65	58 (50%)	50 (46%)	108 (48%)
Mean	62.1	62.1	62.1
Minimum	-	-	-
Maximum	-	-	-
Race			
White	80 (69%)	53 (49%)	133 (59%)
Hispanic	26 (22%)	49 (45%)	75 (33%)
Black	10 (9%)	7 (6%)	17 (8%)

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The type of skin infections present at baseline in the clinical intent-to-treat group are summarized in the table below (Table B from the applicant's Study Report);

Table B. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects	
	Trovafloracin 200 mg (N=224)
Type of Infection^a	Number and Percentage (%) of Subjects
Cellulitis with a Baseline Pathogen	48 (21%)
Cellulitis without a Baseline Pathogen	13 (6%)
Foot Ulcer	183 (82%)
Other	21 (9%)
Subjects Requiring Surgical Interyention^b	111 (49%)
At Baseline	98 (43%)
Post-Baseline ^c	73 (32%)
Before the EOT Assessment	65 (29%)
After the EOT Assessment	48 (21%)

EOT = End of Treatment
a A subject may have had more than one type of infection.
b Two of these subjects (Subjects 5190-0007 and 5842-0008) required surgical intervention, which occurred either outside of the end of study window (Subject 5842-0008; excision of the toe nail) or the surgical procedure and timing of the procedure was not specified on the case report form (Subject 5190-0007).
c Sixty-two (62) subjects required surgical intervention both prior to and post-baseline (57 subjects had surgical drainage at baseline and before the end of treatment, and 43 subjects had surgical drainage at baseline and after the end of treatment). In addition, two subjects (Subjects 6027-0007 and 6447-0001) had surgical drainage procedures performed post-baseline both before and after the end of treatment.
Ref.: Tables 2.3 and 2.4 in the submission.

1.2.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

	Trovafloracin 200 mg PO
Number of randomized subjects	225
Randomized not treated	0
Number of treated subjects	225
Withdrawn from treatment	15 (7%)
Withdrawn from study when treatment stopped	7 (3%)
Withdrawn from treatment but completed study	8 (4%)
Completed treatment	210 (93%)
Withdrawn from study during follow-up	1 (< 1%)
Completed treatment and study	209 (93%)

The reasons for discontinuation from treatment for the 15 patients are summarized in the following table, (adapted from the applicant's submission; Table C of the Summary Report):

Trovafloracin 200 mg PO

Number of Treated Subjects

225

Discontinued Subjects
Related to Study Drug

15 (6.6%)
10 (4.4%)
3 (1.3%)
7 (3.1%)

Adverse event
Insufficient response

5 (2.2%)

Not Related to Study Drug

1 (<1%)

Lost to follow-up

4 (2%)

Withdrawn consent

210 (93%)

Completed treatment

1.2.7.3 Primary Analyses
Utilizing the criteria described in section 1.2.4 Study Endpoints, the number of patients that were excluded from evaluation were as follows:

1. Clinical

Of the 225 subjects enrolled, 1 had an inappropriate baseline diagnosis, and was excluded from all intent-to-treat and evaluable analyses. Of the remaining 224 subjects, 10 were not clinically evaluable. The most common reasons for exclusions were no post-baseline clinical assessment, no post-baseline clinical response in evaluable window, insufficient therapy, prior antibiotic therapy, and concomitant antibiotic therapy.

2. Bacteriological

Of the 214 clinically evaluable group, 34 did not have a baseline pathogen identified, therefore, only 180 subjects were bacteriologically evaluable for purpose of the study.

The following table summarizes the number of evaluable patients in each category:

Number Randomized	225
Not evaluable (inappropriate baseline diagnosis)	1 (<1%)
Treated and Evaluable Patients	224 (99%)
Negative baseline cultures	34 (15%)
Bacteriological Intent-to-Treat	190 (84%)
Clinical Evaluable	214 (95%)
No baseline pathogen	34 (15%)
Bacteriological Evaluable	180 (80%)

Efficacy Result

The primary endpoint was clinical response at the end of treatment visit, however, the applicant also determined bacteriological response at the end of treatment, and clinical and bacteriological response rates at the end of study, on both, the evaluable and intent-to-treat populations.

1. Clinically evaluable

The following table, adapted from Table D in the applicant's Study Report, summarizes the response rates for the different categories for the clinically evaluable population.

Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits - Clinically Evaluable Subjects

	Trovafoxacin 200 mg (N=214)	
	Number and Percentage (%) of Subjects	
End of Treatment		
Number of Subjects Assessed	209	(100%)
Success (Cure + Improvement)	195	(93%)
Distribution of Clinical Response:		
Cure	93	(44%)
Improvement	102	(49%)
Failure	14	(7%)
End of Study		
Number of Subjects Assessed	206	(100%)
Success (Cure + Improvement)	179	(87%)
Distribution of Clinical Response:		
Cure	146	(71%)
Improvement	33	(16%)
Failure	16	(8%)
Relapse	11	(5%)

Ref.: Table 5.1.1 in the submission.

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2. Clinically Intent-to-treat

The clinically intent-to-treat group analysis had similar results - end of treatment success rate was 91%, and the end of study success rate was 85%.

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3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *S. aureus*, *S. epidermidis*, *E. faecalis*, and *S. haemolyticus*. The following table is reproduced from the Study Report (Table F):

Most frequently isolated baseline pathogens^a

Pathogen	Trovafoxacin 200 mg (N=180)		Trovafoxacin 200 mg (N=174)	
	Number of Subjects			
	End of Treatment		End of Study	
<i>S. aureus</i>	53/59	(90%)	48/60	(80%)
<i>S. epidermidis</i>	27/27	(100%)	25/27	(93%)
<i>E. faecalis</i>	27/32	(84%)	23/32	(72%)
<i>S. haemolyticus</i>	16/16	(100%)	13/15	(87%)
<i>P. aeruginosa</i>	11/14		8/16	(50%)
<i>Corynebacterium sp.</i>	10/10		11/12	
<i>P. mirabilis</i>	10/11		10/11	
<i>E. coli</i>	11/14		11/14	
<i>Staphylococcus sp.</i>	7/7		6/7	
<i>S. simulans</i>	6/6		6/6	
<i>S. hominis</i>	6/6		5/6	
<i>Streptococcus sp.</i>	11/11		10/10	
<i>S. agalactiae</i>	12/13		12/13	
<i>Peptostreptococcus sp.</i>	4/6		4/6	
<i>Peptostreptococcus magnus</i>	2/5		2/5	

^a ≥10 isolates of a given pathogen at either timepoint and ≥5 isolates of any *staphylococcus* and *streptococcus* species; percents displayed only when denominator is ≥15.

A subject could have had more than one pathogen isolated at baseline.

Ref.: Table 5.3.1 in the submission.

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Medical Officer Comment

Although uncontrolled and unblinded, this study is supportive of the findings of Study 154-131 with respect to the following organisms: *Staphylococcus aureus*, and *Enterococcus faecalis*. It is noted that although there were only thirteen (13) patients with *Streptococcus agalactiae*, efficacy was demonstrated. Therefore, although this study could not stand alone as demonstrating efficacy against *S. agalactiae*, it is supportive of Study 153-131. In addition, some of the efficacy data suggest that Trovan may be effective against *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Escherichia coli*.

Review of the case report forms indicates that of the cases identified as having *Staphylococcus epidermidis* (*S. epidermidis*), there were only six (6) patients with *S. epidermidis* as the sole isolate, and of these, only four (4) were bacteriologically evaluable. Due to the fact that *S. epidermidis* is a known component of skin flora, and a common contaminant, this study did not include enough patients where *S. epidermidis* was the sole pathogen to be able to determine the efficacy of this therapeutic regimen against this potential pathogen.

1.2.7.4 Additional Analyses

The sponsor also performed the following analyses:

1. Clinical response stratified by type of infection at baseline.
2. Clinical response stratified by timing of surgical intervention.

Medical Officer Comment

For the first analysis, there was no difference within category (type of infection) between the end of treatment analysis and the end of study analysis. For the second analysis, there was no difference between the two categories 9 those requiring surgical intervention at baseline and those not requiring surgery. This lack of difference was seen at the end of treatment as well as at the end of study evaluations.

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1.3 Study 154-139

Title: A randomized, multicenter, open trial comparing oral trovafloxacin (CP-99,219) (200 mg) and Augmentin™ for the treatment of complicated infections of the skin and skin structure.

Study Dates

23 September 1995 - 10 June 1996

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1.3.1 Study Design and Objectives

Randomized, comparative, multicenter open trial. The duration of treatment was 10-14 days. The treatment groups were:

1. Trovafloxacin, 200 mg/day, as a single active dose (2 x 100 mg tablets)
2. Augmentin™, 1500 mg/day, in three equally divided doses of 500 mg

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The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3	4
Study day	Day 1	Day 4	EDT + 1d	Day 30
Allowable window	(~48 hours)	(Day 3-7)	(Day 11-15)	(Day 28-35)
Treatment period	Day 1 to Day 10 or Day 14			Day 11 or 15 to Day 35
Follow-up period				
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Microbiology				
exudate (or other specimen) culture & sensitivity	x	x	x	x ²
blood culture	x	x ³	abn	
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test ¹	x			
Investigator's assessment of clinical response ⁴			x	x

abn = abnormal at previous visitor clinically significant adverse event

¹ to be done by local site for women of childbearing potential

² to be done if clinically indicated

³ to be done in all subjects with a positive baseline blood culture and in those who discontinue because of clinical failure

⁴ to be done at time of discontinuation, if applicable

The objective of this study was to compare the safety and efficacy of trovafloxacin to Augmentin™ in the treatment of complicated infections of the skin and skin structures.

1.3.2 Eligibility Criteria**Inclusion Criteria**

The inclusion criteria were the same as in Study 154-131.

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Exclusion Criteria

The exclusion criteria were the same as in Study 154-131, except that the following were specifically not mentioned:

1. Significant gastrointestinal, or other condition that could affect study drug absorption.
2. Evidence of current or recent drug or alcohol abuse/dependence that, in the opinion of the investigator, suggested an inability to complete the protocol requirements.

Medical Officer Comment

The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient No.	ID	Treatment arm	Type of deviation	Analyses performed by applicant					
				Clinical			Bacteriological		
				ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
Inclusion criteria				N	N	NA	N	N	NA
6134-0019		Trovafloxacin	Enrolled with osteomyelitis						
Exclusion criteria				Y	Y	N	Y	Y	N
6243-0058		Trovafloxacin	Received >24 hrs of systemic antibiotics before baseline visit and received concomitant prednisone						
6009-0214		Augmentin	Received concomitant antibiotics	Y	Y	N	Y	Y	N
6296-0399		Augmentin	Received concomitant antibiotics	Y	Y	Y	Y	Y	Y
6296-0346		Augmentin	Received concomitant antibiotics and received concomitant prednisone	Y	Y	Y	N	N	NA
6296-0488		Trovafloxacin	Received concomitant antibiotics and received enzymatic chemical debridement	Y	Y	Y	Y	Y	Y
6009-0213		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
6240-0261		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
6240-0262		Trovafloxacin	Received topical antibiotics	Y	Y	N	Y	Y	N
6297-0349		Augmentin	Received topical antibiotics	Y	Y	Y	N	N	NA
6296-0400		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
6296-0486		Augmentin	Received topical antibiotics	Y	Y	Y	N	N	NA
6011-0193		Trovafloxacin	Received enzymatic chemical debridement	Y	Y	N	Y	Y	N
6296-0399		Augmentin	Received enzymatic chemical debridement	Y	Y	Y	Y	Y	Y
5294-0030		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6300-0380		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6370-0130		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	N	NA	Y	N
6456-0387		Trovafloxacin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6577-0429		Augmentin	History of epilepsy and/ or anticonvulsant therapy	Y	Y	Y	Y	Y	Y
6417-0439		Trovafloxacin	Previously enrolled in the study as another subject	Y	Y	Y	Y	Y	Y

After review of the case report forms, it was felt by the reviewer that most of the protocol violations did not have a significant impact on the study results. It was noted that there it appears that Subject #6417-0439 was deemed evaluable twice (as subject #6417-0416). However, it was felt that the inclusion of this subject twice in the analyses would not significantly alter the overall result of the study.

1.3.3 Study Drugs and Randomization Method

Subjects were given enough for 14 total course of treatment of one of the following:

- Trovafloracin, 200 mg as a single daily dose (2 x 100 mg tablets)
- Augmentin™, 1500 mg daily, in three divided doses of 500 mg

A masked randomization list was provided to the investigators by the applicant, consisting of a list of numbers to which the study drugs have been assigned. The investigator assigned study numbers sequentially to patients as it was determined that they were eligible for the study.

1.3.4 Study Endpoints

As with the other studies for this indication, the applicant indicated that the primary efficacy endpoint would be clinical response at the end of therapy. Bacteriological response at the end of therapy, and clinical and bacteriological response at the end of the study would be secondary endpoints. The clinical evaluation would be assessed by the investigator at Visits # 3 (Day 11 or 15) and 4 (Day 30), and classified as either a cure, improvement or failure, based on the overall assessment of the clinical presentation compared to baseline. Bacteriological response was to be evaluated by the applicant, at the end of therapy (either Day 11 or 15) and at the end of follow-up (Day 30).

The definitions for the clinical response and bacteriological response classification were similar as for Study 153-131, except for the following exceptions:

1. Concomitant antibiotic use for treatment of an intercurrent illness would classify a subject as *indeterminate*, and preclude the evaluation of a bacteriological response.
2. The category "Eradication with Reinfection" was included in the bacteriological definitions.

The definitions for establishing whether a subject was evaluable were comparable to those used in Study 154-131, except for the following additional conditions also made a subject non-evaluable:

1. No clinical signs or symptoms recorded at baseline.
2. Patient entered into study more than once.

Medical Officer Comment

As with the other two studies, the timepoint preferred by the Division for clinical assessment was the End of Study visit.

1.3.5 Termination and Follow-up

If the patient discontinued prior to the prescribed end of treatment, a final evaluation was to be performed. If the discontinuation was due to clinical failure, then the final clinical and microbiological evaluations were to be performed. If the discontinuation was due to adverse events, then appropriate therapeutic measures would be taken and the patient would be followed through Visit 4 (Day 30), with performance of all clinical and microbiological evaluations.

1.3.6 Sample Size and Statistical Plan

The definition of equivalence that was used required that the 95% confidence interval for the difference in response rates between two arms must be within 10% when the satisfactory response rate for the reference treatment is 90%. Their calculations for sample size indicated that in order to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy between the two arms not exceed 10%, then 142 subjects would need to be clinically evaluable, for it was assumed that the response rate of the reference drug was 90%. The

applicant also assumed that 10% of patients would be clinically non-evaluable, therefore, they would need to enroll at least 158 patients per treatment group.

The applicant also used the Cochran-Mantel-Haenzel test to control for center effect.

1.3.7 Study Results

1.3.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 323 patients were randomized to therapy - 166 to the trovafloxacin arm, and 157 to the Augmentin™ treatment group. Six patients in the in trovafloxacin treatment group did not receive therapy, 1 in the Augmentin™ group. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

Demographic characteristics of treated Subjects

	Trovafloxacin 200 mg PO			Augmentin™ 500 mg tid		
	Male	Female	Total	Male	Female	Total
Number of Subjects	87	73	160	77	79	156
Age (yr)						
16-44	37 (43%)	18 (25%)	55 (34%)	34 (44%)	18 (23%)	52 (33%)
45-64	29 (33%)	14 (19%)	43 (27%)	24 (31%)	23 (29%)	47 (30%)
>=65	21 (24%)	41 (56%)	62 (39%)	19 (25%)	38 (48%)	57 (37%)
Mean	49.7	61.8	55.2	49.6	58.6	54.2
Minimum						
Maximum						
Race						
White	82 (94%)	72 (99%)	154 (96%)	75 (97%)	71 (90%)	146 (94%)
Black	0	1 (<1%)	1 (<1%)	1 (<1%)	6 (8%)	7 (4%)
Hispanic	3 (3%)	0	3 (2%)	1 (<1%)	1 (<1%)	2 (1%)
Asian	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Polynesian	1 (<1%)	0	1 (<1%)	0	0	0

In addition, the type of skin infections present at baseline are summarized in the table below (adapted from Table B from the applicant's Study Report):

Table B. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects				
	Trovafloxacin 200 mg (N=165)		Augmentin™ 500 mg tid (N=156)	
Type of Infection^a	Number and Percentage (%) of Subjects			
Diabetic Foot Ulcer Without Osteomyelitis	24	(15%)	26	(17%)
Other Ischemic Ulcer	36	(22%)	38	(24%)
Infected Burn	8	(5%)	7	(4%)
Major Abscess	26	(16%)	26	(17%)
Other Skin Structure Infection Requiring Surgery	9	(5%)	5	(3%)
Ulcer	1	(<1%)	1	(<1%)
Cysts	3	(2%)	0	
Hydrantitis	1	(<1%)	1	(<1%)
Post-Operative Surgical Wound Infection	1	(<1%)	0	
Other ^b	3	(2%)	3	(2%)
Other Deep Soft Tissue Infections (e.g., Post-Operative Surgical Wound Infection)	62	(38%)	55	(35%)
Abscess	0		1	(<1%)
Ulcer	3	(2%)	4	(3%)
Cellulitis	17	(11%)	13	(8%)
Erysipelas	2	(1%)	2	(1%)
Hydrantitis	1	(<1%)	1	(<1%)
Post-operative Surgical Wound Infection	16	(10%)	16	(10%)
Cysts	1	(<1%)	1	(<1%)
Other ^c	21	(13%)	17	(11%)
Subjects Requiring Surgical Drainage Procedure^d	39	(24%)	37	(24%)
At Baseline	33	(20%)	30	(19%)
Post-Baseline	16	(10%)	16	(10%)
Before the EOT Assessment	12	(7%)	12	(8%)
After the EOT Assessment	8	(5%)	10	(6%)
EOT = End of Treatment				
a A subject may have had more than one type of infection.				
b Other types of skin structure infections requiring surgery included a laceration, infected hematoma, pimple, abrasion, toe infection, and whitlow.				
c Other types of deep soft tissue infections included chronic infections, pyogenic granule, wound infections, sequelae [sic] of osteomyelitis, chronic edema, paronychia, furuncle, fistula, bursitis, eczema, infected insect bites, vasculitis, impetiginous lesion, thrombophlebitis, whitlow, pyoderma, and blister infected dermatitis.				
d Subjects were counted in each timepoint that they had a surgical drainage procedure. Therefore, numbers do not add up to the total.				
Ref.: Tables 2.3 and 2.4.				

Medical Officer Comment

The demographic characteristics, baseline diagnoses, and baseline medical histories were comparable between the two treatment arms. There were 40 (25%) patients in the trovafloxacin arm, and 33 (21%) patients in the Augmentin™ arm with diabetes mellitus. Peripheral vascular disease was slightly more prominent, with 47 (29%) patients in the trovafloxacin arm and 48 (31%) in the Augmentin™ arm reporting this condition.

1.3.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

	Trovafloracin 200 mg PO	Augmentin™ 500 mg tid
Number of randomized subjects	166	157
Randomized not treated	6	1
Number of treated subjects	160	156
Withdrawn from treatment	15 (9%)	23 (15%)
Withdrawn from study when treatment stopped	7 (4%)	9 (6%)
Withdrawn from treatment but completed study	8 (5%)	14 (9%)
Completed treatment	145 (91%)	133 (85%)
Withdrawn from study during follow-up	3 (2%)	1 (< 1%)
Completed treatment and study	142 (89%)	132 (85%)

Of the patients that were discontinued while on treatment, a total of 15 patients (9%) were discontinued from the trovafloxacin arm, and 23 (15%) discontinued from the Augmentin™ arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table C of the Summary Report):

	Trovafloracin 200 mg po	Augmentin™ 500 mg tid
Number of Treated Subjects	160	156
Discontinued Subjects	15 (9%)	23 (15%)
Related to Study Drug	5 (3%)	14 (9%)
Adverse event	4 (3%)	13 (8%)
Insufficient response	1 (< 1%)	1 (< 1%)
Not Related to Study Drug	10 (6%)	9 (6%)
Adverse event	4 (3%)	3 (2%)
Does not meet randomization criteria	1 (< 1%)	0
Other	4 (3%)	5 (3%)
Protocol violation	1 (< 1%)	0
Withdrawn consent	0	1 (< 1%)
Completed treatment	145 (91%)	133 (85%)

Medical Officer Comment

The number of patients that discontinued due to an adverse event related to the study drug was greater in the Augmentin™ treatment arm. This will be further addressed in more detail in the safety assessment section (Section 1.5).

1.3.7.3 Primary Analyses

Utilizing the criteria identified above in the section 1.3.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

1. Clinical

In the trovafloxacin treatment arm, 166 patients were randomized but only 160 were treated. One (1) had incorrect administration of study drug, therefore, only 165 were including in the clinical intent-to-treat group. Of these, ten (10) were not clinically evaluable leaving only 155 clinically evaluable.

In the Augmentin™ treatment arm, 157 were randomized, but only 156 were treated, One patient had incorrect administration of study drug, leaving only 155 in the clinical intent-to-treat group. The applicant indicates that of the treated patients, 10 were not evaluable, therefore 146 patients constitutes the clinically evaluable group for this treatment arm.

2. Bacteriological

Of the 155 clinically evaluable group in the trovafloxacin arm, 32 patients were excluding from the bacteriologically evaluable analyses due to the lack of a baseline culture. Therefore, the bacteriologically evaluable group consisted of 123 patients.

In the Augmentin™ treatment arm, 38 patients from the clinically evaluable group (N=146) lacked baseline culture information, therefore the bacteriologically evaluable group consisted of 108 patients.

Efficacy results

As was done in Study 154-131, the applicant performed several analyses comparing the results of the investigator-defined response rates for clinical success, with the applicant-defined clinical response rates. These were done for both timepoints - end of treatment as well as end of study. The outcomes for the for the clinically intent-to-treat group were also analyzed.

1. Clinically evaluable

In the clinically evaluable group of subjects, the applicant-defined clinical success rates (cure and improvement) were as follows: In the trovafloxacin arm, of the 155 in the clinically evaluable group, 154 were assessed at the end of treatment, with a success rate of 93%. In the Augmentin™ arm, of the 146 in the clinically evaluable group, 140 were assessed at the end of treatment, with a success rate of 93% [95% CI around the difference: (-5.9, 5.9)].

The applicant's analysis at the end-of-study timepoint reported the following: In the trovafloxacin arm, of the 155 in the clinically evaluable group, 139 were assessed, with a success rate of 86%. In the Augmentin™ arm, of the 146 in the clinically evaluable group, 141 were assessed at the end of study, with a success rate of 86% [95% CI around the difference: (-8.4, 8.0)].

The following table, adapted from Table D in the applicant's submission, summarizes the clinical response rate for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)					
	Trovafloxacin 200 mg q d (N=155)		Augmentin™ 500 mg tid (N=146)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	154	(100%)	140	(100%)	
Success (Cure + Improvement)	143	(93%)	130	(93%)	(-5.9, 5.9)
Distribution of Clinical Response:					
Cure	49	(32%)	45	(32%)	
Improvement	94	(61%)	85	(61%)	
Failure	11	(7%)	10	(7%)	
End of Study:					
Number of Subjects Assessed	139	(100%)	141	(100%)	
Success (Cure + Improvement)	119	(86%)	121	(86%)	(-8.4, 8.0)
Distribution of Clinical Response:					
Cure	86	(62%)	81	(57%)	
Improvement	33	(24%)	40	(28%)	
Failure	11	(8%)	11	(8%)	
Relapse	9	(6%)	9	(6%)	
CI=confidence interval Ref.: Table 5.1.1 in the submission.					

2. *Clinical intent-to-treat*

The clinical intent-to-treat group analysis also showed equivalence between the two treatment groups. At the end of treatment, the trovafloxacin arm had a 88% success rate in 164 subjects assessed out of a possible 165; the Augmentin™ arm, 90% success rate in 149 subjects assessed out of a possible 156. The 95% confidence interval around the difference was (-9.1, 4.8).

At the end of study the trovafloxacin arm had a 82% success rate in 165 subjects assessed out of a possible 165; the Augmentin™ arm, 84% success rate in 156 subjects assessed out of a possible 156. The 95% confidence interval around the difference was (-9.7, 6.6).

Medical Officer Comment

The assessment of the clinical response differed between the applicant and the investigator for several patients at the end of study. There were 11 patients in the trovafloxacin group and 10 patients in the Augmentin™ group. In each of these cases, the applicant assigned a more conservative assessment.

The 95% confidence interval around the difference supported the applicant's claim of equivalence.

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3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Proteus mirabilis*. In the clinically evaluable subjects, the response rates were comparable between the two arms, although it was noted that trovafloxacin tended to do a little better than Augmentin™ against *Pseudomonas aeruginosa*, but a little worse than Augmentin™ against *Enterococcus faecalis*. The following table is reproduced from the Study Report (Table F):

Most frequently isolated baseline pathogens^a

Pathogen	Trovafloxacin 200 mg (N=155)	Augmentin 500 mg TID (N=146)	Trovafloxacin 200 mg (N=155)	Augmentin 500 mg TID (N=146)
	Number of Subjects			
	End of Treatment		End of Study	
<i>S. aureus</i>	56/59 (95%)	52/58 (90%)	48/54 (89%)	48/56 (86%)
<i>P. aeruginosa</i>	21/21 (100%)	14/15 (93%)	18/20 (90%)	12/15 (80%)
<i>E. faecalis</i>	15/16 (94%)	11/11 (100%)	13/14 (93%)	13/13 (100%)
<i>P. mirabilis</i>	14/15 (93%)	5/5 (100%)	12/13 (92%)	6/6 (100%)
<i>S. epidermidis</i>	6/8	8/10	4/6	8/10
<i>E. coli</i>	8/9	5/5	7/9	5/5
<i>K. oxytoca</i>	7/7	5/5	5/6	5/5
<i>Staphylococcus sp.</i>	4/5	4/4	3/4	4/4
<i>S. haemolyticus</i>	0/1	1/1	0/1	1/1
<i>S. hominis</i>	1/1	3/3	1/1	3/3
<i>S. saprophyticus</i>	0/0	1/1	0/0	1/1
Coagulase Negative <i>Staphylococcus</i>	0/0	1/1	0/0	1/1
<i>Streptococcus sp.</i>	0/1	2/4	0/1	2/4
Anaerobic <i>Streptococcus</i>	1/1	0/0	1/1	0/0
<i>S. agalactiae</i>	7/8	5/5	5/8	4/5
<i>S. anginosus</i>	1/1	0/0	1/1	0/0
<i>S. equisimilis</i>	5/5	3/3	2/2	3/3
<i>S. oralis</i>	1/1	0/0	1/1	0/0
<i>S. pyogenes</i>	4/4	6/6	2/2	6/6
Group A Beta <i>streptococcus</i>	0/0	2/2	0/0	2/2
Group B Beta <i>streptococcus</i>	0/0	1/1	0/0	0/1
Group G Beta <i>streptococcus</i>	4/4	0/0	1/2	0/0
Beta hemolytic <i>streptococcus</i>	0/0	1/1	0/0	1/1
<i>Peptostreptococcus sp.</i>	0/0	2/2	0/0	2/2
<i>P. prevotti</i>	0/1	2/2	0/1	2/2
<i>P. magnus</i>	0/0	2/2	0/0	2/2

a ≥5 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15 at least once for a given pathogen in either treatment group. A subject could have had more than one pathogen isolated at baseline.
Ref.: Table 5.3.1

Similar results were noted among clinical intent-to-treat subjects.

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Medical Officer Comment

This study is supportive of the applicant's claim for treatment of complicated infections due to the following organisms: *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*. Although the study did not have many patients with *Streptococcus agalactiae*, the clinical response observed in this study was consistent with the other two studies, and therefore, supportive. In addition, this study was also supportive of trovafloxacin's efficacy against *Escherichia coli*.

This study reported 8 patients with *Staphylococcus epidermidis* as the baseline pathogen in the trovafloxacin treatment group, but as with the other studies, there was a paucity of bacteriologically evaluable patients with pure *S. epidermidis* cultures. Therefore, this

study was not able to support the applicant's claim of efficacy against this potential pathogen.

1.3.7.4 Additional Analyses

The applicant also performed the following analyses:

1. Clinical response stratified by type of infection at baseline.
2. Clinical response stratified by timing of surgical intervention.
3. Presence and severity of clinical signs/symptoms at baseline, end-of-treatment, and end-of-study.

Medical Officer Comment

The results were comparable for the three analyses between the two arms.

1.4 Efficacy Summary

The applicant provided data from three studies to support their claim of efficacy in the treatment of complicated skin and skin structure infections, including diabetic foot infections. The pivotal study was 154-131, a multi-center, randomized, double-blind study using Zosyn™, followed by Vantin™, as the comparator treatment. The other studies were supportive, with 154-132 being an open-labeled, uncontrolled study in diabetic patients, and 154-139 being a multi-center, randomized, open-labeled, controlled study using Augmentin™ as the comparator.

The following summarizes the observations made regarding the three studies:

- 1) The combination of alatrovafloxacin/trovafloxacin demonstrated similar efficacy to the combination of Zosyn™ and Vantin™. This equivalence was seen at the end of study, as well as at the end of treatment visits.
- 2) The alatrovafloxacin/trovafloxacin treatment combination appears to have more toxicity associated with it than the comparator arm. The more common side effects particular to this treatment group were dizziness and injection site complications. This will be expanded upon in the safety section (see below).
- 3) Based on the number of patients studied in the three studies, the applicant was able to support the claim of efficacy against the following pathogens: *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, and *Proteus mirabilis*.

1.5 Safety Assessment

1.5.1 Integrated Safety Assessment

It is acknowledged that the patient population between the three studies were not exactly alike. However, it is believed that they were similar enough in demographic characteristics, baseline diagnoses, and disease severity that it may be possible to evaluate the safety profile for the three studies simultaneously.

1.5.2 Extent of Drug Exposure

The applicant reported the following amounts of subject-day exposures.

	Study 154-131	Study 154-132	Study 154-139
	Alatrofloxacin to Trovafoxacin (200 mg q d)	Zosyn™ (3.375 mg IV) to Vantin™ (400 mg bid)	Trovafoxacin (200 mg q d)
Subject-days of exposure	1445	1622	2882
			Trovafoxacin (200 mg q d)
			Augmentin™ (500 mg tid)
			1978
			1914

1.5.3 Adverse Events

As noted above, there were some minor differences in the patient populations between the three studies, however it is believed that it would be useful to compare the three studies simultaneously.

1.5.3.1 All causalities

The following table summarizes the total number of adverse events (all causality) reported for the three studies:

Number of subjects ...	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafoxacin	Zosyn™/ Vantin™	Trovafoxacin	Trovafoxacin	Augmentin™
who were treated	144	142	225	160	156
with at least 1 AE*	101 (70%)	98 (69%)	74 (33%)	54 (34%)	53 (34%)
with serious AE's	22 (15%)	24 (17%)	10 (4%)	9 (6%)	5 (3%)
with severe AE's	21 (15%)	18 (13%)	4 (2%)	9 (6%)	5 (3%)
who discontinued due to AE's	29 (20%)	8 (6%)	8 (4%)	9 (6%)	16 (10%)
with dose reductions/ temp. discontinuation due to AE's	4 (3%)	3 (2%)	1 (<1%)	3 (2%)	5 (3%)
who discontinued due to objective test findings	3 (2%)	2 (1%)	0	0	0

*AE - Adverse event

There were no patients in any study who had a dose reduction or temporary discontinuation due to objective test findings.

Adapted from Table 6.1 of the applicant's submission

Medical Officer Comments

The oral studies (154-132 and 154-139) were comparable in the number of serious and severe adverse events observed, and in the number of discontinuations due to adverse events. Study 154-131, which had an intravenous administration component, had a higher incidence of in almost all categories. It is noted that the increased incidence was comparable in both arms of 154-131, except for the number of discontinuations due to adverse events, which was disproportionately higher in the trovafloxacin treatment arm. The types of adverse events reported by body system are enumerated further on in this review.

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The type of adverse event, by WHO term classification are summarized in the following table, adapted from the respective "All-Causalities Adverse Events" tables from the Study Reports:

Most Commonly Reported Adverse Events by Body System - All Causalities

	Study 154-131 a,b,c,d		Study 154-132 b, d, e		Study 154-139 b, d, f	
	Alatrofloxacin/ Trovafoxacin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafoxacin (N=225)	Trovafoxacin (N= 160)	Augmentin™ (N=156)	
No. of subjects with at least one adverse event	101 (70%)	98 (69%)	74 (33%)	54 (34%)	53 (34%)	
Body System (WHO Terminology)						
APPL./INJ./INCISION/ INSERTION SITE	17 (12%)	8 (6%)	--	--	--	--
-Appl./inj./Incision/Insertion Site Reaction	11 (8%)	1 (<1%)	--	--	--	--
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	29 (20%)	26 (18%)	26 (12%)	19 (12%)	4 (3%)	
Headache	17 (12%)	15 (11%)	5 (2%)	5 (3%)	2 (1%)	
Dizziness	--	--	20 (9%)	12 (8%)	1 (<1%)	
GASTROINTESTINAL SYSTEM	49 (34%)	48 (34%)	25 (11%)	19 (12%)	35 (22%)	
Constipation	22 (15%)	7 (5%)	--	5 (3%)	1 (<1%)	
Diarrhea	7 (5%)	17 (12%)	--	2 (1%)	23 (15%)	
Nausea	20 (14%)	23 (16%)	9 (4%)	5 (3%)	9 (6%)	
Vomiting	10 (7%)	11 (8%)	--	3 (2%)	4 (3%)	
Dyspepsia	--	--	5 (2%)	--	--	--
Abdominal pain	--	--	--	3 (2%)	8 (5%)	
GENERAL	27 (19%)	26 (18%)	14 (6%)			
Infection (aggravated)	9 (6%)	2 (1%)	--	9 (6%)	6 (4%)	
Fever	--	--	5 (2%)	4 (3%)	0	
PSYCHIATRIC	15 (10%)	10 (7%)	--	--	--	--
Insomnia	4 (3%)	8 (6%)	--	--	--	--
REPRODUCTIVE SYSTEM	3 (2%)	8 (6%)	--	--	--	--
Vaginitis ^e	3 (5%)	6 (11%)	--	--	--	--
SKIN/APPENDAGES	24 (17%)	15 (11%)	14 (6%)	--	--	--
Pruritus	7 (5%)	6 (4%)	4 (2%)	--	--	--

^a ≥5 % of subjects in either treatment group.

^b Includes data up to 7 days after last dose of active study medication.

^c Term is gender specific, and the percentages are based on the number of females.

^d Ref.: Tables 6.2 and 6.4 in the submission

^e ≥2 % of subjects

^f ≥3 % of subjects in either treatment group.

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Medical Officer Comment

Although the number of subjects that experienced at least one adverse event in Study 154-131 was comparable between the two arms, it is noted that a disproportionate number of trovafloxacin patients had insertion site adverse events. This is despite the fact that Zosyn was a thrice daily intravenous administration, and trovafloxacin was only once daily. The other notable observation is that a disproportionate number of trovafloxacin patients in Study 154-139 complained of dizziness. This particular adverse event was also noted in Study 154-132, but its incidence was not as high in Study 154-131. It is hypothesized that the patients in Study 154-131 were more likely to be hospitalized, and that this particular adverse event was not as prominent - perhaps because they were not as ambulatory as the patients in the other studies.

1.5.3.2 Treatment related

The treatment related adverse events reported are summarized in the table below:

Most Commonly Reported Adverse Events by Body System - Treatment Related

No. of subjects with at least one adverse event Body System (WHO Terminology)	Study 154-131 a,b,c,d		Study 154-132 b, d, e		Study 154-139 b, d, e		
	Alatrofloxacin/ Trovafoxacin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafoxacin (N=225)	Trovafoxacin (N=160)	Trovafoxacin (N=160)		Augmentin™ (N=156)
APPL./INJ./INCISION/ INSERTION SITE	39 (27%)	37 (26%)	37 (16%)	25 (16%)	36 (23%)		
Appl./Inj./Incision/Insertion Site Pain	9 (6%)	4 (3%)	--	--	--	--	--
Appl./Inj./Incision/Insertion Site Reaction	4 (3%)	2 (1%)	--	--	--	--	--
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	7 (5%)	0	22 (10%)	14 (9%)	1 (<1%)		
Headache	11 (8%)	8 (6%)	5 (2%)	4 (3%)	0		
Dizziness	8 (6%)	7 (5%)	18 (8%)	8 (5%)	1 (<1%)		
GASTROINTESTINAL SYSTEM	4 (3%)	1 (<1%)	16 (7%)	11 (7%)	31 (20%)		
Constipation	15 (10%)	19 (13%)	--	3 (2%)	0		
Diarrhea	--	--	--	1 (<1%)	22 (14%)		
Nausea	5 (3%)	12 (8%)	6 (3%)	4 (3%)	7 (4%)		
Vomiting	8 (6%)	5 (4%)	--	2 (1%)	4 (3%)		
Abdominal pain	--	--	--	2 (1%)	8 (5%)		
REPRODUCTIVE SYSTEM	3 (2%)	4 (3%)	--	--	--		
Vaginitis ^e	3 (5%)	4 (7%)	--	--	--		

- ^a ≥3 % of subjects in either treatment group.
- ^b Includes data up to 7 days after last dose of active study medication.
- ^c Term is gender specific, and the percentages are based on the number of females.
- ^d Ref.: Tables 6.3 and 6.5 in the submission
- ^e ≥2 % of subjects

Medical Officer Comment

Several of the adverse events noted in the previous table have dropped out, as one would expect, however, the overall impressions regarding the intravenous administration in Study 154-131 and the dizziness in the oral studies are unchanged. It is also noted that dizziness was still reported in Study 154-131, but the incidence was much lower.

1.5.3.3 Serious adverse events

The number of serious adverse events per study are summarized in the table below:

No. of subjects with serious adverse events No. of subjects with serious adverse events - treatment related	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafoxacin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafoxacin (N=225)	Trovafoxacin (N=160)	Augmentin™ (N=156)
	30 (21%)	39 (27%)	17 (8%)	12 (8%)	7 (4%)
	3 (2%)	1 (<1%)	0	0	0

Medical Officer Comment

This summary is supportive of the observations made in the previous two tables - a higher incidence and a greater severity of adverse events were reported in Study 154-131. It is noted, however, that the investigators felt that most of the serious adverse events were not study drug related.

1.5.3.4 Discontinuation from studies

1.5.3.4.1 Discontinuation due to adverse events

The number of patients that discontinued due to adverse events are summarized below:

	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafloracin (N=144)	Zosyn™/ Vantin™ (N=142)	Trovafloracin (N=225)	Trovafloracin (N= 160)	Augmentin™ (N=156)
No. of subjects discontinued due to adverse events	29 (20%)	8 (6%)	8 (4%)	9 (6%)	16 (10%)
No. of subjects discontinued due to adverse events - treatment related	13 (9%)	3 (2%)	3 (1%)	4 (3%)	13 (8%)
Temporary discontinuations	5 (3%)	3 (2%)	1 (<1%)	3 (2%)	5 (3%)

Medical Officer Comment

In Study 154-131, the most common treatment related adverse event that resulted in discontinuation in the trovafloracin group were insertion site pain/reaction, dizziness, flushing/hot flushes, headache, and nausea.

1.5.3.4.2 Discontinuation due to laboratory abnormalities

The following table summarizes the incidence of significant laboratory abnormalities, with special emphasis on liver enzymes, creatinine, and hemoglobin.

	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafloracin (N=137)	Zosyn™/ Vantin™ (N=139)	Trovafloracin (N=221)	Trovafloracin (N= 158)	Augmentin™ (N=149)
No. of subjects with clinically significant lab. abnormalities	61 (45%)	63 (45%)	66 (30%)	50 (32%)	48 (32%)
Liver enzyme abnormalities	14 (10%)	12 (9%)	6 (3%)	3 (2%)	1 (<1%)
Creatinine abnormalities	5 (4%)	4 (3%)	5 (2%)	1 (<1%)	1 (<1%)
Decrease in hemoglobin	12 (9%)	11 (8%)	5 (2%)	3 (2%)	3 (2%)
No. of subjects discontinued due to lab. abnormalities	1 (<1%)	1 (<1%)	0	0	0

Medical Officer Comment

The number of subjects in each of the treatment groups has changed because the applicant corrected these totals for baseline laboratory abnormalities. The laboratory abnormalities were slightly higher in the intravenous study, but they were comparable between the treatment arms.

1.5.3.5 Mortality experience

There were a total of 11 deaths in Study 143-131, and two (2) in each in the other two studies. The following table summarizes their distribution among the treatment arms.

	Study 154-131		Study 154-132	Study 154-139	
	Alatrofloxacin/ Trovafloracin	Zosyn™/ Vantin™	Trovafloracin	Trovafloracin	Augmentin™ M
Within 30 days of last dose of study drug	2	2	0	1	1
After 30 days of last dose of study drug	3	4	2	0	0

Medical Officer Comment

All case report forms of the patients that died were reviewed; this reviewer agrees that none of the deaths could be attributed to the study drug.

2. Uncomplicated Skin and Skin Structure Infection

2.1 Study 154-130

Title: A randomized, double-blind, multicenter trial comparing oral therapy with trovafloxacin (CP-99,219) (100 mg daily) and oral cefpodoxime proxetil (Vantin™)(400 mg bid) for the treatment of uncomplicated infections of the skin and skin structure.

Study Dates

1 June 1995 - 18 April 1996

2.1.1 Study Design and Objectives

A randomized, double-blind double-dummy, comparative, multicenter trial. The duration of treatment was 7-10 days. The treatment groups were:

1. Trovafloxacin, 100 mg/day, orally, as a single dose (1 x 100 mg tablet)
2. Cefpodoxime proxetil (Vantin™) 800 mg daily in two equally divided doses (2 x 200 mg capsules)

The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3	4
Study day	Day 1	Day 4	End Rx Day + 1	Day 30
Allowable window	(~48 hours)	(Day 3-5)	(Day 8-14)	(Day 28-35)
Treatment period	Day 1 to Day 7 or Day 10			
Follow-up period	Day 8 or 11 to Day 35			
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Microbiology				
exudate (or other specimen)	x	x	x	x ²
culture & sensitivity				
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test ¹	x			
Adverse events				
routine events		x	x	x
serious adverse events		x	x	x
Investigator's clinical evaluation ³		x ⁴	x	x

abn = abnormal at previous visitor clinically significant adverse event

¹ to be done by local site for women of childbearing potential

² to be done if clinically indicated

³ to be done at time of discontinuation, if applicable

⁴ this evaluation is used to determine if total length of therapy will be 7 or 10 days

The objective of this study was to compare the safety and efficacy of trovafloxacin to cefpodoxime in the treatment of uncomplicated infections of the skin and skin structures.

2.1.2 Eligibility Criteria

The following inclusion/exclusion criteria are reproduced from the applicant's submission.

Inclusion Criteria

1. Age greater than or equal to 18 years at baseline.
2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or ≤ 1 year post-menopausal) were to have had a negative pregnancy test prior to entry into the study, have used adequate contraception both during the study, and for one month after the end of treatment.
3. Clinically documented uncomplicated infection of the skin or skin structure.
4. Culturable material was to be obtained. In the case of cellulitis, a culture of an aspirate from the margin of the infected area was to be attempted, if no other culturable material was present.
5. Written informed consent.

Exclusion Criteria

1. Treatment with other antibiotics under the following conditions:
 - a. Treatment with any other systemic antibiotic for 24 hours or longer, within 72 hours prior to the baseline visit (unless there was documented evidence of clinical failure).
 - b. Treatment with a topical antibiotic within 24 hours prior to the baseline visit or during the study.
 - c. The need for treatment with an antibiotic other than the study drugs or treatment for longer than 14 days.
2. Skin or skin structure infection that requires extensive surgical intervention, or whose severity is sufficient to warrant initial intravenous antibiotic therapy.
3. Evidence of or history of significant gastrointestinal, hematological, neurologic, renal, cardiovascular, or immunological disease.

Medical Officer Comment

The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient No.	ID	Treatment arm	Type of deviation	Analyses performed by applicant					
				Clinical			Bacteriological		
				ITT	EOS Eval	EOS Eval	ITT	EOS Eval	EOS Eval
Inclusion criteria				--	--	--	--	--	--
5643-9004*		-----	No informed consent	Y	Y	Y	Y	Y	Y
5149-0633		Trovafloxacin	Age < 18	Y	Y	Y	Y	Y	Y
Exclusion criteria				Y	Y	Y	Y	Y	Y
5034-0668		Trovafloxacin	Known hypersensitivity to quinolones or beta-lactams	Y	Y	Y	N	N	NA
5733-0139		Trovafloxacin	Known hypersensitivity to quinolones or beta-lactams	Y	Y	Y	Y	Y	Y
5149-0268		Cefpodoxime	Known hypersensitivity to quinolones or beta-lactams	Y	Y	Y	Y	Y	Y
5017-0377		Trovafloxacin	Evidence of drug or alcohol abuse	Y	Y	Y	Y	Y	N
5553-0427		Trovafloxacin	Evidence of drug or alcohol abuse	Y	Y	Y	Y	Y	N
5034-0540		Trovafloxacin	Treated with systemic antibiotics for >24 hrs within 72 hours of baseline	Y	N	NA	N	N	NA
5817-0065		Cefpodoxime	Treated with systemic antibiotics for >24 hrs within 72 hours of baseline	Y	N	NA	Y	N	NA
5017-0554		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
5839-0238		Trovafloxacin	On chronic immunosuppressive therapy	Y	N	NA	Y	N	NA

*Patient 5643-9004 withdrew consent on the first day, never receiving any drug.

The case report forms were reviewed for all the patients that had an entry criteria protocol violation. Of the violations that had a potential to alter the clinical or bacteriological outcome, the medical reviewer felt that the violations were not significant enough, in quality or quantity, to have a significant impact on the overall study results.

2.1.3 Study Drugs and Randomization Method

A double-dummy technique was used to maintain blinding. Trovafloxacin tablets and cefpodoxime capsules were provided in blister packs. A computer-generated randomization list was provided to the investigator in the study and the patients were randomized in a 1:1 ratio to one of the following treatment arms:

Trovafloxacin - 100 mg daily as a single dose (1 x 100 mg tablet)

Cefpodoxime proxetil - 800 mg daily in two divided doses (2 x 200 mg capsules)

2.1.4 Study Endpoints

The primary endpoint was to be clinical response at the end of therapy. Clinical and bacteriological response at the end of study were to serve as secondary endpoints.

The definitions for clinical response, bacteriological response, and subject evaluability were the same as for Study 154-131, and will not be reproduced here.

Medical Officer Comment

As with the other studies performed in the complicated skin and skin structure infections patient population, the timepoint for clinical assessment preferred by the Division was the End of Study visit.

2.1.5 Termination and Follow-up

If the patient discontinued prior to the prescribed end of treatment, a final evaluation was to be performed. If the discontinuation was due to clinical failure, then the final clinical and microbiological evaluations were to be performed. If the discontinuation was due to adverse events, then appropriate therapeutic measures would be taken and the patient would be followed through Visit 4 (Day 30), with performance of all clinical and microbiological evaluations.

2.1.6 Sample Size and Statistical Plan

The study sought to prove equivalence of the study drug to the comparator, defined as having the 95% confidence interval around the point estimates of the difference between the two arms not be more than 10% (when the response rate of the reference drug is 90% or better).

Based on the premise that the reference drug had a 95% efficacy rate, the applicant calculated that the number of evaluable patients that would be needed 75 subjects per treatment arm. This would ensure with 80% probability that the lower limit of the 95% confidence interval for the true difference in efficacy is greater than -10%. Further, the applicant assumed that 10 to 20% of the patients would be non-evaluable, therefore, they anticipated that at least 90 patients/arm would need to be enrolled to protect the power of the study.

The Cochran-Mantel-Haenzel Test was also used to control for center effect.

2.1.7 Study Results

2.1.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 446 patients were randomized to therapy - 221 to the trovafloxacin arm, and 225 to the Cefpodoxime (Vantin™) treatment group. Every patient that was randomized received therapy. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

Demographic characteristics of treated Subjects

	Trovafloracin 100 mg q d			Vantin™ 400 mg bid		
	Male	Female	Total	Male	Female	Total
Number of Subjects	127	94	221	118	107	225
Age (yr)						
16-44	68 (54%)	40 (43%)	108 (49%)	65 (55%)	53 (50%)	118 (52%)
45-64	36 (28%)	30 (32%)	66 (30%)	34 (29%)	35 (33%)	69 (31%)
>=65	23 (18%)	24 (26%)	47 (21%)	19 (16%)	19 (18%)	38 (17%)
Mean	44.8	49.7	46.9	45.6	45.6	45.6
Minimum						
Maximum						
Race						
White	99 (78%)	56 (60%)	155 (70%)	90 (76%)	62 (58%)	152 (68%)
Hispanic	15 (12%)	23 (24%)	38 (17%)	14 (12%)	26 (24%)	40 (18%)
Black	11 (9%)	15 (16%)	26 (12%)	12 (10%)	16 (15%)	28 (12%)
Asian	2 (2%)	0	2 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
Mixed Hispanic/Native	0	0	0	1 (<1%)	0	1 (<1%)
Native American	0	0	0	0	1 (<1%)	1 (<1%)
South American Indian	0	0	0	0	1 (<1%)	1 (<1%)

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In addition, the type of skin infections present at baseline are summarized in the table below (Table B from the applicant's Study Report):

Table A. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects				
	Trovafoxacin 100 mg (N=221)		Vantin 400 mg BID (N=225)	
Type of Infection^a	Number and Percentage (%) of Subjects			
Simple Abscess	50	(23%)	56	(25%)
Impetiginous Lesion	15	(7%)	17	(8%)
Furuncle	22	(10%)	21	(9%)
Minor Wound Infection	52	(24%)	37	(16%)
Cellulitis with a Baseline Pathogen	32	(14%)	40	(18%)
Cellulitis without a Baseline Pathogen	25	(11%)	17	(8%)
Other	34	(15%)	52	(23%)
Subjects Requiring Surgical Intervention ^b	59	(26%)	72	(32%)
At Baseline	54	(24%)	68	(30%)
Post-Baseline ^c	4	(1%)	7	(3%)
Before the EOT Assessment	3	(1%)	6	(2%)
After the EOT Assessment	1	(<1%)	1	(<1%)

EOT = End of Treatment

a A subject may have had more than one type of infection.

b Two subjects in the trovafoxacin group (Subjects 5531-0463 and 5606-0359) and two subjects in the Vantin group (Subjects 5531-0340 and 5553-0426) had a surgical procedures done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report forms.

c One subject (5017-0377) in the trovafoxacin group and five subjects (5013-0443, 5125-0283, 5177-0438, 5553-0511, and 5816-0286) in the Vantin group had surgical drainage procedures performed both prior to and post-baseline.

Ref.: Tables 2.3 and 2.4 in the submission.

Medical Officer Comment

The demographic characteristics and baseline medical histories were comparable between the treatment groups. It was noted that there was a slight imbalance in the type of baseline diagnoses: more patients in the trovafoxacin treatment group had the diagnosis of "minor wound infection," and fewer had the diagnosis of "other." The first difference was not statistically significant, and the second marginally statistically significant. For additional details regarding the statistical issues, please refer to the Dr. Silliman's (the Division's Biometrics reviewer) review. Neither difference was felt to have had a significant clinical impact on the study.

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2.1.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

	Trovafloracin 100 mg	Cefpodoxime (Vantin™) 400 mg tid
Number of randomized subjects	221	225
Randomized not treated	0	0
Number of treated subjects	221	225
Withdrawn from treatment	16 (7%)	20 (9%)
Withdrawn from study when treatment stopped	4 (2%)	16 (7%)
Withdrawn from treatment but completed study	12 (5%)	4 (2%)
Completed treatment	205 (93%)	205 (91%)
Withdrawn from study during follow-up	5 (2%)	5 (2%)
Completed treatment and study	200 (90%)	200 (89%)

Of the patients that were discontinued while on treatment, a total of 16 patients (7%) were discontinued from the trovafloxacin arm, and 20 (9%) discontinued from the Vantin™ arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table C of the Summary Report):

	Trovafloracin 100 mg q d	Vantin™ 400 mg bid
Number of Treated Subjects	221	225
Discontinued Subjects	16 (7%)	20 (9%)
Related to Study Drug	10 (5%)	8 (4%)
Adverse event	6 (3%)	6 (3%)
Insufficient response	4 (2%)	2 (<1%)
Not Related to Study Drug	6 (3%)	12 (5%)
Adverse event	0	4 (2%)
Lost to follow-up	0	5 (2%)
Other	3 (1%)	1 (<1%)
Patient died	0	1 (<1%)
Protocol violation	1 (<1%)	0
Withdrawn consent	2 (<1%)	1 (1%)
Completed treatment	205 (93%)	205 (91%)

Medical Officer Comment

The patient disposition was comparable between the treatment groups.

2.1.7.3 Primary Analyses

Utilizing the criteria described in section 2.2.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

1. *Clinical*

In the 221 subjects in the trovafloxacin treatment arm, 10 were not clinically evaluable. In the 225 patients in the Vantin™ arm, 17 were not clinically evaluable. The most common reason was insufficient therapy (6 in the trovafloxacin arm, and 13 in the Vantin™ arm), as well as prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical assessment, and no post-baseline clinical assessment in the evaluable window

2. *Bacteriological*

Of the 211 clinically evaluable trovafloxacin patients, and 208 clinically evaluable Vantin™ patients, 44 and 46 were not included in the bacteriologically evaluable population, respectively. The predominant reason was lack of a baseline pathogen.

The following table summarizes the number of evaluable patients in each category, for each treatment arm:

	Trovafloracin	Vantin
Number Randomized	221	225
Not treated	0	0
Treated patients	221 (100%)	225 (100%)
Negative baseline cultures	45 (20%)	50 (22%)
Bacteriological Intent-to-Treat	176 (80%)	175 (78%)
Clinically Evaluable	211 (95%)	208 (92%)
Negative baseline cultures	43 (19%)	46 (20%)
No post-baseline culture	1 (<1%)	0
Bacteriologically Evaluable	167 (76%)	162 (72%)

Efficacy Results

The applicant performed several analyses comparing the results of the investigator-defined response rates and the applicant defined response rates. This was done for both timepoints - at the end-of-treatment and at the end-of-study visits. In addition, the patient subgroups analyzed included the clinically intent-to-treat, clinically evaluable, and bacteriologically evaluable patients.

1. Clinically Evaluable

The following table, adapted from Table D in the applicant's submission, summarizes the clinical response rates for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)			
	Trovafloracin 100 mg (N=211)	Vantin™ 400 mg BID (N=208)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment			
Number of Subjects Assessed	207 (100%)	207 (100%)	
Success (Cure + Improvement)	194 (94%)	192 (93%)	(-3.9, 5.8)
Distribution of Clinical Response:			
Cure	114 (55%)	100 (48%)	
Improvement	80 (39%)	92 (44%)	
Failure	13 (6%)	15 (7%)	
End of Study			
Number of Subjects Assessed	204 (100%)	194 (100%)	
Success (Cure + Improvement)	179 (88%)	168 (87%)	(-5.4, 7.7)
Distribution of Clinical Response:			
Cure	152 (75%)	137 (71%)	
Improvement	27 (13%)	31 (16%)	
Failure	13 (6%)	15 (8%)	
Relapse	12 (6%)	11 (6%)	
CI=confidence interval Ref.: Table 5.1.1 in the submission			

2. Clinical intent-to-treat

The clinically intent-to-treat group analysis yielded similar results: At the end of treatment, the trovafloracin arm had a 93% success rate in 217 subjects assessed out of a possible 221; the Vantin™ arm, 88% success rate in 224 subjects assessed out of a possible 225. The 95% confidence interval around the difference was (-0.3, 10.6).

At the end of study the trovafloxacin arm had a 87% success rate in 221 subjects assessed out of a possible 221; the Vantin™ arm, 83% success rate in 225 subjects assessed out of a possible 225. The 95% confidence interval around the difference was (-2.4, 10.8).

Medical Officer Comment

Both analyses support the applicant's claim for therapeutic equivalence compared to Vantin™ in for this indication.

3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. In the clinically evaluable subjects, the response rate was comparable between the treatment arms. The following table is reproduced from the Study Report (Table F):

Most frequently isolated baseline pathogens^a

Pathogen	Trovafloracin 100 mg (N=211)	Vantin™ 400 mg BID (N=208)	Trovafloracin 100 mg (N=204)	Vantin™ 400 mg BID (N=194)
	Number of Subjects			
	End of Treatment		End of Study	
<i>S. aureus</i>	71/76 (93%)	59/64 (92%)	63/73 (86%)	53/60 (88%)
<i>S. epidermidis</i>	30/34 (88%)	27/29 (93%)	30/35 (86%)	24/27 (89%)
<i>P. aeruginosa</i>	15/15 (100%)	8/8	15/15 (100%)	7/8 (88%)
<i>E. faecalis</i>	13/13	13/13	12/13	10/13
<i>E. coli</i>	5/5	10/11	5/5	10/11
<i>Staphylococcus spp.</i>	10/10	2/2	9/10	2/2
<i>S. haemolyticus</i>	10/10	10/11	10/10	9/10
<i>S. hominis</i>	4/5	4/4	3/5	4/4
<i>S. simulans</i>	1/1	5/5	1/1	4/5
Coagulase Negative staphylococci	0/0	2/2	0/0	1/1
<i>Streptococcus sp.</i>	6/6	6/7	3/4	5/7
<i>S. agalactiae</i>	8/9	10/13	8/10	9/12
<i>S. aginosus</i>	2/2	0/0	2/2	0/0
<i>S. mitis</i>	1/1	0/0	1/1	0/0
<i>S. pyogenes</i>	9/9	6/6	9/9	5/5
<i>S. sanguis I</i>	0/0	1/1	0/0	1/1
<i>S. sanguis II</i>	1/1	2/2	1/1	1/2
Group G Beta streptococci	2/2	1/1	2/2	1/1
Alpha haemolytic streptococci	0/0	1/1	0/0	1/1

a ≥10 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.
Ref.: Table 5.3.1 in the submission.

Medical Officer Comment

Trovafloracin demonstrated good response rates against *Staphylococcus aureus* and *Staphylococcus epidermidis*, comparable to the comparator treatment group:

For *S. aureus* - 93% (trovafloracin) vs. 92% (cefepodoxime) at the end of treatment; 86% (trovafloracin) vs. 88% (cefepodoxime) at the end of study.

For *S. epidermidis* - 88% (trovafloracin) vs. 93% (cefepodoxime) at the end of treatment; 86% (trovafloracin) vs. 89% (cefepodoxime) at the end of study.

2.1.7.4 Secondary Analyses

The applicant also performed the following analyses:

1. Clinical response by type of infection at baseline
2. Clinical response by timing of surgical intervention.
3. Presence of signs and symptoms.

Medical Officer Comment

The results were comparable between the treatment arms for the three analyses.

2.2 Study 154-129

Title: A randomized, double-blind, multicenter trial comparing oral therapy with trovafloxacin (CP-99,219) (100 mg daily) and flucloxacillin (500 mg qid) for the treatment of uncomplicated infections of the skin and skin structure.

Study Dates

10 July 1995 - 10 January 1996

2.2.1 Study Design and Objectives

A randomized, double-blind, double-dummy, comparative, multicenter trial. The duration of treatment was 7 days. The treatment groups were:

1. Trovafloxacin, 100 mg/day, as a single dose (1 x 100 mg tablet)
2. Flucloxacillin, 2000 mg daily, in four equally divided doses of 500 mg

The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3
Study day	Day 1	End Rx Day + 1	Day 30
Allowable window	(~48 hours)	(Day 8-14)	(Day 28-35)
Treatment period	Day 1 to Day 7		
Follow-up period	Day 8 to 11 to Day 35		
Informed consent	x		
Demographic information	x		
Physical examination	x		
Concomitant medication	x	x	x
Vital signs	x	x	x
Dosing record		x	x
Clinical signs & symptoms	x	x	x
Microbiology			
exudate (or other specimen)	x	x	x ²
culture & sensitivity			
Safety laboratory tests			
hematology	x	x	abn
biochemistry	x	x	abn
urinalysis	x		abn
Pregnancy test ¹	x		
Adverse events			x
Investigator's assessment of clinical response		x	x

abn = abnormal at previous visitor clinically significant adverse event

¹ to be done by local site for women of childbearing potential

² to be done if clinically indicated

³ to be done at time of discontinuation, if applicable

Medical Officer Comment

Although the table in the submission did not have anything denoted as Footnote # 3, it is believed that it was probably meant to clarify when the investigator's assessment was to be performed.

The objective of this study was to compare the safety and efficacy of trovafloxacin to flucloxacillin in the treatment of uncomplicated infections of the skin and skin structure.

2.2.2 Eligibility Criteria

The inclusion and exclusion criteria were similar to study 154-130 except that the age at entry could be as young as 16 years of age.

Medical Officer Comment

The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient No.	ID	Treatment arm	Type of deviation	Analyses performed by applicant					
				Clinical			Bacteriological		
				ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
Inclusion criteria									
5883-0197		Trovafloxacin	Target infection was a post-surgical infection	Y	Y	Y	Y	Y	Y
Exclusion criteria									
5867-0281*		Trovafloxacin	Treated with systemic antibiotics within 72 hours of baseline	Y	N	NA	N	N	NA
5272-0099		Trovafloxacin	Treated with a topical antibiotic within 24 hours of baseline	Y	Y	Y	N	N	A

*The study report indicates this patient identification number, however it does not appear in the data listings, nor is there a case report form for this patient. After review of the case report forms, it is believed that this represents a typographical error in the study report, i.e. a transposition of two digits in the identification number. It is believed that the patient identification number should be #5876-0281 - a patient that had been treated with systemic antibiotics and subsequently deemed unevaluable.

After review of the case report forms, it was that the protocol violations were not significant enough to potentially affect the patient's result, nor have a significant impact on the overall study results.

2.2.3 Study Drugs and Randomization Method

A double-dummy technique was used to maintain blinding. Trovafloxacin tablets and flucloxacillin capsules were provided in blister packs. The patients were randomized in a 1:1 ratio to one of the following treatment arms:

Trovafloxacin - 100 mg daily as a single dose (1 x 100 mg tablet)

Flucloxacillin - 2000 mg daily in four divided doses (1 x 500 mg capsules)

2.2.4 Study Endpoints

As with all the other studies for this indication, the primary efficacy endpoint was the clinical response at the end of therapy. The bacteriological response at the end of therapy, and the clinical and bacteriological responses at the end of study were secondary endpoints.

The definitions for the clinical response, bacteriological response, and subject evaluability were similar to Study 153-131, except for the following:

1. The bacteriological response classifications included "Eradication with Infection."
2. The evaluability criteria stipulated that a subject must receive at least 3 days of dosing.

Medical Officer Comment

As with all the other studies, the timepoint preferred by the Division for the primary efficacy endpoint was the end-of-study visit.

2.2.5 Termination and Follow-up

Visit # 2 was the end-of-treatment visit, at which time safety and efficacy assessments were performed. Patients were followed until Day 30 (Visit #3), which was considered the end-of-study visit, at which time end of study safety and efficacy assessments were repeated. If a subject was discontinued from therapy prior to the end of the study, they were still to be followed until Visit #3 for safety.

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2.2.6 Sample Size and Statistical Plan

Study sample size was calculated as before, with the intent to show equivalence to the comparator arm as previously defined. The applicant assumed an efficacy response rate of 95% for the reference drug, and determined that at least 90 subjects per treatment arm would need to be enrolled. This would allow for the potential loss of 10 to 20% of subjects, and still ensure with 80% probability that the lower limit of the confidence interval for the true difference in efficacy would not exceed 10%.

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2.2.7 Study Results

2.2.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 280 patients were randomized to therapy - 141 to the trovafloxacin arm, and 139 to the flucloxacillin treatment group. One patient in each treatment arm did not receive therapy. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

Demographic characteristics of treated Subjects

	Trovafoxacin 100 mg q d			Flucloxacllin 500 mg qid		
	Male	Female	Total	Male	Female	Total
Number of Subjects	69	71	140	70	68	138
Age (yr)						
16-44	41 (59%)	37 (52%)	78 (56%)	37 (53%)	30 (44%)	67 (49%)
45-64	20 (29%)	20 (28%)	40 (29%)	18 (26%)	19 (28%)	37 (27%)
>=65	8 (12%)	14 (20%)	22 (16%)	15 (21%)	19 (28%)	34 (25%)
Mean	42.1	46.0	44.1	46.5	48.3	47.3
Minimum						
Maximum						
Race						
White	69 (100%)	70 (99%)	139 (>99%)	68 (97%)	68 (100%)	136 (99%)
Asian	0	1 (<1%)	1 (<1%)	2 (3%)	0	2 (3%)

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In addition, the type of skin infections present at baseline are summarized in the table below (Table A from the applicant's Study Report):

Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects		
	Trovafoxacin 100 mg (N=141)	Flucloxacillin 500 mg QID (N=139)
Type of Infection ^a	Number and Percentage (%) of Subjects	
Simple Abscess	28 (20%)	24 (17%)
Impetiginous Lesion	23 (16%)	24 (17%)
Minor Wound	17 (12%)	21 (15%)
Cellulitis with a Baseline Pathogen	12 (9%)	19 (14%)
Cellulitis without a Baseline Pathogen	19 (13%)	19 (14%)
Otitis Externa	19 (13%)	19 (14%)
Paronychia	16 (11%)	11 (8%)
Leg Ulcers	8 (6%)	3 (2%)
Other	11 (8%)	12 (9%)
Subjects Requiring Surgical Intervention	18 (12%)	13 ^b (9%)
At Baseline	14 (9%)	9 (6%)
Post-Baseline	5 (3%)	3 (2%)
Before the EOT Assessment	4 (2%)	2 (1%)
After the EOT Assessment	1 (<1%)	1 (<1%)
EOT = End of Treatment		
a A subject may have had more than one type of infection.		
b Subject 6080-0239 had a surgical procedure done post-baseline. The type and timing of the procedure was not listed on the subject's case report form.		
Ref.: Tables 2.3 and 2.4 in the submission.		

Medical Officer Comment

The baseline demographics, baseline diagnoses, and baseline medical histories were comparable between the treatment arms.

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2.2.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial:

	Trovafoxacin 100 mg	Flucloxacillin 500 mg qid
Number of randomized subjects	141	139
Randomized not treated	1 (<1%)	1 (<1%)
Number of treated subjects	140	138
Withdrawn from treatment	12 (9%)	5 (4%)
Withdrawn from study when treatment stopped	5 (4%)	2 (2%)
Withdrawn from treatment but completed study	7 (5%)	3 (2%)
Completed treatment	128 (91%)	133 (96%)
Withdrawn from study during follow-up	1 (<1%)	2 (2%)
Completed treatment and study	127 (90%)	131 (94%)

Of the patients that were discontinued while on treatment, a total of 12 patients (9%) were discontinued from the trovafoxacin arm, and 5 patients (4%) discontinued from the flucloxacillin

arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table B of the Summary Report):

	Trovafloracin 100 mg q d	Flucloxacillin 500 mg qid
Number of Treated Subjects	140	138
Discontinued Subjects	12 (9%)	5 (4%)
Related to Study Drug	9 (6%)	4 (3%)
Adverse event	8 (6%)	3 (2%)
Insufficient clinical response	1 (<1%)	1 (<1%)
Not Related to Study Drug	3 (2%)	1 (<1%)
Adverse event	2 (1%)	0
Lost to follow-up	1 (<1%)	1 (<1%)
Completed treatment	128 (91%)	133 (96%)

Medical Officer Comment

More patients were withdrawn from the trovafloracin arm than the flucloxacillin arm, and more of these withdrawals were attributed to the study drug. This will be further addressed in the safety section of this review.

2.2.7.3 Primary Analyses

Utilizing the criteria described in section 2.2.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

1. Clinical

In the 141 subjects randomized to the trovafloracin treatment arm, 11 were not clinically evaluable; and in the flucloxacillin arm, 6 were not evaluable. The most common reason was insufficient therapy (8 in the trovafloracin arm and 4 in the flucloxacillin arm). Other reasons included randomized but not treated, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical assessment, and no post-baseline clinical assessment in the evaluable window.

2. Bacteriological

Of the 130 bacteriologically evaluable patients in the trovafloracin arm, only 76 patients were bacteriologically evaluable because of lack of baseline pathogen in 54 patients. In the flucloxacillin arm, 50 patients lacked baseline pathogens, therefore only 83 were bacteriologically evaluable.

The following table summarizes the number of patients in each of the categories:

	Trovafloracin	Flucloxacillin
Number Randomized	141	139
Not treated	1 (<1%)	1 (<1%)
Treated patients	140 (99%)	138 (99%)
Negative baseline cultures	60 (43%)	53 (38%)
Bacteriological Intent-to-Treat	80 (57%)	85 (61%)
Clinically Evaluable	130 (92%)	133 (96%)
Negative baseline cultures	54 (38%)	50 (36%)
Bacteriologically Evaluable	76 (54%)	83 (60%)

Efficacy Results

The applicant performed several analyses comparing the results of the investigator-defined response rates and the applicant defined response rates. This was done for both timepoints - at the end-of-treatment and at the end-of-study visits. In addition, the patient subgroups analyzed included the clinically intent-to-treat, clinically evaluable, and bacteriologically evaluable patients.

1. Clinically Evaluable

The following table, adapted from Table C in the applicant's submission, summarizes the clinical response rates for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)			
	Trovafoxacin 100 mg (N=130)	Flucloxacillin 500 mg QID (N=133)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment			
Number of Subjects Assessed ^a	129 (100%)	133 (100%)	
Success (Cure + Improvement)	117 (91%)	115 (86%)	(-3.4, 11.9)
Distribution of Clinical Response:			
Cure	72 (56%)	60 (45%)	
Improvement	45 (35%)	55 (41%)	
Failure	12 (9%)	18 (14%)	
End of Study			
Number of Subjects Assessed	125 (100%)	123 (100%)	
Success (Cure + Improvement)	106 (85%)	97 (79%)	(-3.6, 15.5)
Distribution of Clinical Response:			
Cure	97 (78%)	92 (75%)	
Improvement	9 (7%)	5 (4%)	
Failure	12 (10%)	18 (15%)	
Relapse	7 (6%)	8 (7%)	
CI=confidence interval			
a Subject 5895-0252 in the trovafoxacin group was not assessed at the end of treatment visit.			
Ref.: Table 5.1.1 in the submission.			

2. Clinical intent-to-treat

The clinically intent-to-treat group analysis yielded similar results: At the end of treatment, the trovafoxacin arm had a 88% success rate in 138 subjects assessed out of a possible 141; the flucloxacillin arm, 86% success rate in 139 subjects assessed out of a possible 139. The 95% confidence interval around the difference was (-5.9, 10.1).

At the end of study the trovafoxacin arm had a 83% success rate in 141 subjects out of a possible 141; the flucloxacillin arm, 79% success rate in 139 subjects out of a possible 139. The 95% confidence interval around the difference was (-5.3, 130.).

Medical Officer Comment

Both analyses support the applicant's claim for therapeutic equivalence compared to flucloxacillin in for this indication.

3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline was *Staphylococcus aureus*. In the clinically evaluable subjects, the response rate was comparable between the treatment arms. The following table is reproduced from the Study Report (Table E):

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Most frequently isolated pathogens^a

Pathogen	Trovafoxacin 100 mg (N=130)		Flucloxacillin 500 mg QID (N=133)		Trovafoxacin 100 mg (N=125)		Flucloxacillin 500 mg QID (N=123)	
	Number of Subjects							
	End of Treatment				End of Study			
<i>S. aureus</i>	39/42	(93%)	42/47	(89%)	34/40	(85%)	33/42	(79%)

a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.
 Ref.: Table 5.3.1 in the submission.

Medical Officer Comments

It is uncertain why this was the only baseline pathogen identified in this study. However, the findings are supportive of Study 154-130.

2.2.7.4 Secondary Analyses

Additional analyses performed by the applicant included:

1. Clinical response by type of infection at baseline.
2. Clinical response by timing of surgical intervention.
3. Presence of signs and symptoms.

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Medical Officer Comment

The findings were overall comparable between the treatment arms for the resolution of signs and symptoms. There were not enough patients in the surgical intervention subsets to be able to make any definitive conclusions. However, with regards to the baseline diagnoses, there appeared to be a trend for higher clinical success rate with trovafoxacin compared to flucloxacillin with respect to simple abscess. It was noted that in this study, trovafoxacin was less effective against leg ulcers, but the number of patients with this diagnosis was small.

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2.3 Efficacy Summary

For this indication, the pivotal study was 154-130, a multi-center, randomized, double-blind, controlled study, using cefpodoxime (Vantin™) as the comparator. The second study, 154-129, was entirely supportive in nature. It was a multi-center, randomized, unblinded, controlled study, and used flucloxacillin as the comparator, which is presently not approved for use in this country.

The findings of Study 154-130 support the applicant's claim of efficacy for trovafoxacin, at a dose of 100 mg per day, for 7-10 days, for the treatment of uncomplicated skin/skin structure infections due to *Staphylococcus aureus*.

In addition, the study provided evidence that trovafoxacin had demonstrated efficacy against *Streptococcus agalactiae*, but there were not enough patients studied. In view of the fact that this organism was evaluated in the complicated infections studies, and that the response rates were comparable to what was found in those studies, it is believed that Study 154-130 would have shown effectiveness against *Streptococcus agalactiae* if the frequency of isolation would have been greater. Therefore the recommendation is to include this organism in the list of organisms for this indication.

Furthermore, it is noted that trovafoxacin had shown efficacy against *Streptococcus pyogenes*, but again, there were a limited number of patients identified with this organism as a baseline pathogen. However, it is believed that this organism should be included in the list of organisms, citing the caveats identified in the Division's Points to Consider

document, which are referenced on page 4 of this review (Section A5: Regulatory Background).

With respect to the other organisms requested by the applicant, the number of patients identified with pure cultures for those organisms was not sufficient to adequately evaluate trovafloxacin's efficacy.

This was also true for *Staphylococcus epidermidis* (*S. epidermidis*), for which only 14 patients were deemed to be bacteriologically evaluable, out of an initial 17 patients identified as having pure cultures at baseline. However, *S. epidermidis* posed additional concerns because, although a potential pathogen, it is also a component of normal skin flora and a common culture contaminant. Therefore, whenever *S. epidermidis* is isolated from a culture, it becomes imperative to ascertain whether its role is as a pathogen or a contaminant in order to determine whether treatment is warranted.

It is believed that if *S. epidermidis* is included in the list of organism for this indication, there is a risk that it would be interpreted that trovafloxacin is indicated for the treatment of the isolation of *S. epidermidis* from skin cultures. Realizing that with human nature it is often natural to seek the path of least resistance, there is the potential that clinicians might find it easier to use trovafloxacin to "treat" the *S. epidermidis* that was isolated, rather than make a determination as to whether treatment is warranted. This could result in the inappropriate use of trovafloxacin, with all of the concerns that would accompany that situation - including the possibility of the development of microbial resistance.

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2.4 Safety Assessment

2.4.1 Integrated Safety Assessment

Since the baseline demographic data of the two studies were comparable enough to allow both studies were evaluated for safety simultaneously. As described in the study design section, the doses of trovafloxacin used in the uncomplicated studies was less than in the complicated studies.

2.4.2 Extent of Drug Exposure

The applicant reported the following amounts of subject-day exposures.

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	Study 154-129		Study 154-130	
	Trovafloxacin (100 mg q d)	Vantin™ (400 mg bid)	Trovafloxacin (100 mg q d)	Flucloxacillin (500 mg qid)
Subject-days of exposure	1954	1997	984	995

Medical Officer Comment

Within each study, the number of subject-day exposures were comparable between the treatment groups.

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2.4.3 Adverse Events

The following table summarizes information regarding the number of patients that experienced adverse events, and is adapted from Table 6.1 from the applicant's submission:

	Study 154-130		Study 154-129	
	Trovafloxacin	Vantin	Trovafloxacin	Flucloxacillin
Number of subjects . . . who were treated	221	225	140	138
with at least 1 AE*	71 (32%)	86 (38%)	31 (22%)	27 (20%)
with serious AE's	3 (1%)	5 (2%)	3 (2%)	0
with severe AE's	4 (2%)	8 (4%)	7 (5%)	1 (<1%)
who discontinued due to AE's	8 (4%)	11 (5%)	12 (9%)	3 (2%)
with dose reductions/ temp. discontinuation due to AE's	3 (1%)	0	1 (<1%)	4 (3%)
who discontinued due to objective test findings	0	0	0	0

*AE - Adverse event

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Medical Officer Comment

Overall, trovafloxacin compared favorably against the comparator arm. However, there were more dose reductions or temporary discontinuations due to adverse events in the

trovafloxacin arm compared to Vantin™, and more discontinuations due to adverse events in the trovafloxacin arm compared to flucloxacillin.

2.4.3.1 All causalities

The type of adverse event, by WHO term classification are summarized in the following table, adapted from the respective "All-Causalities Adverse Events" tables from the Study Reports:

Most Commonly Reported Adverse Events by Body System - All Causalities

	Study 154-130 a,b		Study 154-129 b,c	
	Trovafloxacin (N=221)	Vantin (N=225)	Trovafloxacin (N=140)	Flucloxacillin (N=138)
No. of Subjects With at Least One Adverse Event	71 (32%)	86 (38%)	31 (22%)	27 (20%)
Body System (WHO Terminology)				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM				
Dizziness	9 (4%)	6 (3%)	4 (3%)	1 (<1%)
Headache	14 (6%)	15 (7%)	5 (4%)	2 (1%)
GASTROINTESTINAL SYSTEM				
Abdominal Pain	5 (2%)	3 (1%)	--	--
Diarrhea	10 (5%)	20 (9%)	--	--
Dyspepsia	0 (0%)	4 (2%)	1 (<1%)	7 (5%)
Flatulence	0 (0%)	5 (2%)	--	--
Nausea	7 (3%)	9 (4%)	4 (3%)	4 (3%)
Vomiting	3 (1%)	4 (2%)	4 (3%)	2 (1%)
URINARY SYSTEM				
Urinary Tract Infection	--	--	2 (1%)	5 (4%)
GENERAL				
Fatigue	5 (2%)	4 (2%)	--	--
OTHER				
Accidental Injury	4 (2%)	1 (<1%)	--	--
SKIN/APPENDAGES				
Rash	4 (2%)	2 (<1%)	--	--

a ≥2 % of subjects in any treatment group.
 b Includes data up to 7 days after last dose of active study medication
 c ≥3 % of subjects in any treatment group.
 Ref.: Tables 6.2 and 6.4 in the submission

Medical Officer Comment

Dizziness was one of the more commonly reported adverse event, and consistently greater in the trovafloxacin treatment group. The other systemic category commonly affected was the gastrointestinal system.

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2.4.3.2 Treatment related

The following table is adapted from the treatment-related adverse event summary tables in the applicant's submission:

Most Commonly Reported Adverse Events by Body System - Treatment related

	Study 154-130 a,b		Study 154-129 a,b		Study 154-130 a,b		Study 154-129 a,b	
	Trovafoxacin (N=221)	Vantin (N=225)	Trovafoxacin (N=140)	Flucloxacillin (N=138)	Trovafoxacin (N=140)	Flucloxacillin (N=138)	Trovafoxacin (N=140)	Flucloxacillin (N=138)
No. of Subjects With at Least One Adverse Event	38 (17%)	48 (21%)	13 (9%)	18 (13%)	13 (9%)	18 (13%)	13 (9%)	18 (13%)
Body System (WHO Terminology)								
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	15 (7%)	10 (4%)	7 (5%)	0	7 (5%)	0	7 (5%)	0
Dizziness	7 (3%)	5 (2%)	3 (2%)	0	3 (2%)	0	3 (2%)	0
Headache	9 (4%)	3 (1%)	4 (3%)	0	4 (3%)	0	4 (3%)	0
GASTROINTESTINAL SYSTEM	14 (6%)	34 (15%)	7 (5%)	15 (11%)	7 (5%)	15 (11%)	7 (5%)	15 (11%)
Diarrhea	7 (3%)	18 (8%)	--	--	--	--	--	--
Dyspepsia	--	--	1 (<1%)	7 (5%)	1 (<1%)	7 (5%)	1 (<1%)	7 (5%)
Flatulence	0 (0%)	4 (2%)	--	--	--	--	--	--
Nausea	5 (2%)	7 (3%)	2 (1%)	3 (2%)	2 (1%)	3 (2%)	2 (1%)	3 (2%)
Vomiting	--	--	3 (2%)	2 (1%)	3 (2%)	2 (1%)	3 (2%)	2 (1%)
URINARY SYSTEM	--	--	2 (1%)	5 (4%)	2 (1%)	5 (4%)	2 (1%)	5 (4%)
Urinary Tract Infection	--	--	0 (0%)	4 (3%)	0 (0%)	4 (3%)	0 (0%)	4 (3%)

a ≥2 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication

Ref.: Tables 6.2 and 6.4 in the submission

Medical Officer Comment

This table highlights that dizziness remained a significant type of adverse event that was reported by the patients on the trovafoxacin treatment group. It was difficult to ascertain from the case report form as to the degree of severity of the dizziness, but the applicant indicates that no untoward events were reported in which dizziness was considered a precipitating factor.

APPEARS THIS WAY
ON ORIGINAL

2.4.3.3 Serious adverse events

The following table summarizes the number of serious events reported for the treatment arms in the two studies:

	Study 154-130		Study 154-129	
	Trovafoxacin (N=221)	Cefpodoxime (N=225)	Trovafoxacin (N=140)	Flucloxacillin (N=138)
No. of subjects with serious adverse events	5	8	3 (2%)	1 (<1%)
No. of subjects with serious adverse events - treatment related	0	1	0	0

Medical Officer Comment

The number of serious adverse events were comparable between the treatment groups.

2.4.3.4 Discontinuation from studies

2.4.3.4.1 Discontinuation due to adverse events

The following table summarizes the number of patients that were discontinued from the studies, and were adapted from the applicant's submission:

	Study 154-130		Study 154-129	
	Trovafloxacin (N=221)	Cefpodoxime (N=225)	Trovafloxacin (N=140)	Flucloxacillin (N=138)
No. of subjects discontinued due to adverse events	8 (4%)	11 (5%)	12 (9%)	3 (2%)
No. of subjects discontinued due to adverse events - treatment related	6 (3%)	6 (3%)	10 (7%)	3 (2%)
Temporary discontinuations	3	0	0	2 (1%)

Medical Officer Comment

The number of patients that discontinued due to adverse events (all-causality and treatment related) were comparable in the study against cefpodoxime (Vantin™). However, more patients discontinued for these reasons when compared to flucloxacillin. Although it is helpful to do cross-studies comparisons to evaluate for trends in type and/or incidences of adverse events, it is difficult to deduce a reason as to the possible reason for this observation. It is particularly difficult since the adverse event causality attribution is not always an objective finding and subject to the individual center's investigator's assessment.

APPEARS THIS WAY
ON ORIGINAL

2.4.3.4.2 Discontinuation due to laboratory abnormalities

The following table is adapted from the applicant's submission. The number of patients assessed in each treatment group has changed to account for the patients that baseline laboratory abnormalities:

	Study 154-130		Study 154-129	
	Trovafloxacin (N=210)	Cefpodoxime (N=208)	Trovafloxacin (N=128)	Flucloxacillin (N=132)
No. of subjects with clinically significant lab. abnormalities	28 (13%)	26 (13%)	21 (16%)	16 (12%)
Liver enzyme abnormalities	5 (2%)	2 (1%)	3 (2%)	1 (<1%)
Creatinine abnormalities	1 (<1%)	0	0	0
Decrease in hemoglobin	0	0	0	3 (2%)
No. of subjects discontinued due to lab. abnormalities	0	0*	0	0

*One subject was discontinued on Day 3 of the study due to a high baseline alkaline phosphatase value.

Medical Officer Comment

There were more patients in the trovafloxacin treatment group that experienced elevated liver enzymes, but were otherwise comparable to the comparators. Of the liver transaminases, two patients had elevations in alanine aminotransferase and two had elevations in aspartate aminotransferase. The overall incidence was felt to not be significant.

2.4.3.5 Mortality experience

There was one death reported for both studies. It was in Study 154-130, in the cefpodoxime (Vantin™) treatment group, on Day 7 of the study. Review of the case report form confirmed that it was not study-drug related.

C. Medical Reviewer Conclusions

The five studies provided in the NDA support the applicant's claim that alatrofloxacin and trovafloxacin are effective in treating complicated and uncomplicated infections of skin and skin structure, utilizing the applicant's dosage guidelines:

Skin and Skin Structure Infections, Complicated, including diabetic foot infections
200 mg oral or 200 mg I.V. followed by 200 mg oral for 10-14 days duration

Skin and Skin Structure Infections, Uncomplicated
100 mg oral for 7-10 days duration

APPEARS THIS WAY
ON ORIGINAL

However, due to the minimal data provided regarding certain pathogens in the uncomplicated studies, it is believed that it will not be possible to maintain the indication as presently written, combining the two types of infections for all the pathogens listed. Separation of the two types of infection would also maintain consistency with the Points to Consider document, which recommends separation. In addition, there should a statement in the label indicating that trovafloxacin has not been studied in the treatment of osteomyelitis. This caveat will be important in patients with complicated skin and skin structure infections, which included patients with diabetes mellitus.

It was also noted that although the alatrofloxacin/trovafloxacin treatment group had a higher incidence of adverse events and discontinuations in these studies, the cost/benefit ratio is in favor of the applicant's product in this patient population with this disease process. It is acknowledged that the incidence of adverse events noted in the uncomplicated skin/skin structure infection studies, except for the complaint of dizziness, was comparable between the treatment groups.

Therefore, the recommendation is for approval, with the condition that the label should be re-written as follows for this indication:

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

Complicated skin and skin structure infections, including diabetic foot infections, caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, or *Proteus mirabilis*. **Note:** Trovan™ has not been studied in the treatment of osteomyelitis. The safety and efficacy of Trovan™ given for > 4 weeks have not been studied.

TSI

Rigoberto A. Roca, M.D.
Reviewing Medical Officer
HFD-590

Concurrences:

/S/

Brad Leissa, M.D.
Medical Team Leader
Division of Special Pathogen and
Immunologic Drug Products

/S/

Mark Goldberger, M.D., M.P.H.
Division Director
Division of Special Pathogen and
Immunologic Drug Products

APPROVED FOR
SUBMITTAL

cc:
Original NDA 20-759/20-760
HFD-590/Div. Dir/Goldberger
HFD-590/Dep. Div. Dir/Albrecht
HFD-590/MTL/Leissa
HFD-590/MO/Roca
HFD-590/Chem/
HFD-590/Micro/
HFD-590/Pharmtox/
HFD-590/CSO/
HFD-880/Biopharm/

2.4.3.5 Mortality experience

There was one death reported for both studies. It was in Study 154-130, in the cefpodoxime (Vantin™) treatment group, on Day 7 of the study. Review of the case report form confirmed that it was not study-drug related.

C. Medical Reviewer Conclusions

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100 mg oral for 7-10 days duration

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However, due to the minimal data provided regarding certain pathogens in the uncomplicated studies, it is believed that it will not be possible to maintain the indication as presently written, combining the two types of infections for all the pathogens listed. Separation of the two types of infection would also maintain consistency with the Points to Consider document, which recommends separation. In addition, there should a statement in the label indicating that trovafloxacin has not been studied in the treatment of osteomyelitis. This caveat will be important in patients with complicated skin and skin structure infections, which included patients with diabetes mellitus.

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Therefore, the recommendation is for approval, with the condition that the label should be re-written as follows for this indication:

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

Complicated skin and skin structure infections, including diabetic foot infections, caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, or *Proteus mirabilis*. **Note:** Trovan™ has not been studied in the treatment of osteomyelitis. The safety and efficacy of Trovan™ given for > 4 weeks have not been studied.

- /S/

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APPROVED THIS WAY
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cc:
Original NDA 20-759/20-760
HFD-590/Div. Dir/Goldberger
HFD-590/Dep. Div. Dir/Albrecht
HFD-590/MTL/Leissa
HFD-590/MO/Roca
HFD-590/Chem/
HFD-590/Micro/
HFD-590/Pharmtox/
HFD-590/CSO/
HFD-880/Biopharm/

JUL 15 1998

NDA 20-759

Medical Review of Original NDA Indication: Uncomplicated Gonorrhea

Name of Drug: Trovan (trovafloxacin mesylate)

Name of Applicant: Pfizer Inc, East Point Road, Groton, CT 06340
(203) 441-4100

Date of NDA Submission: December 30, 1996

Date of Medical Review: October 17, 1997

INTRODUCTION:

The original NDA's for Trovan Tablets, NDA 20-759 and for Trovan IV (atrofloxacin mesylate injection), NDA 20-760, were submitted December 30, 1996 and the applicant requested approval for seventeen different indications:

nosocomial pneumonia, community acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis, complicated intra-abdominal infections (including post-surgical infections), gynecologic and pelvic infections (including post-surgical infections) surgical prophylaxis in colorectal surgery, vaginal and abdominal hysterectomy; uncomplicated and complicated skin and skin structure infections, uncomplicated bacterial prostatitis, uncomplicated gonorrhea, pelvic inflammatory disease, and

The review of these indications has been divided among several reviewers. This document summarizes the results of the medical review of the indication for UNCOMPLICATED GONORRHEA.

COMMENT:

In addition to completing the review of the indication, a second goal of this process was to learn and use the electronic version of the NDA submission to perform this review. However, based on several demonstrations, instruction sessions and attempts by other reviewers to use the electronic version of the SAS PH Clinical software, it was concluded that this particular electronic submission of data had severe limitations. Thus, the review was conducted using the paper submission of the study report, tables and related line summaries in Appendixes. In addition, the electronic version of some case report forms were examined; CRFs picked at random were examined and other CRFs were examined if specific questions about a given patient. In all, approximately 10% of the electronically-submitted CRF's were examined in part in or whole. Unfortunately, poor resolution of many CRF pages and especially of the ad hoc pages

of laboratory forms added to the case report forms made the review process unusually tedious. Even magnification of the images did not always allow resolution of data elements.

An interesting phenomenon was that sometimes a very poor image on the screen could be more easily discerned when the page was printed out. Other times the entry was still not legible (see examples in appendix to this report). However, as can be imagined, printing out CRF pages just to be able to read and check/verify a date of culture or a site of the specimen source is both a waste of time and paper.

The organization of the paper and electronic submission was good, however, the various subgroupings of patient data across multiple appendixes made review labor-intensive. Specifically, some lists or tables presented All Randomized patients, others All Trovafloxacin or All Ofloxacin patients, still others Trovafloxacin Female, Trovafloxacin Male, Ofloxacin Female and Ofloxacin Male. Then within these groupings, separate listings were presented for Evaluable patients, or Nonevaluable patients, etc. Thus trying to obtain an overall picture of the patient disposition, etc. involved flipping back and forth among multiple listings both in paper CRTs and electronic CRTs.

PROPOSED INDICATION:

The applicant is requesting approval of the following wording for the gonorrhea indication:

Acute, uncomplicated urethral, cervical, pharyngeal and rectal gonorrhea due to *Neisseria gonorrhoeae*, including both penicillinase- and non-penicillinase producing strains (See WARNINGS.)

Within the WARNINGS section, there is the class labeling statement,

Trovafloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

Under DOSAGE AND ADMINISTRATION, the proposed regimen for the treatment of uncomplicated gonorrhea is 100 mg of trovafloxacin, given as a single oral dose.

STUDIES SUBMITTED:

In support of the proposed labeling statements, the applicant has submitted results of two clinical trials.

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ON ORIGINAL

Study Report 154-120:

A randomized, multicenter, double-blind, double-dummy trial comparing single dose oral therapy of trovafloxacin (CP-99,219) (100 mg) with that of ofloxacin (400 mg) for the treatment of uncomplicated gonorrhea. In this trial, a total of 625 male and female patients were enrolled by 10 investigators. The applicant reports a bacterial efficacy of greater than 95% in the eradication of *Neisseria gonorrhoeae* from urethral and cervical sites. Information on some rectal and pharyngeal data were also presented.

Study Report 154-107:

An open randomized, non-comparative, single center dose-ranging study of trovafloxacin (CP-99,219) in the treatment of uncomplicated gonorrhea. In this single-center dose-ranging trial, 39 patients were randomized to a single dose of trovafloxacin 50 mg, 100 mg or 200 mg. The applicant reports 100% bacterial eradication of *Neisseria gonorrhoeae* from all evaluable patients. This trial served as the basis for dose selection for the multicenter randomized trial, 154-120.

REGULATORY CONSIDERATIONS:

In 1992, the Division of Anti-Infective Drug Products (DAIDP) made available the POINTS TO CONSIDER document and in 1997, the Guidance to Industry document on Evaluating Clinical trials of Antimicrobials in the DAIDP was made available. Both of these documents address the topic of uncomplicated gonorrhea.

For approval of the indication of uncomplicated gonorrhea, it is expected that at least 100 male and at least 100 female patients be evaluable for bacterial eradication and that at least 95% of these patients have *Neisseria gonorrhoeae* eradicated from the urethral and cervical site, respectively. For the approval of rectal and pharyngeal infections, it is recommended that data from at least 20 patients per gender per site (per drug) be evaluated and that at least 90% of the isolates for each of these subgroups be eradicated.

In the Guidance to Industry document, it is recommended that results of clinical trials of uncomplicated gonorrhea focus on bacterial eradication of *Neisseria gonorrhoeae* as the primary endpoint, and that eradication be assessed from a repeat culture taken 3-7 days after the (usually) single-dose treatment.

COMMENT:

A brief examination of the studies submitted in preparation for the 45-day filing meeting indicates that these issues were taken into consideration by the company. However, it is noted that there is a probability that not all sites in all genders will be approvable. This is addressed in greater detail in this review.

REVIEW OF STUDIES:

The two studies are reviewed below:

STUDY 154-120:**TITLE:**

A randomized, multicenter, double-blind, double-dummy trial comparing single dose oral therapy of trovafloxacin (CP-99,219) (100 mg) with that of ofloxacin (400 mg) for the treatment of uncomplicated gonorrhea.

PURPOSE:

To demonstrate the safety and effectiveness of trovafloxacin 100 mg orally, compared to ofloxacin 400 mg orally, in the treatment of uncomplicated gonorrhea in male and female patients.

STUDY DESIGN:

The study was a double-blind, double-dummy trial conducted at 10 centers in the USA, comparing single dose trovafloxacin to ofloxacin for the treatment of gonorrhea. The plan was to enroll up to 500 patients ages 16 and over.

STUDY CONDUCT: December 20, 1994 to October 11, 1995

INCLUSION CRITERIA:

- outpatient men or women ≥ 16 years of age were enrolled and treated with either trovafloxacin tablets or ofloxacin capsules, packaged in blister packs
- written informed consent was obtained from the patient or parent/legal guardian in patients under 18 years of age
- women of childbearing potential had to have a negative pregnancy test prior to study
- females with presumptive gonococcal urethritis and/or cervicitis, defined as urethral or cervical discharge which on Gram stain showed PMLs with intracellular Gram-negative diplococci or a history of sexual exposure within 2 weeks to a man with urethral gonorrhea.
- men with presumptive gonococcal urethritis, defined as the presence of a urethral discharge which on Gram stain shows polymorphonuclear leucocytes with intracellular Gram-negative diplococci

EXCLUSION CRITERIA:

- pregnant or nursing women
- known hypersensitivity to quinolone class
- inpatient
- clinical evidence of gonococcal pharyngitis*, proctitis* (see comment below), disseminated gonococcal infection, or the presence of any other infection at enrollment that may require additional antimicrobial treatment
- treatment with any systemic antibiotic within 72 hours prior to entry into study

- treatment with another investigational drug within 30 days prior to entry
- evidence of significant gastrointestinal disorder that may inhibit absorption
- evidence of clinically significant hematologic, renal, cardiovascular disease or immunologic compromise or AIDS
- history of epilepsy or seizures
- prior enrollment in the protocol
- subject suspected to be noncompliant with the protocol

COMMENT:

The protocol and resulting study report state that "subject with clinical evidence of gonococcal pharyngitis, proctitis, disseminated gonococcal infection..." were to be excluded. Clearly, this is in part contrary to the goal of the study and the proposed label, which specifically requests approval of the treatment of pharyngeal and rectal gonorrhea. Dr. Johnson at Pfizer explained that the key word was "clinical" evidence of disease, thus patients who had symptoms of pharyngitis or proctitis were excluded. However, if these patients had cultures at these sites and the cultures were positive, this information was included in the microbiological evaluation. And, as noted in the results below, some patients did have cultures positive at these sites and met all other protocol criteria and were thus included in the evaluation.

DRUGS AND DOSAGE REGIMEN:

Trovafloxacin 100 mg orally, single-dose administered as one tablet (or matching placebo)

Ofloxacin 400 mg orally, single-dose administered as two capsules (or matching placebo).

Ofloxacin at this dose is approved for the treatment of uncomplicated cervical and/or urethral gonorrhea.

All drug doses were administered in the clinic under direct observation. Dosing was to be done two hours before or two hours after a meal or after use of antacid.

A randomization schedule was provided, with different blocks of numbers for male patients and female patients (to ensure adequate enrollment of each gender).

An amendment to the protocol was made November 14, 1994 changing the ofloxacin from tablet to capsule and administering 2x200 mg capsules; 2 ofloxacin placebo capsules were given to maintain the blind.

CONCOMITANT MEDICATIONS:

No concomitant systemic antibiotic was allowed, unless the patient was a treatment failure.

After completion of the final evaluation visit, patients were treated with either doxycycline or other agent for culture-positive *Chlamydia trachomatis*.

COMMENT:

Approximately of the bacteriologically evaluable men and of the bacteriologically evaluable females had a culture positive for Chlamydia trachomatis. Approximately one-half of all enrolled patients received treatment for Chlamydia that was started at the time of the test-of-cure visit and thus did not confound the assessment of bacteriological outcome and interpretation of gonorrhea treatment.

EFFICACY EVALUATION:

Patients were evaluated at baseline when a history was taken and physical examination and laboratory testing was performed. The patients were then seen at 7 days post therapy (range of 5-9 days), and follow-up evaluation, including all bacteriology was to be repeated.

COMMENT:

As noted above, the Guidance document recommends a follow-up culture at 3 - 7 days after treatment of uncomplicated gonorrhea. However, because trovafloxacin has a half-life of 10 hours (appx), it is justified to use a longer follow-up period for evaluation. Therefore, the timing selected in the protocol is acceptable.

Bacteriology: swab specimens were obtained from the following sites:

- Men: urethra and pharynx. Anorectal cultures were necessary only if history indicated rectal sexual exposure.
- Women: endocervix, pharynx, and rectum. (Women who had hysterectomy would have a urethral culture performed.)

Susceptibility testing was to be performed by agar dilution for all *N. gonorrhoeae* isolates, the tentative interpretive criteria were as follows: Susceptible ≤ 2 , Intermediate 4, Resistant ≥ 8 .

Patients were also evaluated for syphilis (FTA or RPR) and *Chlamydia trachomatis*.

Treatment for *C. trachomatis* was to be initiated at the time of the second visit, as noted above.

APPEARS THIS WAY
ON ORIGINAL

Bacteriological response to therapy was to be assessed based on a comparison of the bacterial culture pre-therapy and at the 7 day evaluation time point (5 - 9 days post treatment).

COMMENT: Bacterial response, by site of infection, is considered the primary efficacy endpoint. Thus, all patient case report tabulations (CRTs) were examined for consistency with the protocol. In addition, a random sample of case report forms (CRFs) was evaluated to determine consistency in data transfer from the CRF to the CRTs, and to evaluate interpretation of patient data. The majority of this examination consisted of verifying the bacteriological data, although some demographic, dosing,

concomitant medication and conditions, clinical course and adverse events were also checked. As stated below, there was general agreement with the information presented.

Bacteriological outcome was classified as follows:

Eradication: *N. gonorrhoeae* not present in the post-treatment culture at 5-9 days.

Persistence: Isolation of *N. gonorrhoeae* from the post-treatment culture at 5-9 days.

Clinical response to therapy was to be assessed by the sponsor on day 7 (between day 5 and 9) and based on the investigator's global assessment of the patient's clinical condition before and after treatment.

COMMENT:

It was noted that among the bacteriologically-evaluable population, men in the study were symptomatic, and approximately 10-20% of women were clinically asymptomatic. A brief examination of several case report forms and tabulations did not reveal any major disagreement in assessment of this secondary efficacy endpoint. Thus, for the purpose of this review, the applicant's evaluation of clinical response is considered acceptable.

Clinical outcome was classified by the applicant as the following:

Cure: complete resolution of signs and symptoms

Improvement: incomplete resolution of signs and symptoms

Failure: no apparent response or progression of signs and symptoms

The applicant performed a variety of clinical and bacteriological analyses on the evaluable population as well as intent-to-treat (ITT) populations, including various subsets. These can be located in the submission but are not presented here. In general, these showed comparability between the two regimens although in some analyses the reported rates were lower than in the evaluable sets because protocol noncompliance was classified as failure in the ITT analyses.

SAFETY EVALUATION:

Adverse events and laboratory tests were monitored at the post-therapy visit.

COMMENT:

Because this drug is also being evaluated for multiple other indications at multiple dose regimens ranging from 50 - 200 mg for up to two weeks, a full assessment of trovafloxacin's safety profile is deferred to the primary reviewer. A summary is provided in this review.

RESULTS OF STUDY 154-120:

A total of 625 male and female patients were enrolled at 10 centers in the United States. Two additional patients were screened but never randomized. There were 311 patients (133 men, 178 women) randomized to trovafloxacin and 314 patients (137 men, 177 women) randomized to ofloxacin. Enrollment by center and the number of patients considered evaluable by the applicant is presented below:

SITE	PRINCIPAL INVESTIGATOR	TROVAFLOXACIN		OFLOXACIN	
		ENROLL	EVAL *	ENROLL	EVAL *
5003	James McCarty, M.D. Fresno, CA	3	3	3	3
5012	Z. A. Dalu, M.D. St Louis, MO	35	21 (60%)	35	26 (74%)
5068	Robert B. Jones, M.D. Indianapolis, IN	70	38 (54%)	72	46 (64%)
5069	David Martin, M.D. New Orleans, LA	27	18 (67%)	27	17 (63%)
5162	Myron Cohen, M.D. Chapel Hill & Raleigh, NC	29	21 (72%)	29	27 (93%)
5163	John Douglas, M.D. Denver, CO	20	13 (65%)	22	17 (77%)
5164	H. Hunter Handsfield, M.D. Seattle, WA	14	12 (86%)	14	11 (79%)
5165	Jane Schwebke, M.D. Birmingham, AL	50	35 (70%)	50	38 (76%)
5166	William McCormack, M.D. Brooklyn, NY	24	19 (79%)	23	17 (74%)
5167	Edwin Thorpe, Jr., M.D. Memphis, TN	39	24 (62%)	39	29 (74%)
TOTAL**		311	204 (66%)	314	231 (74%)

*Number in parentheses represents the percent of patients evaluable by study center and then overall.

**Of the 311 trovafloxacin patients (133 men, 178 women), 204 were evaluable (105 men, 99 women)
Of the 314 ofloxacin patients (137 men, 177 women), 231 were evaluable (111 men, 120 women).

COMMENT:

Clinical review of the patient line listings (CRTs) and spot checking of the CRFs showed that there were minimal differences in the sponsor's classification of outcome and the reviewer's classification. Specifically, there were approximately one or two

patients, both male and female, in both the trovafloxacin arm and the ofloxacin arm that could have been reclassified as evaluable, although technically their follow-up visit was at day 10 or 11. Spot checking did not disclose any serious differences, such as failures that were not recognized or reported. Within the limits of the CRT review and the random examination of the CRFs, no discrepancies were noted; thus, the applicant's data are accepted for review. The effect of accepting one or two additional patients as demonstrating eradication is to marginally raise the efficacy. Therefore, the reviewer accepts the applicant's analysis of the data.

REASONS FOR EXCLUSION OF PATIENTS FROM EVALUATION OF EFFICACY

KEY: M=male, F=female

TOTAL ENROLLED	TROVAFLOXACIN			OFLOXACIN		
	All	M	F	ALL	M	F
	311	133	178	314	137	177
Reason for Exclusion						
No pathogen	73	8	65 (37%)	54	10	44 (25%)
No follow-up visit	31	19	12	28	15	13
Concom antibiotic	2	1	1	1	1	0
Previously enrolled	1	0	1	0	0	0

EVALUABLE						
Bacteriological	204	105	99(56%)	231	111	120 (68%)

	TROVAFLOXACIN		OFLOXACIN	
	MALE	FEMALE	MALE	FEMALE
ENROLLED PATIENTS	133	178	137	177
BACTERIOLOGICALLY EVALUABLE PATIENTS	105 (79%)	99 (56%)	111 (81%)	120 (68%)

COMMENT:

As far as the issue of evaluable vs. nonevaluable patients, it is apparent that approximately 80% of all men (either treatment group) are evaluable. In contrast, there is a greater loss of women from the evaluable pool. The explanation for fewer evaluable women is that many more are screened because the disease can often be asymptomatic in women. The bigger question is that there is a difference between the proportion of trovafloxacin evaluable patients (56%) and the ofloxacin evaluable patients (68%) which should not have occurred by chance. Dr. Johnson at Pfizer commented that the study was conducted double-blind, and that all cultures were evaluated at a central laboratory. There is no obvious explanation for the greater percentage of negative cultures among the trovafloxacin female patients, but this has reduced the number of evaluable females on the test drug.

DEMOGRAPHIC CHARACTERISTICS for the enrolled population and the bacteriologically evaluable population are presented in the table below.

	<u>TROVAFLOXACIN</u>		<u>OFLOXACIN</u>	
	<u>MALE</u>	<u>FEMALE</u>	<u>MALE</u>	<u>FEMALE</u>
<u>ENROLLED PATIENTS</u>	133	178	137	177
Age (yr)				
Mean	26	25	27	24
Range				
Race				
Black	125 (94%)	159 (89%)	127 (93%)	159 (90%)
White	5	17	7	12
Other	3	2	3	6
Weight (kg)				
Mean	79	71	78	68
Range				

	<u>TROVAFLOXACIN</u>		<u>OFLOXACIN</u>	
	<u>MALE</u>	<u>FEMALE</u>	<u>MALE</u>	<u>FEMALE</u>
<u>BACTERIOLOGICALLY EVALUABLE PATIENTS</u>	105	99	111	120
Age (yr)				
Mean	27	24	27	24
Range				
Race				
Black	97 (92%)	89 (90%)	104 (94%)	107 (89%)
White	5	8	5	8
Other	3	2	2	5
Weight (kg)				
Mean	78	70	78	68
Range				

COMMENT:

At entry, the patient characteristics for all patients are balanced across the different treatment groups. The balance in demographic characteristics remains also among the bacteriologically-evaluable population as well.

CONCOMITANT MEDICATION:

Approximately 30 women in each arm were taking OCP, some treated for vaginitis. At the end of the follow-up visit about one-half of the patients received treatment for chlamydia.

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BACTERIOLOGICAL OUTCOME IN BACTERIOLOGICALLY EVALUABLE PATIENTS

EVALUABLE PATIENTS	TROVAFLOXACIN N = 204		OFLOXACIN N = 231	
	MALE	FEMALE	MALE	FEMALE
	105	99	111	120
SITE OF INFECTION				
URETHRA	104	2	111	0
CERVIX	n/a	94	n/a	116
RECTUM	0	27	0	18
PHARYNX	5	9	4	8

COMMENT:

As would be expected, the major site of infection was urethra in men, cervix in women. Urethra was the site of infection in 104/105 evaluable trovafloxacin and 111/111 ofloxacin men, 1 trovafloxacin patient had gonorrhea involving only the pharynx (by culture). Cervix was the site of involvement in 94/99 evaluable trovafloxacin women; the other 5 had urethral (2), rectal (2) or pharyngeal (1) involvement. Among ofloxacin women, 116/120 had cervix as the primary site of involvement, while the remaining 4 had either rectal (2) or pharyngeal (2) involvement.

BACTERIOLOGICAL OUTCOME IN MALES:

ERADICATION RATES	TROVAFLOXACIN	OFLOXACIN
URETHRA	103/104 (99%)	111/111 (100%)
CERVIX	n/a	n/a
RECTUM	0/0	0/0
PHARYNX	5/5	4/4

BACTERIOLOGICAL OUTCOME IN FEMALES:

ERADICATION RATES	TROVAFLOXACIN	OFLOXACIN
URETHRA	2/2	0/0
CERVIX	93/94 (99%)	112/116 (97%)
RECTUM	27/27 (100%)	18/18 (100%)
PHARYNX	9/9	8/8

COMMENT:

The bacteriological results presented above indicate that trovafloxacin is 99% effective at eradicating gonorrhea from the urethra in men and cervix in women. The size of the study meets the recommended number for men but is slightly shy of the recommended number of 100 women. As noted earlier, another two could be considered

evaluable although their follow-up was marginally longer. This issue will be reconsidered after the results of Study 154-107 are reviewed.

In addition, the data are adequate to support approval of treatment of rectal gonorrhea in women. However, inadequate data have been submitted to support approval of the treatment of rectal gonorrhea in males or for the treatment of pharyngeal gonorrhea in either gender.

Penicillinase-Producing Isolates:

The applicant has requested that the labeling grant approval for both penicillinase-producing and non-producing isolates. Information on how many bacteriologically-evaluable patients had isolates that were penicillinase producing was not provided in the study report but was generated by the company as an additional analysis. The information was confirmed in Appendix 5 of the study report and is summarized below (numerator represents number of patients with penicillinase producing isolates; denominator represents number of bacteriologically-evaluable patients):

	<u>Trovafloxacin</u>	<u>Ofloxacin</u>
Males	15/105	14/111
Female	15/99	13/120

Among men, each of them had only one isolate (urethra). Among women, there were 7 trovafloxacin and 3 ofloxacin women who had two isolates each (cervix and rectum); thus there were 22 and 16 penicillinase-producing isolates from women, respectively. All of the penicillinase-producing isolates tested were susceptible to trovafloxacin. All of the penicillinase-producing isolates from bacteriologically-evaluable patients were eradicated.

Clinical outcome was reported by the applicant and is presented below:

CLINICAL OUTCOME IN MALES:

	TROVAFLOXACIN	OFLOXACIN
Cure	91/105 (87%)	102/111 (92%)
Improvement	12/105 (11%)	9/111 (8%)
Failure	2/105 (2%)	0/111
Asymptomatic	0	0

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CLINICAL OUTCOME IN FEMALES:

	TROVAFLOXACIN	OFLOXACIN
Cure	65/99 (66%)	81/120 (68%)
Improvement	6/99 (6%)	16/120 (13%)
Failure	6/99 (6%)	4/120 (3%)
Asymptomatic	22 (22%)	19 (16%)

Intent-to-treat analyses of clinical outcome and bacteriological outcome were also performed by the sponsor, and patients who had missing values were counted as a persistence or eradication, respectively. Therefore, the ITT analyses showed consistently lower rates; however, they did not show a difference in outcome between the two arms which would have suggested that some bias or imbalance may exist.

USE OF CONCOMITANT ANTIBIOTICS

There appear to be only one or two patients per arm who used concomitant antibiotics during the study. One example is a patient who was prescribed SMX/TMP for sinusitis two days into the follow-up. Although trovafloxacin is being developed for the sinusitis indication also, the dosing regimen is more than the single dose given for GC. In addition, about one-half of the patients received treatment for Chlamydia after completion of the study.

STATISTICAL EVALUATION:

The applicant performed a 95% C.I. test for the study and the evaluable population actually fell within their planned + or - 10%. However, a 95% C.I. is irrelevant in this indication, where the lowest acceptable limit of the point estimate is 95%, and approximately 100 women and 100 men should be evaluated.

SAFETY RESULTS:

One female patient in the ofloxacin arm discontinued the study due to vomiting, it was not considered drug related.

There were 33 trovafloxacin patients and 27 ofloxacin patients who did not return for follow-up.

Adverse events were reported in 14% of the trovafloxacin patients and 15% of the ofloxacin patients, 8% in each arm were considered treatment-related. The table below summarizes the more common events. In addition, laboratory abnormalities were reported in approximately 15% of the patients.

	TROVAFLOXACIN	OFLOXACIN
ANY ADVERSE EVENT	44/311 (14%)	46/314 (15%)
Treatment Related Adverse Event	24/311 (8%)	24/314 (8%)
Discontinued due to Adverse Event	0	1/314

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The following specific adverse events considered treatment related were reported.

	Trovafloxacin N = 311	Ofloxacin N = 314
Dry Mouth	1	0
Dizziness	5 (1.6%)	3 (1.0%)
Headache	1	2
Tongue paralysis	0	1
Insomnia	0	1
Somnolence	1	2
Altered bowel habit	0	1
Diarrhea	2	0
Dyspepsia	1	0
Nausea	0	3
Vomiting	1	1
Asthenia	1	1
Moniliasis	0	1
Vaginitis	5	9
Pruritus	4	2
Rash	3	1
Urticaria	1	0
Micturition frequency	<u>1</u>	<u>0</u>
total events	27	26

COMMENT:

The adverse event profile of the two regimens appears similar overall with perhaps the following suggested differences. Dizziness was noted in 5 Trovan and 3 ofloxacin patients, yet overall when headache, insomnia, somnolence etc are added there were 7 Trovan events vs. 9 ofloxacin events in the "neurologic"-type category.

Vaginitis/moniliasis was reported by 5 Trovan patients vs. 10 ofloxacin patients (approximately 55% of the patients were females). Rash, pruritus or urticaria was noted in 8 Trovan patients vs. 3 ofloxacin patients. These observations need to be compared to the safety profile of Trovan overall in the review conducted by Dr. Coyne. Over 90% of the reported events were considered mild, no serious events were reported. However, for an overall conclusion regarding the safety profile of Trovan, including multiple dose use, the reader is referred to the comprehensive safety review by Dr. Coyne.

Laboratory changes, defined as clinically significant, were reported to be identified in 15% of Trovan patients and 17% of ofloxacin patients. It should be noted that approximately 80% of the enrolled patients had laboratory testing performed before and after treatment to assess for changes in laboratory values following a single dose of trovafloxacin or ofloxacin.

	Trovafloxacin	Ofloxacin	Definition of Clin. Significant. (relative to normal)
Any abnormality	35/236 (15%)	42/242 (17%)	
Hemoglobin	0	0	(< 80% LLN)
Hematocrit	0	0	(< 80% LLN)
RBC	0	0	(< 75% LLN)
Platelets	0	0	(<75% to > 125%)
WBCs	2	3	(<75% to > 125%)
Bilirubin	1	0	(> 1.5 x ULN)
ALT	0	0	(> 2 x ULN)
AST	0	0	(> 2 x ULN)
Protein	0	0	(<0.9 or > 1.1)
Albumin	0	0	(<0.8 to > 1.2)
BUN	0	0	(> 1.3 x ULN)
Creatinine	0	0	(> 1.3 x ULN)
Sodium	0	0	(< 95 or > 1.05)
Potassium	0	1	(<0.9 or > 1.1)
Chloride	0	0	(<0.9 or > 1.1)
Bicarbonate	0	0	(<0.9 or > 1.1)
Urine RBC	14	16	(> 6/HPF)
Urine WBC	12	19	(> 6/HPF)
Urine SG	2	6	(<1 or > 1.035)
Urine pH	0	0	(<0.9 or > 1.1)
Urine Protein	3	2	(> 2+)
Urine Glucose	0	0	(> 2+)
Urine Ketones	1	2	(> 1+)

COMMENT:

There were relatively few laboratory abnormalities noted; the majority related to Urine WBC and RBC in both groups.

STUDY 154-107:**TITLE:**

An open, randomized, non-comparative, single center dose-ranging study of trovafloxacin (CP-99,219) in the treatment of uncomplicated gonorrhea.

PURPOSE:

To assess the safety and effectiveness of three different doses of trovafloxacin in the treatment of uncomplicated gonorrhea in male and female patients.

STUDY DESIGN:

The study was a dose-ranging, randomized, single-center trial conducted in the USA, comparing a single dose of trovafloxacin 50 mg, 100 mg or 200 mg. The plan was to enroll approximately 30 male and female patients.

STUDY CONDUCT: March 31, 1994 to July 11, 1994

INCLUSION AND EXCLUSION CRITERIA:

analogous to study 154-120

DRUGS AND DOSAGE REGIMEN:

Trovafloxacin 50 mg, 100 mg or 200 mg orally, single-dose administered as a powder to be reconstituted to suspension or as a tablet

All drug was administered under direct observation. Dosing was to be done two hours before or two hours after a meal or use of antacid.

A randomization schedule was provided, with different blocks of numbers for male patients and female patients (presumably to ensure adequate enrollment of each gender).

CONCOMITANT MEDICATIONS:

analogous to study 154-120

EVALUATION OF EFFICACY:

analogous to study 154-120

SAFETY ASSESSMENT:

analogous to study 154-120

STUDY RESULTS:

A total of 39 men and women were enrolled by Dr. Edward Hook at Birmingham, Alabama. The number of patients randomized to each group, excluded from evaluation and evaluable for assessment of efficacy is summarized in the table below:

	Trovafloracin Doses					
	50 mg		100 mg		200 mg	
	male	female	male	female	male	female
Randomized	4	7	6	8	6	8
No pathogen	0	2	0	3	1	2
No follow-up	0	1	0	0	1	0
Bacteriologically Evaluable	4	4	6	5	4	6

DEMOGRAPHIC DATA for all enrolled subjects:

	Trovafloracin Doses					
	50 mg		100 mg		200 mg	
	male	female	male	female	male	female
Age: mean	23	24	25	23	24	28
range						
Race: black	4	6	5	8	6	8
other	0	1	1	0	0	0
Weight: (kg)						
mean	72	64	77	79	77	69
range						

The demographic data on the bacteriologically-evaluable subjects were comparable.

BACTERIOLOGICAL OUTCOME

	Trovafloracin Doses					
	50 mg		100 mg		200 mg	
	male	female	male	female	male	female
Bacteriologically Evaluable	4	4	6	5	4	6
Site of infection						
Urethra	4	0	6	0	4	0
Cervix	0	4	0	5	0	5
Pharynx	0	1	3	1	1	1
Rectum	0	1	0	1	0	3

Note that all patients had eradication of *Neisseria* isolates from all sites, thus the total eradication rates supporting the efficacy of 100 mg of trovafloxacin are presented below, based on combining the results from the 50 mg and 100 mg groups. It is recognized that the study formulations included powder and tablet.

	MALES	FEMALES
URETHRA	10/10	0
CERVIX	0	9/9
PHARYNX	3/3	2/2
RECTUM	0	2/2

SAFETY EVALUATION:

Two patients in the 200 mg group reported somnolence(1) and asthenia (1). No other treatment related events were noted.

	Trovafloxacin N = 37	Definition of Clinically Dsginifant (relative to normal)
Any abnormality		
Hemoglobin	0	(< 80% LLN)
Hematocrit	0	(< 80% LLN)
RBC	0	(< 75% LLN)
Platelets	0	(< 75% to > 125%)
Neutrophil	2	(< 75% to > 125%)
Eosinophil	1	(> 10%)
Bilirubin	0	(> 1.5 x ULN)
ALT	1	(> 2 x ULN)
AST	1	(> 2 x ULN)
Protein	1	(< 0.9 or > 1.1)
Albumin	0	(< 0.8 to > 1.2)
BUN	0	(> 1.3 x ULN)
Creatinine	0	(> 1.3 x ULN)
Sodium	0	(< 95 or > 1.05)
Potassium	6	(< 0.9 or > 1.1)
Chloride	0	(< 0.9 or > 1.1)
Bicarbonate	0	(< 0.9 or > 1.1)
Urine RBC	5	(> 6/HPF)
Urine WBC	5	(> 6/HPF)
Urine SG	0	(< 1 or > 1.035)
Urine pH	0	(< 0.9 or > 1.1)
Urine Protein	0	(> 2+)
Urine Glucose	0	(> 2+)
Urine Ketones	0	(> 1+)
Urine Casts	0	(> 1)

COMMENT:

Several patients had elevations in potassium, presence of urinary RBC and WBC. Two patients had neutrophils less than 1000/mm³. These findings need to be taken in context of the overall safety profile of this agent from other studies.

SUMMARY AND RECOMMENDATIONS:

Two clinical studies were conducted, a dose ranging study 154-107 testing 50 mg, 100 mg or 200 mg or trovafloxacin in a total of 39 male and female patients and study 154-120 comparing 100 mg of trovafloxacin to 400 mg of ofloxacin in 625 male and female patients.

The eradication rates for *Neisseria gonorrhoeae* in bacteriologically evaluable patients from each of the studies is summarized in the table below.

BACTERIOLOGICAL OUTCOME IN MALES treated with trovafloxacin:

	<u>154-107</u>	<u>154-120</u>	<u>TOTAL</u>
URETHRA	10/10	103/104	113/114 (99%)
PHARYNX	3/3	5/5	8/8
RECTUM	0	0	0

BACTERIOLOGICAL OUTCOME IN FEMALES treated with trovafloxacin:

	<u>154-107</u>	<u>154-120</u>	<u>TOTAL</u>
CERVIX	9/9	93/94	102/103 (99%)
RECTUM	2/2	27/27	29/29
PHARYNX	2/2	9/9	11/11
URETHRA	0	2/2	2/2

Thus, based on these results, it is recommended that trovafloxacin be approved for the treatment of uncomplicated gonorrhea (cervical and urethral) at a dose of 100 mg orally. In addition, the treatment of rectal gonorrhea in women may be approved. The data submitted are inadequate to approve treatment of rectal gonorrhea in males and the treatment of pharyngeal gonorrhea in any gender.

The applicant has provided data on at least 10 penicillinase-producing isolates of *N. gonorrhoeae* that were treated and eradicated, per gender. These isolates were susceptible to trovafloxacin. To date, the Division has not placed information on the penicillinase status of *Neisseria gonorrhoeae* in the approved labeling of any quinolone antimicrobial, because this mechanism of resistance is not linked to resistance to quinolones. Thus, the approved labeling for trovafloxacin should not mention the penicillinase status of the isolates at this time.

PROPOSED LABELING REVISION:

/S/

Carmen DeBellas, R.Ph.

/S/

Renata Albrecht, M.D.

cc: NDA 20-759
HFD-590
HFD-590/DepDir/Albrecht
HFD-520/Pharm/Ellis
HFD-520/Micro/Altaie
HFD-590/Chem/
HFD-590/CSO/Fogarty
Clinical Review GC
HFD-590/LEISSA

Concurrence:

HFD-590/DD/Goldberger

HFD-590/TL/Leissa

/S/ 7/10/98
/S/ 7/13/98

7.0.9

MEDICAL REVIEW OF NDA 20-759, 20-760

Applicant:

Pfizer Inc.
Central Research Division
Eastern Point Road
Groton, CT 06340
Contact person: Ronald Trust, Ph.D., M.B.A.

NOV 19 1998

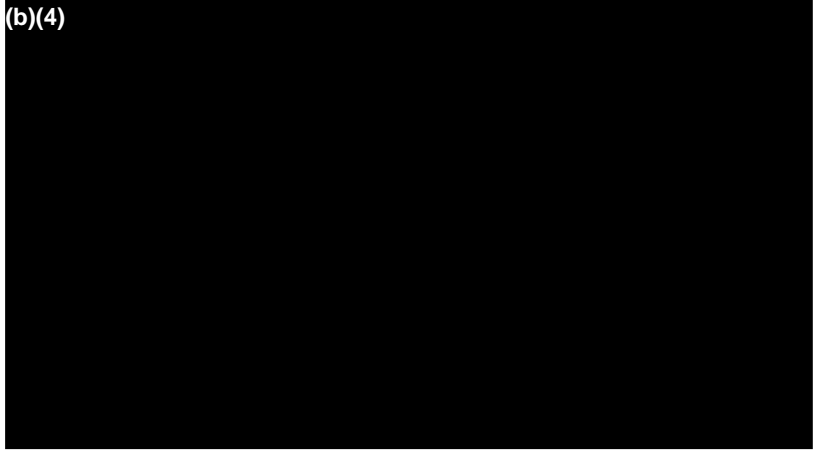
Date of submission:	December 27, 1996
Date received by reviewer:	January 14, 1997
Date review begun:	September 15, 1997
Date draft of review completed:	December 2, 1997
Date review received from secondary reviewer:	October 21, 1998
Date review completed:	November 17, 1998

Currently approved indications: none

Material reviewed: Electronic submission

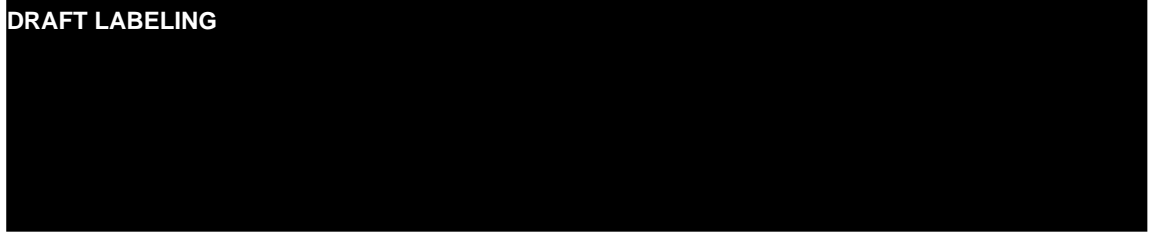
REGULATORY BACKGROUND

(b)(4)



PROPOSED LABELLING

DRAFT LABELING



REGULATORY GUIDANCE

A. 1992 DAIDP Points to Consider

1. Establish equivalence or superiority to an approved product in one statistically adequate and well-controlled, multicenter trial
2. At least 50% of the clinically evaluable patients must be bacteriologically evaluable

B. IDSA/FDA guidelines [Clin Infectious Dis 1992; 15(S1): 53-61]

1. Subjects (b)(4) are considered adults except when age-specific safety issues need to be considered.
2. Patients should be stratified at enrollment according to the type of pelvic inflammatory disease (PID)—uncomplicated or complicated
3. A diagnosis of PID must be confirmed by meeting clinical and microbiologic criteria and/or by laparoscopy and/or endometrial biopsy.
4. Patients who are seropositive for syphilis should be excluded from the study and considered to have an indeterminate outcome.
5. It is expected that the clinical cure rates for acute PID and tubo-ovarian abscess (TOA) will be (b)(4) respectively.
6. Treatment for acute PID due to *N. gonorrhoeae* and mixed anaerobes must be given parenterally for at least 4 days, and then for at least 48 hours after a favourable clinical response. Antichlamydial therapy should be given for a total of 14 days. The minimum duration of parenteral therapy for TOA should be 7 days.
7. Patients must be followed for 2-4 weeks after therapy to be eligible for evaluation of efficacy. The presence of *C. trachomatis* or *N. gonorrhoeae*, even in the absence of symptoms, is indicative of the failure of treatment.

NON-CLINICAL STUDIES

(b)(4)

Animal Pharmacology/Toxicology

See Toxicology review by A. Ellis, Ph.D.

Microbiology

See Microbiology review by S. Altaie, Ph.D.

CLINICAL STUDIES*Human Pharmacokinetics/Pharmacodynamics*

See full review by P. Colangelo, Ph.D.

Trovafloxacin's biologic half-life is approximately 9 to 11 hours. The mean bound fraction in plasma samples is approximately (b)(4). Steady state concentrations are achieved by the third daily dose. In adult subjects, the pharmacokinetics of trovafloxacin are not affected by age or gender. Peak blood level (C_{max}) of trovafloxacin at a 200 mg oral dose is 2.5 ug/mL and tissue/serum concentration ratios in the cervix after single and multiple doses of trovafloxacin 200 mg were 0.5 ug/mL (3-29 hr postdose) and 0.6 ug/mL (3-16 hr postdose), respectively.

Human Clinical Experience

The efficacy and safety of trovafloxacin for several indications was evaluated in 45 phase I studies and 31 phase II/III studies.

INTRODUCTION TO CLINICAL TRIALS

The applicant submitted 2 pivotal clinical trials in support of this indication- a randomized, comparative trial to assess the efficacy of trovafloxacin in ambulatory patients with PID, and the second, a randomized, double-blind, comparative trial to evaluate trovafloxacin for the treatment of hospitalized patients with complicated PID.

Study 154-122

Title: "A randomized, multi-center, investigator-blind, comparative trial of CP-116,517/CP-99,219 and cefoxitin/doxycycline for the treatment acute pelvic inflammatory disease in hospitalized subjects"

Primary objective

To compare the efficacy and safety of alatrofloxacin/trovafloxacin and cefoxitin/doxycycline in the treatment of hospitalized subjects with acute pelvic inflammatory disease.

Study Design Summary

Location	USA (36 sites), Republic of South Africa (5 sites)
Patients	16 years and older
Study dates	5 June 1995 - 9 May 1996
Amendment dates	March 21, 1995; August 18, 1995
Study dose and duration	Alatrofloxacin IV and Trovafloxacin orally 200 mg qd for 14 days
Comparator	Cefoxitin 2gm IV q 6h <u>PLUS</u> Doxycycline 100mg IV q 12h then doxycycline 100mg for total 14 days
Blinding	investigator-blind
Method of assignment	1:1 random assignment at each center
Primary efficacy variable	clinical outcome at visit 4
Safety variables	clinical signs and symptoms, laboratory results
Therapy evaluation, days (window)	
Baseline	1 (within 48 hours)
Visit 2	72 hours after initiation of treatment
End of treatment-EOT	14 (14-20)
End of study-EOS	week 4-6 after initiation of therapy
Number of subjects randomized	79 (alatrofloxacin/trova)/ 79 (cefoxitin/doxycycline)

STUDY POPULATION

Inclusion criteria

1. Hospitalized women. Women of childbearing potential (i.e., not surgically sterile $\leq$ one year post menopausal) with a negative urine or serum gonadotropin pregnancy test immediately prior to entry in the study and using adequate contraception both during and for one month after the end of treatment.
2. At least 16 years of age.
3. Presumptive diagnosis of acute PID. While subject enrollment may have been based on a diagnosis established solely on clinical grounds, the diagnosis may, at the investigator's discretion, have been confirmed by laparoscopy or by endometrial biopsy (with the histological finding of polymorphonuclear leukocytes and/or plasma cells). Clinical and/or laparoscopic staging followed Hager's criteria (see below). Clinical diagnosis must have been substantiated by all of the following (a through c):

- a. Lower abdominal tenderness, with or without rebound (unilateral or bilateral)
- b. Tenderness upon motion of the cervix and uterus
- c. Adnexal tenderness (unilateral or bilateral)
- d. In addition, at least one of the following must have been present:
 - (1) Evidence suggesting cervical infection with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*:
 - (a) Mucopurulent endocervicitis
 - (b) Positive Gram stain for Gram-negative intracellular diplococci
 - (c) Endocervical Gram stain demonstrating ≥ 10 WBC/oil immersion field (x 1,000)
 - (d) Positive result in a rapid diagnostic screening test for *C. trachomatis*
 - (2) Purulent material obtained by culdocentesis or laparoscopy (if performed)
 - (3) Inflammatory mass suspected on bimanual examination and confirmed by ultrasound
 - (4) Fever (admission temperature $\geq 38^{\circ}\text{C}$ [100.4°F])
 - (5) Leukocytosis ($\text{WBC} \geq 10,500/\text{mm}^3$)
 - (6) Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
 - (7) Plasma cell endometritis (> 1 plasma cell/HPF on endometrial biopsy [if performed])

Medical officer's comments:

The medical reviewer agrees with the criteria as outlined, which are standard diagnostic criteria for PID.

GRADING OF PID BY CLINICAL EXAMINATION

- I. Uncomplicated: Limited to tube(s) and/or ovary(ies)
 - A. Without pelvic peritonitis
 - B. With pelvic peritonitis
 - II. Complicated: Inflammatory mass or abscess involving tube(s) and/or ovary(ies)
 - A. Without pelvic peritonitis
 - B. With pelvic peritonitis
 - III. Spread to structures beyond pelvis, i.e., ruptured tubo-ovarian abscess
- NOTE:** Subjects with Grade III PID were excluded from the study.

SEVERITY OF DISEASE BY LAPAROSCOPIC EXAMINATION

- Mild: Erythema, edema, no spontaneous purulent exudate;* tubes freely moveable
- Moderate: Grossly purulent material evident; erythema and edema more marked. Tubes may not be freely moveable, and fimbria stoma may not be patent.
- Severe:
 1. Pyosalpinx or inflammatory complex
 2. Abscess⁺

* The tubes may have required manipulation to produce purulent exudate.

⁺ The size of any pelvic abscess should be measured.

Exclusion criteria

1. Pregnant women, nursing mothers, or women of childbearing potential not practicing adequate means of contraception
2. Known or suspected hypersensitivity or intolerance to any quinolone antibiotic, clindamycin, or lincomycin.
3. Outpatients.
4. Suspected ruptured tubo-ovarian abscess (TOA) on admission.
5. Intrauterine device in place which the subject refuses to have removed within 24 hours of entry into the study.
6. History of pelvic or abdominal surgery within the 30 days prior to admission.
7. Presence of any other infection at enrollment that may have required treatment with an antibiotic other than the study drugs. A single dose regimen for treatment of trichomoniasis after clinical response had been demonstrated was acceptable.
8. Treatment with any systemic antibiotic for 24 hours or longer within two weeks prior to entry into the study, unless there was documented evidence of clinical failure.
9. Treatment with another investigational drug within 30 days prior to entry into the study.
10. Evidence of significant gastrointestinal or other conditions which may have affected drug absorption.
11. Evidence or history of clinically significant hematologic, renal (i.e., serum creatinine greater than 2.0 mg/dL or creatinine clearance or immunologic compromise (i.e., neutropenia [total white blood cell count 1000/mm³] or known AIDS).
12. History of epilepsy or seizures.

Medical officer's comments:

The reviewer agrees with criteria as outlined. Patients with trichomoniasis during the study could receive a single dose of therapy with an appropriate agent after the assessment of clinical and microbiologic outcome; these patients were not excluded and were eligible for evaluability.

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SUBJECT EVALUATION VISITS**Visit 1 at day 1 (Baseline)**

Within 24 hours prior to the start of therapy, baseline visit assessments included a history and a targeted physical examination, a serum or urine gonadotropin pregnancy test for women of childbearing potential, a standard panel of blood and urine safety tests, and a serologic test for syphilis (FTA or RPR).

In an attempt to standardize and semiquantitate clinical severity of PID and to assess the clinical response to therapy, a Clinical Tenderness Score (CTS) was used (see below). Upon entry into the study, the CTS (maximum CTS = 42), extent of fever, and white blood cell count were determined for each subject. The subject's body temperature and CTS were also assessed at the follow-up visits, two and four to six weeks following initiation of therapy.

CLINICAL TENDERNESS SCORE FOR PID (MAXIMUM = 42)

- A. The following areas were assessed:
 1. Abdominal tenderness (direct); score each quadrant
 2. Abdominal tenderness (rebound); score each quadrant
 3. Cervical motion tenderness
 4. Uterine tenderness
 5. Adnexal tenderness, left

6. Adnexal tenderness, right
7. Adnexal mass, left
8. Adnexal mass, right

B. Scoring

1. Tenderness

- 0 = tenderness absent
- 1 = tenderness described by subject but not manifested by changes in facial expression or abdominal muscle tone
- 2 = tenderness resulting in altered facial expression or abdominal muscle tone
- 3 = tenderness causing observable marked distress

2. Adnexal masses, scored by size

- 0 = no mass
- 1 = mass < 2 cm
- 2 = mass 2-5 cm
- 3 = mass > 5 cm

While they may have been obtained by use of culdocentesis, the following specimens were required from each subject (a and b):

a. Culture by swab of the endocervix and rectum for *N. gonorrhoeae*, and *C. trachomatis* from the endocervix by culture (strongly recommended), antigen detection, or other acceptable rapid nonculture test.

b. endometrial material for anaerobic and facultative culture and for isolation of *N. gonorrhoeae*, and *C. trachomatis* by culture (strongly recommended), antigen detection, or other acceptable rapid nonculture test. All isolates of *C. trachomatis* were to be frozen at -70°C for possible susceptibility testing later.

c. For those subjects undergoing laparoscopy (at the investigator's discretion), a directed culture from the fallopian tube was to be obtained for aerobic and anaerobic cultures and for isolation of *N. gonorrhoeae*. *C. trachomatis* was to be sought by culture, antigen detection, or other acceptable rapid nonculture test. Peritoneal fluid was to be cultured for the same microorganisms.

Visit 2 at 72 hours

Failure to demonstrate response at 72 hours after initiation of therapy (i.e., reduction in the CTS, and/or reduction in fever, and/or reduction in white blood cell count) constituted clinical failure, and the investigator was to remove the subject from study treatment and institute alternative treatment. The battery of blood and urine tests performed at baseline was repeated.

Switching from intravenous to oral therapy

The subject's need for continued intravenous therapy was checked daily between days 3 and 7 of therapy. It was appropriate to switch to oral therapy if:

- a. Resolution of fever (based on daily maximum temperature) and reduction in white blood cell count, ESR, and CRP were documented
- b. Improving CTS noted

Visit 3 at 2-4 days following completion of therapy

Endocervical and rectal specimen cultures for *N. gonorrhoeae*, and endocervix culture (strongly recommended), antigen detection, or other acceptable rapid non-culture test for *C. trachomatis* were repeated. At the investigator's discretion, endometrial biopsy could be repeated for

anaerobic and facultative culture and for isolation of *N. gonorrhoeae*. Bacteriological response of *N. gonorrhoeae* and *C. trachomatis* was based on the assessments at visits 3 and 4.

The battery of blood and urine tests performed at baseline was repeated and an interval sexual history was obtained.

On the assumption that some investigators would perform a repeat endometrial biopsy at this visit, the primary assessment of bacteriological response of anaerobic and aerobic bacteria was made at this visit.

Visit 4 at 2-4 weeks following completion of therapy

Visit 4 was the primary efficacy endpoint for clinical response and final bacteriological response of *N. gonorrhoeae* and *C. trachomatis*.

Endocervical and rectal specimens were assessed for *N. gonorrhoeae* and *C. trachomatis* (endocervix only). Endometrial biopsy was not required at this visit. Other procedures performed at visit 4 included recording of interval sexual history, vital signs, adverse events and repeat of the battery of blood and urine tests performed at baseline and at visits 2 and 3.

Medical officer's comments:

The reviewer agrees with the overall design and notes that the timing of visits, including the TOC visit, was consistent with the IDSA/FDA guidelines. The guidelines note that interim analyses could be performed to assess clinical response 72 hours after the start of therapy and 2-4 days after the completion of therapy. Patients with *N. gonorrhoeae* or *C. trachomatis* isolated at the final evaluation, even in the absence of symptoms, were considered treatment failures.

Susceptibility testing

Susceptibility to CP-99,219, ofloxacin, and clindamycin was determined by disk diffusion and minimum inhibitory concentrations (MICs) for all pathogenic isolates (except *C. trachomatis*), whether at baseline or at follow-up.

Criteria for determining susceptibility to the study drugs ("susceptibility breakpoints") are summarized below.

Criteria	Trovafoxacin		Ofloxacin		Clindamycin	
	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) (5 μg Disk)	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) (5 μg Disk)	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) (2 μg Disk)
Susceptible (For <i>N. gonorrhoeae</i>)	≤ 2	≥ 15	≤ 2 (≤ 0.25)	≥ 16 (≥ 31)	≤ 0.5	≥ 21
Intermediate (For <i>N. gonorrhoeae</i>)	4	11-14	4 (-)	13-15 (-)	1-2	15-20
Resistant (For <i>N. gonorrhoeae</i>)	≥ 8 (-)	≤ 10 (-)	≥ 8	≤ 12	≥ 4	≤ 14

Note: Results using the 10 μg disks were not available during the study report period.
(-) No intermediate or resistant strains of *N. gonorrhoeae* currently identified.

Clinical Evaluations

On the basis of the investigator's assessments of the CTS, extent of fever, and white blood cell count, clinical efficacy was classified by the sponsor at two interim timepoints (72 hours after the initiation of therapy and 2-4 days following completion of therapy), with a final classification at 2-4 weeks following completion of therapy. The following guidelines were used:

Interim assessments

- a. *Presumptive clinical cure*
 - 1) Reduction of the CTS by $\geq 70\%$ AND
 - 2) Resolution of fever and leukocytosis

- b. *Presumptive clinical improvement*
 - 1) Reduction of the CTS by 30-70% AND
 - 2) Resolution of fever and leukocytosis

- c. *Unsatisfactory response*
 - 1) Reduction of the CTS by $< 30\%$ within 2-4 days following completion of therapy AND
 - 2) Persistence of fever and/or leukocytosis

- d. *Unevaluatable response*
 - 1) Subject's withdrawal from the study for other than clinical failure
 - 2) Institution of an additional antibiotic for the treatment of an infection unrelated to PID
 - 3) Erroneous diagnosis
 - 4) Surgical intervention during the first 48-72 hours of therapy
(NOTE: Subjects requiring such surgery after 72 hours were considered clinical failures).

In addition, failure to demonstrate response at 72 hours after initiation of therapy constituted clinical failure.

Final assessment

The overall clinical response was based on the global assessment of the subject by the investigator at visit 4 (2-4 weeks following completion of therapy). The potential outcomes were:

- a. *Clinical cure*
 - 1) Reduction of the CTS and mass score by $\geq 70\%$ AND
 - 2) Resolution of fever and leukocytosis AND
 - 3) No known clinical recurrence within 2-4 weeks following completion of therapy

- b. *Clinical failure*
 - 1) Reduction of the CTS and mass score of $< 70\%$ OR
 - 2) Persistence of fever and/or leukocytosis OR
 - 3) Recurrence of signs and symptoms of PID within 2-4 weeks following completion of therapy OR
 - 4) Therapy required for longer than 14 days

Bacteriological Evaluations

The bacteriological response was determined 2-4 days following completion of therapy and 2-4 weeks following completion of therapy. Definitions of bacteriological response were as follows:

a. Satisfactory response

1) Eradication of *N. gonorrhoeae* and *C. trachomatis*, and actual or presumptive eradication of anaerobic and aerobic bacteria from the endometrium at the 2-4 day post-therapy assessment (determined by performance of repeat endometrial biopsy). If cultures were obtained at repeat endometrial biopsy, bacterial eradication could be determined. Without repeat endometrial biopsy, presumptive bacteriological eradication was based on the assessment of the subject's clinical response, AND

2) Eradication of *N. gonorrhoeae* and/or *C. trachomatis* from the endocervix (and rectum, if applicable, for *N. gonorrhoeae*) at the 2-4 week post-therapy assessment

b. *Unsatisfactory response*-Persistence of *N. gonorrhoeae* or *C. trachomatis* at either of the above assessments or actual or presumptive persistence of anaerobic or aerobic bacteria at the 2-4 day post-therapy assessment (determined by performance of repeat endometrial biopsy). If cultures were obtained at repeat endometrial biopsy, bacterial eradication could be determined. Without repeat endometrial biopsy, presumptive bacteriological eradication was based on the assessment of the subject's clinical response.

Indeterminate (for evaluable subgroup):

- a. no baseline causative pathogen isolated
- b. relevant post-baseline cultures not obtained, unless the lack of such cultures results from concomitant antibiotic use due to bacteriological persistence
- c. concomitant antibiotic use for treatment of an intercurrent illness

Medical officer's comments:

The reviewer agrees with the definitions as outlined by the applicant.

Applicant's Criteria for Clinical evaluability (from study report)

Subject evaluability was based on data collected at Visit 4. If any of the following was present, the subject was considered non-evaluable for clinical efficacy:

1. Study medication discontinued, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement (7 days)
2. Treatment with any systemic antibiotic for 24 hours or longer within 2 weeks prior to enrollment unless clinical failure.
3. Concomitant antibiotic prescribed at any time before the Visit 4 assessment that was potentially effective against the condition under study. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the clinically evaluable subjects subset.
4. Intercurrent Illness whose clinical course confounded the clinical evaluation of the disease or condition under investigation. In order to be evaluable, a subject must have had an assessment in the Visit 4 analysis window, unless:
 - the subject was given an antibiotic for insufficient response at any time during study, up to and including the last day of the Visit 4 analysis window, or
 - the subject was discontinued due to lack of efficacy,

SCHEDULE OF STUDY VISITS AND PROCEDURES
STUDY DAYS

	<u>Posttherapy</u>			
	Baseline Day 1	Visit 2 72 h	Day 14	Visit 3, Days 16-18
Treatment	X		X	Visit 4 Days 28-42
Compliance Checks		X		X
Informed Consent	X			
Demographic Information	X			
Targeted Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Assessments				
Clinical ^a	X	X	X	X
Culdocentesis				
Endometrial Biopsy, ^b and/or Laparoscopy ^b	X		(X) ^c	
Laboratory				
1. Hematology	X	X	X	X
2. Serum Chemistry	X	X	X	X
3. Urinalysis	X	X	X	X
4. Microbiology				
a. <i>N. gonorrhoeae</i> cultures	X		X	X
b. <i>C. trachomatis</i> cultures or assays	X		X	X
c. Anaerobic/aerobic cultures	X		(X) ^c	
5. FTA or RPR	X			
6. Pregnancy Test	X			
Adverse Events	X	X	X	X

^a Assessments to be done daily during hospitalization
^b Dependent upon which procedure(s) is(are) performed; endometrial biopsy required at baseline for microbiology (with histology optional)
^c At investigator's discretion

- the subject had surgical intervention on Day 4 or later, or the investigator's clinical assessment was failure before Visit 4.

Applicant's Criteria for Bacteriological Evaluability (from study report)

If any of the following was present, the subject was considered non-evaluable for bacteriological efficacy.

1. No baseline causative pathogen (*N. gonorrhoeae*, *C. trachomatis* and/or pathogenic anaerobic or aerobic bacteria) was isolated and the subject did not have a positive non-culture chlamydial test at baseline.
2. The baseline culture (and non-culture chlamydial test) was done more than 2 calendar days before the first dose of study medication.
3. No culture (or non-culture chlamydial test) obtained at Visit 4 unless:
 - The subject was given an antibiotic for insufficient response, at any time up to and including the last day of the evaluable End of Study analysis window, or
 - The subject had a baseline pathogenic anaerobic or aerobic bacteria and the investigator's clinical response was recorded in the appropriate window.
 - The subject had a baseline pathogenic anaerobic or aerobic bacteria and the investigator's clinical response was failure prior to the End of Study window.

Medical officer's (MO) evaluability criteria

A. The primary efficacy variable is clinical response at the 4-6 week visit.

Patients were clinically non-evaluable if:

- insufficient therapy ---MO accepted patients who received at least 10 days of the study drug unless they were clinical failures early in the course of treatment
- unprotected sexual contact during study
- no clinical assessment 2-4 weeks after completion of study therapy
- positive serologic test for syphilis (indeterminate status)
- patients who received antibiotics within 2 weeks prior to study initiation
- IUD in place >24 hours after initiation of study therapy
- missing data and data outside study windows
- no baseline clinical assessment
- incorrect baseline diagnosis
- concomitant antimicrobial therapy during study unrelated to PID

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B. Clinical failures will be those patients who:

- require surgery after 72 hours of study therapy
- clinically cured but bacteriologic failure
- insufficient therapy with study drug due to poor clinical response
- required concomitant systemic antimicrobial therapy due to poor clinical response or persistent pathogen
- subjects who were given alternate treatment due to poor response to the study drug or persistent pathogen were considered evaluable

C. Bacteriologically non evaluable:

The reviewer agrees with the applicant's criteria.

Statistical considerations

Assuming the clinical cure rate for the reference drug was 90%, the number of subjects required for each treatment group to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy does not exceed 10% was 142 subjects per treatment group. The planned enrollment of 300 subjects was statistically adequate (under the assumption of a 90% cure rate for the comparative group). All statistical tests of significance were performed as two-sided tests (unless otherwise specified). No adjustments were made to significant levels for multiple endpoints on the same data. Baseline comparability of the treatment groups was assessed for age, race, and weight.

The primary efficacy endpoints were clinical and bacteriological responses at visit 4, four to six weeks following initiation of therapy. Modified "intent to treat" and "evaluable" clinical analyses were performed, comparing clinical and bacteriologic outcomes four to six weeks following initiation of therapy. The Cochran-Mantel-Haenzel test controlling for center were used to compare the treatments for clinical and bacteriological response. Also, 95% confidence intervals were produced for the difference between treatment effects for cure and eradication rates.

Criteria for Safety evaluation

Adverse events including serious adverse events were monitored up to visit 4, four to six weeks following initiation of therapy. Serious adverse events were monitored throughout the study and for 30 days after the last dose of study drug.

The clinical laboratory tests outlined below were performed at baseline and on visits 2 and 3.

- Hemoglobin, hematocrit, red blood cells, white blood cells, differential count, platelets, and ESR.
- AST, ALT, total bilirubin, LDH, alkaline phosphatase, urea, creatinine, total protein, albumin, sodium, potassium, bicarbonate, chloride, and random blood glucose, and C- reactive protein.
- Microscopy and urine chemistry (protein, glucose, ketones, bilirubin, pH, urobilinogen, blood and nitrate).

INVESTIGATORS AND STUDY SITES

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5248	Carol Terregino, MD
	5601	James McGregor, MD
	5602	Stanley Gall, MD
	5604	James West, MD
	5609	Harvey Friedenson, MD
	5748	David Baker, MD
	5749	Gregory Fossum, MD
	5750	David Hemsell, MD
	5751	Abner Korn, MD
	5752	Maurizio Maccato, MD
	5756	Kevin Huddleston, MD
	5757	James Van Hook, MD
	5758	Bernard Gonik, MD
	5759	Richard Sweet, MD
	5763	Rebecca Ryder, MD
	5764	Chong Chang, MD
	5765	Blane Crandall, MD
5766	Sebastian Faro, MD	
5767	Javier Gutierrez, MD	
5768	Peter Marsh, MD	
5805	Robert Holley, MD	
5866	William Koltun, MD	
5904	Richard Derman, MD	

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	5905	Harold Wittcoff, MD
	5906	Dean Coonrod, MD
	5907	Joseph Mortola, MD
	5909	Elizabeth Trupin Campbell, MD
	5919	Mickey Karram, MD
	5920	Harrihar Pershadsingh, MD
	6003	John Larsen, MD
	6109	Mark Martens, MD
	6327	Janice Bacon, MD
	6377	Cheryl Walker, MD
	6378	Edward Zelnick, MD
	6390	Michael Margolis, MD
	6391	Howard Offenberg, MD
South Africa	6506	Peter De Jong, MD
	6507	Hendrik Cronje, MD
	6508	Cornelius Prins, MD
	6509	Barend Lindeque, MD
	6510	Johan DeSouza, MD

RESULTS

PATIENT ENROLLMENT AND DISPOSITION

Table 122.1 Patients evaluable (per applicant) by center

center ID	total randomized	Trovafoxacin			Cefoxitin/doxycycline		
		enrolled	evaluable	% evaluable	enrolled	evaluable	% evaluable
5248	2	1	0	0	1	0	0
5601	2	2	1	50	0	0	0
5602	2	1	1	100	1	1	100
5749	1	0	0	0	1	0	0
5750	5	3	1	33	2	2	100
5751	3	1	0	0	2	1	50
5752	6	2	1	50	4	1	25
5754	6	3	1	33	3	1	33
5756	3	1	0	0	2	2	100
5758	4	2	1	50	2	2	100
5763	4	2	1	50	2	0	0
5765	1	1	0	0	0	0	0
5768	1	1	1	100	0	0	0
5805	1	1	0	0	0	0	0
5866	7	3	2	67	4	2	50
5904	1	0	0	0	1	1	100
5906	2	2	2	100	0	0	0
5909	1	1	1	100	0	0	0
5919	2	1	0	0	1	1	100
5920	4	2	2	100	2	2	100
6109	12	6	4	67	6	3	50
6327	1	1	0	0	0	0	0
6377	2	1	1	100	1	0	0
6390	2	1	1	100	1	1	100
6506	19	9	8	89	10	10	100
6507	26	13	11	85	13	10	77
6508	1	0	0	0	1	1	100
6509	21	10	6	60	11	7	64
6510	16	8	7	88	8	7	88
Total	158	79	53	67.1	79	55	69.6

Medical officer's comments:

Only 4 of 36 US sites (5752, 5754, 5866, 6109) randomized more than 5 patients into the trial and only 1 US (6109) site randomized more than 10 patients into the trial. The 5 South Africa sites (6506-6510) that participated in the trial accounted for 40/79 (50.6%) and 43/79 (54.4%) patients enrolled in the trovafloxacin and ceftioxin/doxycycline arms, respectively; 32/53 (60%) and 35/55 (64%) of the evaluable patients in the alatro/trova and ceftioxin/doxycycline arms, respectively, were from these same South African sites.

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	Alatrofloxacin	Ceftioxin/Doxycycline
	Trovafloxacin	Doxycycline
	Number and Percentage (%) of Subjects	
Randomized Subjects	79	79
All Treated Subjects	79 (100%)	79 (100%)
Withdrawn from Treatment ^a	23 (29%)	10 (13%)
Completed Treatment	56 (71%)	69 (87%)
Withdrawn from Study	19 (24%)	17 (22%)
Withdrawn during Treatment	12 (15%)	8 (10%)
Withdrawn during Follow-Up	7 (9%)	9 (11%)
Completed Study	60 (76%)	62 (78%)
Completed Treatment and Study	49 (62%)	60 (76%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	79 (100%)	79 (100%)
Clinically Evaluable	53 (67%)	55 (70%)
Bacteriological Intent-to-Treat	51 (65%)	49 (62%)
Bacteriologically Evaluable	31 (39%)	33 (42%)
Assessed for Safety		
Adverse Events	79 (100%)	79 (100%)
Laboratory Tests	75 (95%)	77 (97%)

a Of the subjects withdrawn from treatment, 11 alatrofloxacin/trovafloxacin and 2 ceftioxin/doxycycline → doxycycline subjects completed study.

Medical officer's comments:

Fewer patients in the alatro/trova arm completed the study and treatment when compared with the ceftioxin/doxycycline arm.

Based on the applicant's calculations (outlined in the Statistical considerations section on page 12) 142 evaluable patients were needed per arm; however, only 79 patients were randomized to each of the treatment arms. Of the 79 subjects each in the alatro/trova and ceftioxin/doxycycline arms, 67% and 70% were clinically evaluable respectively, and 39% and 42% bacteriologically evaluable, respectively.

Table 122.3 Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Alatrofloxacin ↓ Trovafloracin (N=79)	Cefoxitin/doxycycline ↓ Doxycycline (N=79)
Number and Percentage (%) of Subjects		
Total Discontinued	23 (29%)	10 (13%)
Discontinuations Related to Study Drug:	12 (15%)	2 (3%)
Adverse Event	4 (5%)	1 (1%)
Insufficient Response	8 (10%)	1 (1%)
Discontinuations Unrelated to Study Drug:	11 (14%)	8 (10%)
Adverse Event	3 (4%)	2 (3%)
Did not meet Randomization Criteria	1 (1%)	0
Lost to Follow-up	4 (5%)	5 (6%)
Other	1 (1%)	1 (1%)
Protocol Violation	1 (1%)	0
Withdrawn Consent	1 (1%)	0

Medical officer's comments:

More than twice as many patients in the trovafloracin arm were discontinued from the study overall; discontinuations due to adverse events and insufficient response were more common in the alatro/trova arm.

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Table 122.4 Summary of patients disqualified from efficacy analysis

	Alatrofloxacin/ Trovafloracin	Cefoxitin/Doxycycline
Clinically Not Evaluable	26	24
No post- baseline clinical assessments	15	18
Insufficient Therapy	11	8
Prior Antibiotic Therapy	1	1
Concomitant Antibiotic Therapy	8	3
Intercurrent Illness	2	1
Surgical Intervention	1	3
Other	3	1
Bacteriologically Not Evaluable	22	22
No baseline pathogen	21	22
No post- baseline cultures	20	19

Medical officer's comments:

More patients in the alatro/trova arm were discontinued due to the use of concomitant antimicrobial therapy. Some of the reasons that concomitant antimicrobial agents were used included for an allergic reaction to study drug, and as therapy for trichomoniasis/bacterial vaginosis (metronidazole), respiratory tract infections, syphilis (procaine Penicillin G), and appendicitis.

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After review of case report forms, patients disqualified from the analysis and patients who received concomitant antimicrobial therapy during the study, the reviewer accepted the applicant's evaluable population.

DEMOGRAPHICS

Table 122.5 Demographic Characteristics of Treated Subjects

	Alatro 200mg IV qd -> Trova 200mg PO qd	Cefox 2g IV q6h & Doxy 100mg IV q12h -> Doxy 100mg PO bid
Number of Subjects	79	79
Age (yr)		
16- 44	78(99%)	78(99%)
45- 64	1(1%)	1(1%)
Mean	27.4	26.8
Minimum	(b)(4)	
Maximum		
Race		
ASIAN	1(1%)	0
BLACK	50(63%)	62(78%)
COLOURED	0	1(1%)
HISPANIC	8(10%)	5(6%)
MIXED	8(10%)	4(5%)
WHITE	12(15%)	7(9%)
Weight (kg)		
Mean	62.3	64.1
Minimum	(b)(4)	
Maximum		
Missing	1	0

Medical officer's comments:

There were no significant differences between the two groups with regard to race, weight, and age distribution.

APPLICANT'S EFFICACY ANALYSIS

Table 122.6 Summary of Sponsor-Defined Clinical Response Rates at the End of Study Visit (Clinically Evaluable Subjects)			
	Alatrofloxacin ↓ Trovafloracin (N=53)	Cefoxitin/doxycycline ↓ Doxycycline (N=55)	95% CI
Number and Percentage (%) of Subjects			
End of Study:			
Number of Subjects Assessed	53 (100%)	55 (100%)	
Cure	43 (81%)	50 (91%)	(-22.8, 3.2)
Failure	10 (19%)	5 (9%)	

Medical officer's comments:

Equivalence was not demonstrated for treatment difference in clinical cure rates; at the end of study, the cefoxitin/doxycycline group had higher clinical cure rates in comparison to the alatrofloxacin/trovafloracin group--- 91 vs. 81% respectively (95% CI with continuity correction: -24.6,5.1). An insufficient number of subjects were enrolled in this study.

To see if the difference in baseline severity as manifested by the presence of an adnexal mass had an effect on the treatment response, a subset analysis was performed. The results are summarized in the table that follows.

Table 122.7 Clinical Response Rates at the End of Study for Clinically Evaluable Subjects based on the presence/absence of adnexal mass (table provided by FDA statistician)

Subset	Alatro/Trova (N=53)	Control (N=55)	95% C.I.	P-value Breslow-Day
With Mass	13/20 (65.0%)	17/20 (85.0%)	(-51.1%, 11.1%)	0.616
Without Mass	30/33 (90.9%)	33/35 (94.3%)	(-18.8%, 12.0%)	
All	43/53 (81.1%)	50/55 (90.9%)	(-24.6%, 5.1%)	

Statistician's comments:

The Breslow-Day's test demonstrates that treatment effects were homogeneous (p-value=0.616) between the subjects with mass and the subjects without mass. Please note no conclusions could be drawn from the confidence intervals for the two subgroups due to the small numbers.

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Medical officer's comments:

Comparison of the subsets shows a greater treatment difference in the group with a mass when compared with those without a mass, suggesting that the severity of illness may have been a factor in the clinical response in this study.

Since there were only 3 patients in the alatro/trova and there was 1 patient in cefoxitin/doxy groups with tubo-ovarian abscesses, no subset analysis was performed for patients with tubo-ovarian abscesses.

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Pathogen	Alatrofloracin ↓ Trovafloracin (N=53)	Cefoxitin/doxycycline ↓ Doxycycline (N=55)
	Number of Subjects	
<i>N. gonorrhoeae</i>	11/18 (61%)	16/17 (94%)
<i>Peptostreptococcus</i> sp.	8/11	11/13
<i>C. trachomatis</i>	4/6	10/10
<i>E. coli</i>	5/5	4/5

a Includes ≥5 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Medical officer's comments:

Only 11/18 clinically evaluable patients in the alatro/trova group with *N. gonorrhoeae* and 4/6 with *C. trachomatis* isolated at baseline were considered cured at follow-up, while the cure rates in the cefoxitin/doxycycline arm were 16/17 and 10/10 patients with *N. gonorrhoeae* and *C. trachomatis*, respectively.

Table 122.9 Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at Visit 3 and the End of Study (Clinically Evaluable Subjects)			
Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Alatrofloxacin → Trovafoxacin: <u>Visit 3</u>			
5602-0070	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 5)
6109-0136	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)
6507-0200	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 18)
6507-0301	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 20)
6507-0311	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 15)
6507-0313	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 13)
6510-0272	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 7)
Alatrofloxacin → Trovafoxacin: <u>End of Study</u>			
5768-0013	Not Assessable	Failure	Failure (Day 15) carried forward
6109-0132	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)
6109-0136	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)
6507-0301	Cure	Failure	Concomitant antibiotics for inadequate response (Day 20)
6510-0272	Not Assessable	Failure	Concomitant antibiotic for inadequate response (Day 7)
Cefoxitin/doxycycline → Doxycycline: <u>Visit 3</u>			
6507-0302	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 18)
6509-0232	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 19)
Cefoxitin/doxycycline → Doxycycline: <u>End of Study</u>			
5904-0137	Cure	Failure	Concomitant antibiotics for inadequate response (Day 31)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

Medical officer's comments:

Following review of the case report forms for these subjects, the reviewer is in agreement with the applicant's assessment of outcome for these patients.

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SAFETY

Table 122.10 Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)		
	Alatrofloxacin ↓ Trovafloracin (N=79)	Cefoxitin/Doxycycline ↓ Doxycycline (N=79)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	57 (72%)	53 (67%)
BODY SYSTEM		
WHO Term		
APPL./INJ./INCISION/INSERTION SITE	15 (19%)	19 (24%)
Appl./Inj./Incision/Insertion Site Infection/Inflam.	10 (13%)	9 (11%)
Appl./Inj./Incision/Insertion Site Pain	2 (3%)	7 (9%)
CARDIOVASCULAR	10 (13%)	9 (11%)
Thrombophlebitis	5 (6%)	7 (9%)
CENTRAL AND PERIPHERAL NERVOUS	11 (14%)	8 (10%)
Headache	10 (13%)	6 (8%)
GASTROINTESTINAL	26 (33%)	17 (22%)
Abdominal Pain	7 (9%)	6 (8%)
Constipation	8 (10%)	6 (8%)
Nausea	14 (18%)	9 (11%)
Vomiting	9 (11%)	4 (5%)
REPRODUCTIVE	8 (10%)	12 (15%)
Vaginitis	3 (4%)	9 (11%)
SKIN/APPENDAGES	11 (14%)	3 (4%)
Pruritus	6 (8%)	1 (1%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site		
a ≥5 % of subjects in any treatment group.		
b Includes data up to 7 days after last dose of active study medication		

APPEARS THIS WAY ON ORIGINAL

Table 122.11 Supplemental table of most common adverse events (provided by the FDA statistician)

Safety	Trovafloracin	Ofloxacin/Clindamycin	Fisher's p value
Central and Peripheral nervous system	11(13.9%)	8 (10.1%)	0.626
Dizziness	3 (3.8%)	2 (2.5%)	1.00
Headache	10 (12.7%)	6 (7.6%)	0.43
Discontinuations due to an AE	10/79 (12.7%)	4/79 (5.1%)	0.160
Clinically significant lab abnormalities	42/75 (58.3%)	44/77 (57.1%)	1.000

Medical officer's comments:

The differences in the adverse events for each group were not statistically significant. The rates of dizziness and headache were comparable between the two groups.

Laboratory result abnormalities

No subject in either treatment group was discontinued from treatment due to abnormal laboratory results. When corrected for baseline abnormalities, clinically significant post-baseline laboratory abnormalities were comparable between groups: 56% (42/75) in the alatrofloxacin/trovafloracin group and 57% (44/77) in the cefoxitin/doxycycline group.

One subject (1%) in the cefoxitin/doxycycline group had clinically significant serum creatinine values; one subject (1%) in the alatrofloxacin/trovafloracin group had clinically significant total bilirubin values; and three subjects (4%) in the alatrofloxacin/trovafloracin group and two subjects (3%) in the cefoxitin/doxycycline group had clinically significant hemoglobin values.

Conclusions

An insufficient number of patients was enrolled in this study; equivalence was not demonstrated between alatrofloxacin/trovafloracin and cefoxitin/doxycycline in the treatment of PID in hospitalized patients.

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Study 154-125

Title: "A randomized, multicenter, double-blind comparative trial of trovafloracin and oral ofloxacin plus clindamycin for the treatment of acute pelvic inflammatory disease (PID) in ambulatory subjects"

Objective

to compare the safety and compared efficacy of trovafloracin and ofloxacin/clindamycin in the treatment of ambulatory subjects with acute PID.

STUDY DESIGN

In this double-blind, multicenter, comparative trial, patients with a clinical diagnosis of pelvic inflammatory disease, were treated with trovafloracin or ofloxacin/clindamycin for 14 days on an outpatient basis. The following table summarizes the design of the trial:

Location	USA (55 sites), RSA (1 site)
Centers without enrollment	1 (US site)
Study dates	June 5, 1995-May 8, 1996
Amendment dates:	January 12, 1995, March 22, 1995 August 18, 1995
Patients	16 years and older
Study dose and duration	Trovafloracin 200 mg qd for 14 days
Comparator	Ofloxacin 400 mg (2 capsules) bid for 14 days <u>PLUS</u> Clindamycin 450 mg (3 capsules) qid for 14 days
Blinding	third party blind; double dummy
Method of assignment	1:1 random assignment at each center
Primary efficacy variable	clinical outcome at visit 4
Safety variables	clinical signs and symptoms, laboratory results
Therapy evaluation, days (window):	
Baseline	1 (within 48 hours)
Visit 2	72 hours after initiation of treatment
End of treatment-EOT	14 (14-20)
End of study-EOS	4-6 weeks after study initiation
Number of subjects randomized	155 (trovafloracin)/ 161 (Ofloxacin and clindamycin)

STUDY POPULATION

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Inclusion criteria

Medical officer's comments:

Criteria were the same as in study 122.

GRADING OF PID BY CLINICAL EXAMINATION

- I. Uncomplicated: Limited to tube(s) and/or ovary(ies)
 - A. Without pelvic peritonitis
 - B. With pelvic peritonitis
 - II. Complicated: Inflammatory mass or abscess involving tube(s) and/or ovary(ies)
 - A. Without pelvic peritonitis
 - B. With pelvic peritonitis
 - III. Spread to structures beyond pelvis, i.e., ruptured tubo-ovarian abscess
- NOTE:** subjects with Grade II and III were excluded from the study.

Medical officer's comment:

As in study 122, patients with grade III PID were excluded; additionally, patients with grade II PID were also excluded.

Exclusion criteria

1. Inpatients.
2. Suspected tubo-ovarian abscess (TOA).
3. Severity of PID requiring hospitalization or parenteral therapy.

Medical officer's comments:

Criteria were the same as in study 122 with the exception of the additional exclusion criteria noted above.

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SUBJECT EVALUATION VISITS**Visit 1 at day 1 (Baseline)**

Within 24 hours prior to the start of therapy baseline visit assessments included:

- a) collection of demographic information, concurrent disease, concomitant medication use
- b) targeted physical examination, and vital signs (pulse, respiration, blood pressure, and body temperature)
- c) for women of childbearing potential, a serum or urine gonadotropin pregnancy test.
- d) a standard panel of blood and urine safety tests, a serologic test for syphilis (FTA or RPR).

In an attempt to standardize and semiquantitate clinical severity of PID and to assess clinical response to therapy, a Clinical Tenderness Score (CTS) was used (see study 122). Upon entry into the study, each subject had a determination made of the CTS (maximum CTS = 42), extent of fever, and white blood cell count. The subject's body temperature and CTS were also assessed at the follow-up visits two and four to six weeks following initiation of therapy.

Patients with adnexal masses were excluded from study 125.

Bacteriologic specimens should have been obtained within 24 hours prior to institution of therapy. They were obtained as outlined below or by the use of culdocentesis or endometrial biopsy, at the discretion of the investigator.

- a) Culture by swab of the endocervix and rectum for *N. gonorrhoeae* and of *C. trachomatis* by culture or antigen detection from the endocervix.
- b) At the discretion of the investigator, endometrial cultures could have been obtained. Endometrial material was obtained for anaerobic and facultative culture and for isolation of *N. gonorrhoeae*. *C. trachomatis* was sought by culture or antigen detection. All isolates of *C. trachomatis* were to be frozen at -70°C for possible later susceptibility testing.
- c) All pathogenic isolates (except *C. trachomatis*) identified by the investigator were sent to a central laboratory for testing.

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Visit 2 at 72 hours

Failure to demonstrate response at 72 hours after initiation of therapy (i.e., reduction in the CTS, and/or reduction in fever, and/or reduction in white blood cell count) constituted clinical failure. At any time, depending upon the clinical situation (e.g., deteriorating clinical condition), the investigator could remove the subject from treatment and initiate additional therapeutic measures. In such a case the subject was considered a clinical failure.

No bacteriological assessments were made. APPEARS THIS WAY ON ORIGINAL

Recording of vital signs, concomitant medication, study drug dosing, adverse events was done and repeat of the battery of blood and urine tests performed at baseline were repeated.

Visit 3 at 2 weeks (Days 14-20)

The subject's response to therapy was determined by repeating the following observations:

The CTS, extent of fever, and white blood cell count were assessed. Appropriate cultures, including endocervical, rectal, or endometrial (at the discretion of the investigator) specimens were assessed for *N. gonorrhoeae*, *C. trachomatis*, and anaerobic and aerobic bacteria.

Vital signs, concomitant medication, study drug dosing, adverse events were recorded and the battery of blood and urine tests performed at baseline was repeated. In addition, interval sexual history was obtained.

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Visit 4 at 4-6 weeks (Days 28-42)

The tests and evaluations performed at visit 3 were repeated at visit 4. The battery of blood and urine tests performed at the first three visits were repeated at this visit only if clinically significant results were detected at visit 3. In addition, interval sexual history was obtained.

Visit 4 was the primary efficacy timepoint for overall clinical and bacteriological response.

Medical officer's comments:

The timing of the visits was the same as in study 122 but there were differences in the collection of bacteriological specimens. See study 122 comments.

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Susceptibility testing

Susceptibility to CP-99,219, ofloxacin, and clindamycin was determined by disk diffusion and minimum inhibitory concentrations (MICs) for all pathogenic isolates (except *C. trachomatis*), whether at baseline or at follow-up.

Criteria for determining susceptibility to the study drugs ("susceptibility breakpoints") are summarized below.

Criteria	Trovafloracin		Ofloxacin		Clindamycin	
	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) (5 μg Disk)	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) (5 μg Disk)	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm) (2 μg Disk)
Susceptible (For <i>N. gonorrhoeae</i>)	≤ 2	≥ 15	≤ 2 (≤ 0.25)	≥ 16 (≥ 31)	≤ 0.5	≥ 21
Intermediate (For <i>N. gonorrhoeae</i>)	4	11-14	4 (-)	13-15 (-)	1-2	15-20
Resistant (For <i>N. gonorrhoeae</i>)	≥ 8 (-)	≤ 10 (-)	≥ 8	≤ 12	≥ 4	≤ 14

Note: Trovafloracin 5 μg disks were never approved for clinical trial use and were subsequently replaced with 10 μg disks. Results using the 10 μg disks were not available during the study report period.
(-) No intermediate or resistant strains of *N. gonorrhoeae* currently identified.

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APPLICANT'S CRITERIA FOR EVALUABILITY

see study 122

Medical officer's (MO) evaluability criteria

A. The primary efficacy variable is clinical response at the 4-6 week visit.

Patients were non-evaluable clinically if:

- insufficient therapy ---MO accepted patients who received at least 10 days of the study drug unless they were clinical failures early in the course of treatment
- unprotected sexual contact during study
- no clinical assessment 2-4 weeks after completion of study therapy
- positive serologic test for syphilis (indeterminate status)
- patients who received antibiotics within 2 weeks prior to study initiation
- IUD in place >24 hours after initiation of study therapy
- missing data and data outside study windows
- no baseline clinical assessment
- incorrect baseline diagnosis
- concomitant antimicrobial therapy during study unrelated to PID

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B. Clinical failures will be those patients who:

- require surgery after 72 hours of study therapy
- patients who develop TOA while on therapy
- patients requiring hospitalization
- clinically cured but bacteriologic failure
- insufficient therapy with study drug due to poor clinical response
- required concomitant systemic antimicrobial therapy due to poor clinical response or persistent pathogen
- subjects who were given alternate treatment due to poor response to the study drug or persistent pathogen were considered evaluable

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C. Bacteriologically non evaluable:

The reviewer agrees with applicant's criteria.

Clinical and Microbiologic Endpoints
same criteria as in study 122

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Statistical considerations and Efficacy analyses
see study 122.

Criteria for Safety evaluation

same as for study 122; in addition the following criterion was added:

- Theophylline concentrations--since ofloxacin may raise theophylline levels, at the investigator's discretion, all subjects on concomitant theophylline should have theophylline levels monitored periodically at the local laboratory.

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SCHEDULE OF STUDY VISITS AND PROCEDURES

STUDY DAYS

	Baseline Day 1	Visit 2 72h	Visit 3 2 Weeks (Days 14-20)	Post-Therapy Visit 4 4-6 Weeks (Days 28-42)
Treatment	X		X	
Compliance Checks		X	X	X
Informed Consent	XX			
Demographic Information	XX			
Targeted Physical Examination	XX			
Concomitant Medication	XX	XX	XX	
Vital Signs	XX	XX	XX	
Assessments	XX	X	X	
Clinical	XX ^a			
Culdocentesis	XX ^a		X ^a	X ^a
Endometrial Biopsy	XX			
Laboratory	XX			
1. Hematology	XX	XX	X ^b	
2. Serum Chemistry	XX	XX	X ^b	
3. Urinalysis	XX	XX	X ^b	
4. Microbiology				
a. <i>N. gonorrhoeae</i>	X	X	X	
cultures				
b. <i>C. trachomatis</i>	X	X	X	
cultures or assays				
c. Anaerobic/aerobic	X	X	X	
cultures	XX			
5. FTA or RPR	XX			
6. Pregnancy Test				
Adverse Events	XX	X	X	

^a Optional, and at investigator's discretion

^b To be done only if there is/are significant abnormality(ies) at visit 3

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INVESTIGATORS AND STUDY SITES

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5019	Nazir Memon, MD
	5112	Timothy Kotschwar, PharmD
	5165	Jane Schwebke, MD
	5166	Lorraine Dubouchet/ William McCormack, MD
	5202	Richard Beyerlein, MD
	5248	Carol Terregino, MD
	5601	James McGregor, MD
	5602	Stanley Gall, MD
	5604	James West, MD
	5609	Harvey Friedenson, MD
	5748	David Baker, MD
	5749	Gregory Fossum, MD
	5751	Abner Korn, MD
	5752	Maurizio Maccato, MD/ Charles Ericsson, MD
	5756	Kevin Huddleston, MD
	5757	James Van Hook, MD
	5758	Bernard Gonik, MD
	5759	Richard Sweet, MD
	5763	Rebecca Ryder, MD
	5764	Chong Chang, MD
	5765	Blane Crandall, MD
	5766	Sebastian Faro, MD
	5767	Javier Gutierrez, MD
	5768	Peter Marsh, MD
	5866	William Koltun, MD
	5872	George Wendel, Jr., MD
	5904	Richard Derman, MD
	5905	Harold Wittcoff, MD
	5906	Dean Coonrod, MD
	5907	Joseph Mortola, MD
	5908	Ronald Paul, MD
	5909	Elizabeth Trupin Campbell, MD
	5918	Roy Ducote, MD
	5919	Mickey Karram, MD
	5920	Harrihar Pershadsingh, MD
	6000	Lynn Borgatta, MD
	6001	David Campbell, MD
	6002	Luis Sanchez-Ramos, MD
	6003	John Larsen, MD
6070	Stephen Kasparian, MD	
6109	Mark Martens, MD	
6145	Iris Reyes, MD	
6326	Clarence Alston, MD	
6327	Janice Bacon, MD	
6329	Clifford Callaway, MD	
6330	Jay Falk, MD	
6331	John McGee, MD	
6332	Vincent Pillari, MD	
6334	David Schreck, MD	
6377	Cheryl Walker, MD	
6378	Edward Zelnick, MD	
6390	Michael Margolis, MD	
6391	Howard Offenber, MD	

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	6407	Scott Boone, MD
	6408	Wynne Brown, MD
South Africa	6509	Barend Lindeque, MD

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RESULTS

PATIENT ENROLLMENT AND DISPOSITION

Table 125.1 Applicant's clinically evaluable patients by center

center ID	Trovafloracin				Trovafloracin/clindamycin			
	total randomized	enrolled	evaluable	% evaluable	enrolled	evaluable	% evaluable	
5019	0	0	0	0	0	0	0	
5112	6	3	3	100	3	3	100	
5165	18	9	6	67	9	4	44	
5166	37	19	12	63	18	15	83	
5248	8	4	0	0	4	1	25	
5601	2	1	1	100	1	1	100	
5602	6	2	2	100	4	1	25	
5604	2	1	0	0	1	0	0	
5609	3	1	0	0	2	1	50	
5748	3	1	0	0	2	2	100	
5751	4	2	1	50	2	1	50	
5752	10	5	4	80	5	3	60	
5756	7	3	2	67	4	2	50	
5759	7	4	2	50	3	2	67	
5763	3	2	0	0	1	1	100	
5765	1	0	0	0	1	1	100	
5768	5	3	3	100	2	1	50	
5866	38	19	12	63	19	13	68	
5872	3	1	0	0	2	0	0	
5904	5	2	1	50	3	2	67	
5905	3	2	0	0	1	0	0	
5906	5	2	2	100	3	3	100	
5908	21	10	9	90	11	7	64	
5909	8	4	3	75	4	1	25	
5919	2	1	0	0	0	0	0	
5920	45	22	18	82	23	14	61	
6000	3	1	1	100	2	1	50	
6002	2	1	1	100	1	1	100	
6109	10	4	2	50	6	5	83	
6145	8	4	4	100	4	2	50	
6327	3	1	0	0	2	1	50	
6331	3	2	1	50	1	1	100	
6332	2	2	0	0	0	0	0	
6334	12	6	1	17	6	2	33	
6377	2	1	0	0	1	0	0	
6391	4	2	2	100	2	1	50	
6407	5	2	2	100	3	1	33	
6408	3	2	2	100	1	1	100	
6509	7	3	3	100	4	2	50	
Total	316	155	101	65.2	161	97	60.2	

Medical officer's comments:

Sixty five per cent of the 155 randomized to the trovafloxacin arm and 60% of the 161 patients randomized to the ofloxacin/ clindamycin arm were clinically evaluable. Unlike the inpatient study, there was only 1 South African site, which accounted for a small number of evaluable patients. Six U.S. sites (5165, 5166, 5866, 5908, 5920, 6334) had more than 10 patients randomized into the study.

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	Trovfloxacin		Ofloxacin/Clindamycin	
	Number and Percentage (%) of Subjects			
Randomized Subjects	155		161	
Randomized, Not Treated	6		5	
All Treated Subjects	149	(100%)	156	(100%)
Withdrawn from Treatment ^a	30	(20%)	47	(30%)
Completed Treatment	121	(81%)	109	(70%)
Withdrawn from Study	27	(18%)	31	(20%)
Withdrawn during Treatment	19	(13%)	24	(15%)
Withdrawn during Follow-Up	8	(5%)	7	(4%)
Completed Study	124	(83%)	126	(81%)
Completed Treatment and Study	111	(74%)	102	(65%)
Evaluated for Efficacy ^b				
Clinical Intent-to-Treat	152	(98%)	159	(99%)
Clinically Evaluable	101	(65%)	97	(60%)
Bacteriological Intent-to-Treat	40	(26%)	43	(27%)
Bacteriologically Evaluable	21	(14%)	27	(17%)
Assessed for Safety				
Adverse Events	149	(100%)	156	(100%)
Laboratory Tests	141	(95%)	140	(90%)

a Of the subjects withdrawn from treatment, 11 trovafloxacin and 23 ofloxacin/clindamycin subjects completed study.

b Based on number of randomized subjects.

Medical officer's comments:

There were 21/155 (14%) and 27/161(17%) bacteriologically evaluable patients, and 65% and 60% clinically evaluable patients in the trovafloxacin and ofloxacin/clindamycin groups, respectively.

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Table 125.3 Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Trovafloracin (N=149)		Ofloxacin/Clindamycin (N=156)	
	Number and Percentage (%) of Subjects			
Total Discontinued	30	(20%)	47	(30%)
Discontinuations Related to Study Drug:	17	(11%)	24	(15%)
Adverse Event	17	(11%)	21	(13%)
Insufficient Response	0		3	(2%)
Discontinuations Unrelated to Study Drug:	13	(9%)	23	(15%)
Adverse Event	1	(<1%)	2	(1%)
Did not meet Randomization Criteria	1	(<1%)	0	
Laboratory Abnormality	0		1	(<1%)
Lost to Follow-up	8	(5%)	9	(6%)
Other	1	(<1%)	5	(3%)
Protocol Violation	1	(<1%)	1	(<1%)
Withdrawn Consent	1	(<1%)	5	(3%)

Medical officer's comments:

Although more patients were discontinued from the ofloxacin/clindamycin group overall, the number of discontinuations from adverse events and insufficient response (related to study drug) were the same in each arm.

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Table 125.4 Summary of patients disqualified from efficacy analysis

	Trovafloracin 200 mg qd	Ofloxacin 400mg b. i. d./ Clindamycin 450mg q. i. d.
Clinically Not Evaluable Subjects	51	62
Randomized, Not Treated	5	4
No post- baseline clinical assessments	31	40
Insufficient Therapy	26	35
Concomitant Antibiotic Therapy	23	22
Intercurrent Illness	2	3
Others	0	1
Bacteriologically Not Evaluable Subjects	80	70
No baseline pathogen	76	69
No post- baseline cultures	76	67

Medical officer's comments:

After review of the case report forms for patients on concomitant therapy, and review of the applicant's failures and nonevaluable group, the reviewer accepted the applicant's evaluable population.

DEMOGRAPHICS

Table 125.5 Demographic Characteristics of Randomized and Clinically Evaluable Subjects

	Trovafloracin 200 mg	Ofloxacin 400mg b. i. d. / Clindamycin 450mg q. i. d.
Number of Subjects	149	156
Age (yr)		
16- 44	146(98%)	154(99%)
45- 64	3(2%)	2(1%)
Mean	26.7	26.7
Minimum	(b)(4)	
Maximum		
Race		
BLACK	75(50%)	69(44%)
HISPANIC	18(12%)	33(21%)
NATIVE AMERICAN	0	1(<1%)
ROMANIAN	0	1(<1%)
WHITE	56(38%)	52(33%)
Weight (kg)		
Mean	70.2	67.8
Minimum	(b)(4)	
Maximum		
Missing	1	0

Medical officer's comments:

The groups are comparable for race, weight and age.

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APPLICANT'S EFFICACY ANALYSIS

Table 125.6 Summary of Sponsor-Defined Clinical Response Rates at the End of Study Visit (Clinically Evaluable Subjects)					
	Trovafloracin (N=101)		Ofloxacin/Clindamycin (N=97)		95% CI
Number and Percentage (%) of Subjects					
End of Study:					
Number of Subjects Assessed	101	(100%)	97	(100%)	
Cure	92	(91%)	89	(92%)	(-8.5, 7.1)
Failure	9	(9%)	8	(8%)	
CI=Confidence Interval					

Medical officer's comments:

Statistical equivalence of the two treatment regimens was supported by the 95% confidence intervals for clinical cure rates at the end of study (trovafloracin: 91%; ofloxacin/clindamycin: 92% [CI with continuity correction: (-9.5, 8.1)]).

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Table 125.7 Summary of Clinical Cure Rates at the End of Study Visit For the Most Frequently Isolated Baseline Pathogens ^a (Clinically Evaluable Subjects)		
	Trovafloracin (N=101)	Ofloxacin/Clindamycin (N=97)
	Number of Subjects	
Pathogen	End of Study	
<i>N. gonorrhoeae</i>	12/12	8/8
<i>C. trachomatis</i>	11/12	14/14

a Includes ≥5 isolates of a given pathogen in any treatment; percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

Medical officer's comments:

All the clinically evaluable patients with a baseline pathogen, with the exception of one patient in the trovafloracin arm with *C. trachomatis*, were cured. This is contrast with the inpatient study in which there was a poor clinical response in the trovafloracin arm for patients with *N. gonorrhoeae* (see table 122.8).

APPEARS THIS WAY ON ORIGINAL

Table 125.8 Summary of Bacteriologic Response rates at the EOS for Bacteriologically evaluable subjects (Table J in study report)

	Trovafloracin n=21	Ofloxacin/clindamycin n=27
Satisfactory	21/21 (100%)	25/27 (93%)
Unsatisfactory	0	2 (7%)

Medical officer's comments:

Comparable percentages of satisfactory bacteriologic responses were seen in the two study groups.

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Table 125.9 Summary of the Differences Between Investigator-Defined and Sponsor Defined Clinical Responses at the End of Study (Clinically Evaluable Subjects)			
Subject Number	Investigator Assessment	Sponsor Assessment	Reason
Trovafloracin:			
5906-0024	Cure	Failure	Concomitant antibiotics for inadequate response (Day 28)
5920-0181	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 17)
Ofloxacin/Clindamycin:			
5756-0103	Cure	Failure	Concomitant antibiotics for inadequate response (Day 3)
6109-0218	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)

Medical officer's comment:

The case report forms for these patients were reviewed and the reviewer agrees with the sponsor's assessment in each case.

BEST POSSIBLE

BEST POSSIBLE

SAFETY

Table 125.10 Summary of the Most Commonly Reported Adverse Events ^{a,b} by Body System - All Causality (All Treated Subjects)				
	Trovafloracin (N=149)		Ofloxacin/Clindamycin (N=156)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	114	(77%)	110	(71%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS	69	(46%)	24	(15%)
Dizziness	55	(37%)	10	(6%)
Headache	31	(21%)	12	(8%)
GASTROINTESTINAL	61	(41%)	80	(51%)
Abdominal Pain	12	(8%)	8	(5%)
Diarrhea	10	(7%)	34	(22%)
Dyspepsia	2	(1%)	8	(5%)
Nausea	36	(24%)	41	(26%)
Vomiting	16	(11%)	23	(15%)
REPRODUCTIVE	28	(19%)	34	(22%)
Vaginitis	19	(13%)	27	(17%)
SPECIAL SENSES	10	(7%)	21	(13%)
Taste Perversion	4	(3%)	21	(13%)
a ≥5 % of subjects in any treatment group.				
b Includes data up to 7 days after last dose of active study medication				
Ref.: Tables 6.2 and 6.4				

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Table 125.11 Supplemental table of adverse events (provided by FDA statistician)

Safety	Trovafloracin	ofloxacin/Clindamycin	Fisher's p value
Central and Peripheral nervous system	65 (43.6%)	24 (15.4%)	<0.001
Dizziness	55 (36.9%)	10 (6.4%)	<0.001
headache	31 (20.8%)	12 (7.7%)	0.002
Discontinuations due to an AE	19/149 (12.8%)	24/156 (15.4%)	0.622
Clinically significant lab abnormalities	44/141 (31.2%)	41/140 (29.3%)	0.795

Medical officer's comments:

The percentages of dizziness and headache were higher in the trovafloracin than in the ofloxacin/clindamycin arm, and these differences were statistically significant.

APPEARS THIS WAY ON ORIGINAL

Laboratory Abnormalities

One subject in the ofloxacin/clindamycin group was discontinued from treatment due to laboratory abnormalities.

Two subjects (1%) in the trovafloracin group and 2 subjects (1%) in the ofloxacin/clindamycin group had clinically significant elevations in aspartate aminotransferase (SGOT); one subject

(<1%) in the trovafloxacin group and two subjects (1%) in the ofloxacin/clindamycin group had clinically significant elevations in alanine aminotransferase (SGPT).

APPEARS THIS WAY ON ORIGINAL

Conclusions

Trovafloxacin equivalent to ofloxacin/clindamycin in the treatment of pelvic inflammatory disease caused by *N. gonorrhoeae* or *C. trachomatis* in outpatient ambulatory patients. However, alatrofloxacin/ trovafloxacin did not achieve equivalence with cefoxitin/doxycycline in hospitalized patients with PID caused by *N. gonorrhoeae* or *C. trachomatis* (insufficient number of subjects enrolled).

APPEARS THIS WAY ON ORIGINAL

Recommendations

It is recommended that trovafloxacin be approved for the treatment of pelvic inflammatory disease caused by *N. gonorrhoeae* or *C. trachomatis* in ambulatory patients only.

DRAFT LABELING

/s/ [Redacted Signature]

Mamodikoe K. Makhene, M.D.
Medical Reviewer, HFD-520

APPEARS THIS WAY ON ORIGINAL

cc:

- IND (b)(4)
- IND [Redacted]
- NDA 20-759, 760
- HFD-590/ Deputy Div Director/Albrecht
- HFD-590/Medical TL/Leissa [Signature]
- HFD-344/DSI/Thomas
- HFD-520/PharmTox/Ellis
- HFD-520/Chemistry/Shetty
- HFD-520/Microbiology/Altaie
- HFD-590/Biopharm/Colangelo
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70J.

MEDICAL REVIEW OF NDA 20-759

Applicant:

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NOV 19 1998

Submission/Review dates

Date of submission:	December 27, 1996
Date review begun:	February 24, 1997
First draft of review completed:	June 23, 1997
Second draft completed:	December 31, 1997
Date received from secondary reviewer:	October 21, 1998
Date review completed:	November 17, 1998

Related drugs

(b)(4)

Currently approved indications: none

Material reviewed: Electronic submission

REGULATORY BACKGROUND

(b)(4)

PROPOSED LABELLING

DRAFT LABELING

AGENTS APPROVED FOR THE TREATMENT OF CHLAMYDIA URETHRITIS/CERVICITIS

Ofloxacin, Azithromycin and Grepafloxacin have been approved for the treatment of nongonococcal urethritis due to *Chlamydia trachomatis*; these products achieved eradication rates of 95% or better when compared with doxycycline in the treatment of non-gonococcal urethritis.

REGULATORY GUIDANCE**1. 1992 DAIDP Points to Consider**

Establish equivalence or superiority to an approved product in one statistically adequate and well-controlled, multicenter trial in men, and one statistically adequate and well-controlled, multicenter trial in women.

2. IDSA/FDA Guidelines [Clin Infectious Dis 1992; 15(S1):131-9]

- a) Subjects should be stratified for randomization according to gender if men and women are included in the same trial
- b) Subjects (b)(4) can participate with the consent of a parent/guardian, or if they are considered emancipated minors according to local regulations.
- c) A minimum of two centers with no single site contributing greater than 60% of the evaluable subjects should be involved. One hundred evaluable patients in each trial should be treated with the investigational drug and 100 with the control regimen; these numbers should be attained separately for men and women.
- d) The presumptive enrollment of subjects on the basis of unprotected sexual contact with a documented case of *C. trachomatis* urogenital infection within the preceding 4 weeks is acceptable, but the isolation of *C. trachomatis* or documentation of chlamydial urethritis or cervicitis is necessary for continued participation in the study.
- e) At least 3 follow-up visits should be scheduled:
 - 2-4 days after completing multiple dose treatment
 - 1-2 weeks after this visit
 - 4-6 weeks after the treatment is complete to document the eradication of *C. trachomatis*. At least 60% of those who return for the visit at 2-3 weeks must return for the 4-6 week final visit.
- f) The primary criteria for evaluability include:
 - meeting of the case definition and the inclusion criteria
 - the successful collection of specimens
 - the completion of the treatment regimen (80% or greater compliance).
- g) Eradication of *C. trachomatis* defines the primary outcome measure, microbiologic response and the overall cure. Unless the serotypes differ, isolation of *C. trachomatis* at any visit within the follow-up period represents persistence or reappearance of *C. trachomatis* infection.

APPEARS THIS WAY ON ORIGINAL

NON-CLINICAL STUDIES

(b)(4)

Animal Pharmacology/Toxicology

See Toxicology review by A. Ellis, Ph.D.

Microbiology

See Microbiology review by S. Altaie, Ph.D.

CLINICAL STUDIES**Human Pharmacokinetics/Pharmacodynamics**

See full review by P. Colangelo, Ph.D.

Trovafloxacin's biologic half-life is approximately 9 to 11 hours. The mean bound fraction in plasma samples is approximately (b)(4). Steady state concentrations are achieved by the third daily dose. In adult subjects, the pharmacokinetics of trovafloxacin are not affected by age or gender. The peak blood level (C_{max}) of trovafloxacin

at a 200 mg oral dose is 2.5 ug/mL and tissue/ serum concentration ratios in the cervix after single and multiple doses of trovafloxacin 200 mg were 0.5 ug/mL (3-29 hr postdose) and 0.6 ug/mL (3-16 hr postdose), respectively.

APPEARS THIS WAY ON ORIGINAL

Human Clinical Experience

The efficacy and safety of trovafloxacin for several indications were evaluated in 45 phase I studies and 31 phase II/III studies.

APPEARS THIS WAY ON ORIGINAL

INTRODUCTION TO CLINICAL TRIALS

The applicant submitted 2 pivotal clinical trials in support of this indication. The first was an unblinded, dose ranging study for the treatment of urogenital chlamydial infection with trovafloxacin. After completion of this study, the efficacy and safety of oral trovafloxacin 200 mg qd for 5 days in the treatment of uncomplicated chlamydial urethritis/cervicitis was assessed in a randomized, double-blind, comparative trial, with the standard Center for Disease Control and Prevention (CDC) recommended doxycycline regimen as the comparator.

APPEARS THIS WAY ON ORIGINAL

Study 154-123

Title: "A double blind, randomized, comparative study of trovafloxacin in the treatment of uncomplicated chlamydial urethritis/cervicitis."

APPEARS THIS WAY ON ORIGINAL

Primary objective

To compare the safety and efficacy of trovafloxacin and doxycycline in the treatment of subjects with uncomplicated chlamydial urethritis/ cervicitis.

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Study design Summary

Location	multi-center, international
Total centers	41
Protocol amendments	January 12, 1995 and March 9, 1995
Study dates	27 March 1995-22 May 1996
Patient ages	16 years and older
Study dose and duration	Trovafloxacin 200-mg qd orally for 5 days
Concurrent control	Doxycycline 100 mg bid orally for 7 days
Blinding	third party blind
Method of assignment	1:1; stratification by gender
Efficacy variables	microbiologic, clinical
Safety variables	clinical signs and symptoms, laboratory results
Evaluation days (protocol window):	
Baseline	1 (within 48 hours before the start of therapy)
End of treatment-EOT	10 (9-11)
post	21 (19-23)
Test of cure (TOC) (end of study-EOS)	35 (31-39)
Number of subjects randomized	495 (trovafloxacin)/482 (doxycycline)

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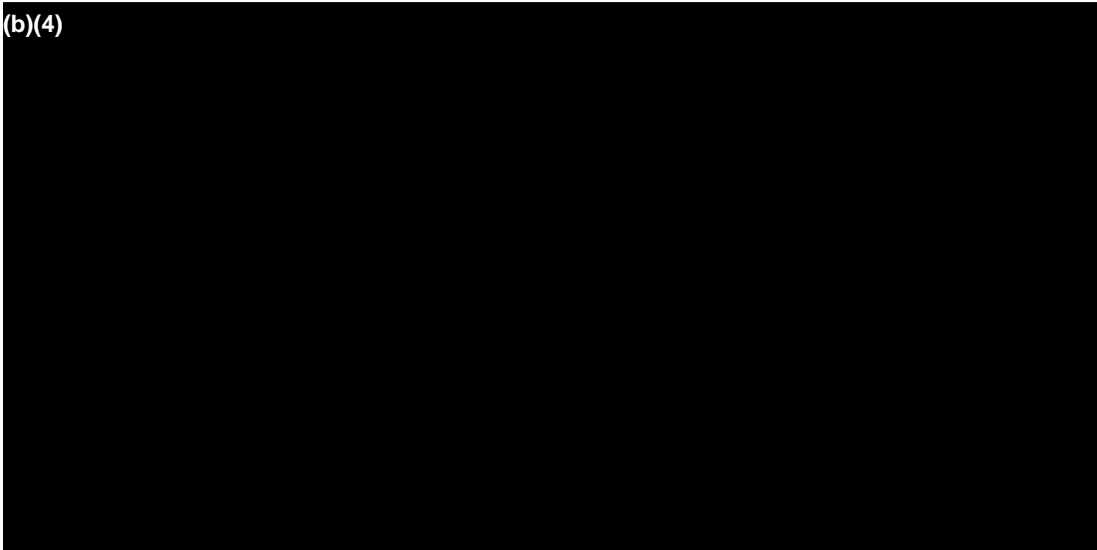
STUDY POPULATION (from the study protocol)

Approximately 500 subjects were to be enrolled in this study in order to obtain the desired 400 evaluable subjects, with 100 males and 100 females per treatment group. Each study site was to attempt to enroll at least 20 subjects.

Inclusion criteria

1. Outpatient men or women. Women of childbearing potential (i. e., not surgically sterile or < one year post-menopausal) must have had a negative urine or serum gonadotropin pregnancy test immediately prior to entry in the study, and must have used adequate contraception both during and for one month after the end of the study.
2. At least 16 years of age.
3. Males with presumptive chlamydial urethritis, defined as the presence of a

(b)(4)



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Exclusion criteria

1. Pregnant women or nursing mothers.
2. History of hypersensitivity or intolerance to any quinolone or tetracycline
3. Inpatients.
4. Clinical evidence of gonococcal pharyngitis, proctitis, disseminated gonococcal infection, or the presence of any other infection at enrollment that may have required treatment with an antibiotic other than the study drug.
5. Treatment with any systemic antibiotic with potential anti-chlamydial activity within 72 hours prior to entry into the study (or up to two weeks or those with a positive culture or non culture test for chlamydia within two weeks prior to enrollment). Agents known to possess anti-chlamydial activity included: azithromycin, tetracycline, erythromycin, ofloxacin, ciprofloxacin, ampicillin, amoxicillin, sulfamethoxazole, clindamycin, rifampin, and rosaramycin.
6. Treatment with another investigational drug within 30 days prior to entry into the study.
7. Evidence of significant gastrointestinal or other conditions , which could affect drug absorption
8. Evidence or history of clinically significant hematologic, renal, or cardiovascular disease or immunologic compromise
9. History of epilepsy or seizures
10. Prior enrollment in this protocol
11. Subjects who for any reason in the opinion of the investigator, were not expected to comply with the requirements of this protocol.

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

The reviewer agrees with the criteria chosen. Although the applicant did not exclude subjects with positive RPR or FTA at baseline, the reviewer excluded these patients.

APPEARS THIS WAY ON ORIGINAL

PROCEDURES (from applicant's submission)

Study medication was in the form of tablets and capsules, packaged in blister cards using a double-dummy technique to maintain blinding. The study drug administration schedule provided one of the following two doses of study drug:

- trovafloxacin 200mg (2 tablets) daily as a single dose for 5 days
- doxycycline 100 mg (1 capsule) bid for 7 days

Subjects began study drug medication with the morning dose (even if it was not morning), and completed a full day of medication on day 1.

Microbiologic measurements and Susceptibility testing

Susceptibility to trovafloxacin and doxycycline was determined by minimum inhibitory concentrations (MICs) for all isolates of *N. gonorrhoeae*, whether at baseline or at follow-up. For *C. trachomatis*, MICs were determined for two baseline isolates from each center and for all treatment failures. Susceptibility testing was subsequently performed at a central location. The criteria for determining susceptibility to the study drugs are summarized below:

	Trovafloxacin*	Doxycycline+
CRITERIA	MIC (ug/ml)	MIC (ug/ml)
SUSCEPTIBILITY	≤2	≤4
INTERMEDIATE	4	8
RESISTANT	≥8	≥16

APPEARS THIS WAY ON ORIGINAL

*Tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing.

+NCCLS criteria...

APPEARS THIS WAY ON ORIGINAL

SUBJECT EVALUATION VISITS

Visit 1 at day 1 (Baseline)

This visit took place within 48 hours prior to the start of therapy.

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Visit 2 at day 10 (9- 11)

All subjects with culture confirmed chlamydial infection had urethral/cervical cultures for chlamydia repeated. In addition, follow-up cultures for *N. gonorrhoeae* were obtained in males or females with positive baseline cultures for *N. gonorrhoeae*, all females (endocervical culture) and any males with persistent, new, or recurrent clinical signs or symptoms of urethritis at this visit. The battery of blood and urine tests performed at baseline were repeated.

Visit 3 at day 21 (19- 23)

APPEARS THIS WAY ON ORIGINAL

Same as visit 2; in addition, the blood and urine tests performed at baseline were repeated at this visit only if clinically significant results were detected at visit 2.

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Visit 4 at day 35 (31- 39)

Visit 4 was the primary efficacy timepoint.

Same as visit 3; the blood and urine tests performed at baseline were repeated at this visit only if clinically significant results were detected at visit 3.

DRAFT LABELING

The sponsor-defined windows for evaluation were:

	<u>protocol visit windows</u>	<u>applicant evaluable windows (post hoc)</u>
Baseline	1 (within 48 hours)	
End of treatment	10 (b)(4)	
post	21	
TOC (end of study)	35	

APPEARS THIS WAY ON ORIGINAL

The subjects were instructed not to donate blood during, and for 6 weeks following administration of study drug. Subjects were to abstain from sexual activity through the first follow-up visit. Thereafter, sexual intercourse with the use of a condom was permissible. (If unable to abstain from sexual activity until the first follow-up visit, the use of a condom was essential for the determination of evaluability).

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BEST POSSIBLE

PROTOCOL OVERVIEW

SCHEDULE OF STUDY VISITS AND PROCEDURES (from the applicant's protocol)

	STUDY DAYS						
	Baseline Day, V1	V2 (9- 11) ^a 10	V3 (19- 23) 21	V4 (31- 39) 35	APPEARS THIS WAY ON ORIGINAL		
Treatment							
Compliance check		x					
History and Physical Assessments:							
Clinical		x	x	x			
Laboratory							
1. ITA or RPR							abn ^b
2. Hematology		x	abn ^b	abn ^b			abn ^b
3. Serum Chemistry		x	abn ^b	abn ^b			abn ^b
4. Urinalysis		x					
5. Gram stain ^c							x ^a
6. Cultures for <i>C. trachomatis</i>		x	x				
7. Cultures for <i>N. gonorrhoeae</i>		x	x				x
8. Pregnancy test ^d		x					
Adverse Events		x					

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^a window for follow-up visit
^b Only for clinically significant abnormalities present at previous visit
^c Where feasible (i.e. presence of urethral or cervical discharge)
^d For women of childbearing potential
 abn=abnormal

Medical reviewer's comments:
 Safety evaluations were done up to visit 3 only indicating that adverse events occurring between visit 3 and the end of the study at visit 4 were likely missed.

Medical reviewer's comments:

The applicant's protocol windows and test-of-cure (TOC) visit at the end of study were consistent with the 1992 IDSA/FDA guidelines. The CDC guidelines [MMWR Sept 24, 1993; 42(RR-14):51] recommend that follow-up of patients treated for urogenital chlamydial infections be done at least 3 weeks after completion of treatment since the validity of testing done before 3 weeks after the completion of therapy has not been established. Based on this recommendation for the timing of the TOC visit, and the fact that few patients in the study had their TOC between days 28-31 (lower limit of protocol vs. post hoc analysis windows), the reviewer accepted the applicant's evaluable windows for the analysis of the data.

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EVALUABILITY CRITERIA

Applicant's Criteria for Bacteriological Evaluability

Subjects were considered non-evaluable for bacteriological efficacy if any of the following was present:

1. a subject who did not have culture confirmation of *C. trachomatis* at baseline.
2. the baseline culture was done more than 2 calendar days prior to the first dose of study medication.
3. cultures were not obtained in the relevant time period after end of therapy, unless a previous post-baseline culture was positive.
4. a subject took an antibiotic with potential anti-chlamydial activity within 3 calendar days before Day 1 (excluded any antibiotic begun on Day 1).
5. a subject was prescribed a concomitant antibiotic (at any time before the end of study assessment) that was potentially effective against the condition under study. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the bacteriologically evaluable subjects subset.
6. A subject who discontinued study medication, for any reason other than insufficient therapeutic effect, before the protocol-specific minimum requirement (4 days).
7. A subject who took study drug for at least the protocol-specific minimum requirement, but was less than 80% compliant with the study drug regimen.

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Medical reviewer's comments:

In addition to the applicant's criteria, the medical reviewer included the criteria outlined below:

- any patient with a positive culture at initial follow-up and within the 6 week follow-up period was bacteriologically evaluable and was considered to have persistent or recurrent infection
- any patient treated for an intercurrent illness with an antimicrobial agent with anti-chlamydial activity during the course of the study was considered an evaluable failure (differs from the applicant's criteria #5 above)
- any patient given concomitant antibiotic for continued clinical symptoms or positive culture was considered an evaluable failure
- patients treated for syphilis were bacteriologically evaluable as long as not treated with an antibiotic with potential anti-chlamydial activity
- patients with unprotected sexual contact during the study period were not evaluable

Applicant's Criteria for Clinical Evaluability

1. Subjects must have had at least one of the following clinical signs or symptoms recorded at the baseline visit:

- urethral discharge
- burning

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- painful urination
- cervical discharge
- cervical erythema
- cervical friability
- cervical edema
- cervical ectopy

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2. A subject who developed an intercurrent illness whose clinical course confounded the clinical evaluation of the disease or condition under investigation was not evaluable.
3. In order to be evaluable, a subject must have had an assessment in the end of study evaluable timepoint window, unless the investigator's clinical response was failure before the beginning of the End of Study window, or if a subject discontinued due to insufficient therapeutic effect before the End of Study visit.

Applicant's Criteria for Indeterminate Outcome

The following subjects were considered as having indeterminate outcomes and excluded from the evaluable visit 4 treatment analysis:

- a. received less than four days of treatment unless discontinued prematurely for treatment failures.
- b. inapplicable diagnosis (i. e., subject did not meet entry criteria for diagnosis of chlamydia)
- c. received concomitant systemic antibiotic(s) (with potential anti-chlamydial activity) for intercurrent illness
- d. no visit at evaluation timepoint unless subject was previously designated as a treatment failure
- e. unprotected sexual contact during the study, prior to the follow-up assessments
- f. asymptomatic subjects with positive cultures for chlamydia were clinically unevaluable but bacteriologically evaluable

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

The reviewer agrees with the applicant's criteria except (c) as discussed in the medical officer comment of bacteriologic evaluability.

APPEARS THIS WAY ON ORIGINAL

CLINICAL AND MICROBIOLOGIC ENDPOINTS

Primary and Secondary Endpoints for Efficacy

The primary efficacy endpoint was bacteriological response at TOC visit.

The secondary efficacy endpoints were:

1. Clinical response at the end of study visit,
2. Pathogen outcome at each visit and pathogen eradication rates at the end of study visit.

Medical reviewer's comments:

Reviewer agrees with the choice of endpoints.

APPEARS THIS WAY ON ORIGINAL

Bacteriological Response

The bacteriological response was determined by the sponsor at visit 4, on the basis of bacterial culture findings compared to those at the pre-treatment assessment.

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Definitions of bacteriological response were as follows:

- a. *Eradication*: *C. trachomatis* not present in any post-treatment culture from the same site
- b. *Persistence*: Isolation of *C. trachomatis* in any post-treatment culture from the same site
- c. *Recurrence*: Positive microbiologic culture at final follow-up visit

Medical reviewer's comments:

Reviewer agrees with definitions of bacteriologic response. Patients categorized with recurrence at the final follow-up visit must have had a negative microbiologic culture at Visit 2 or Visit 3.

APPEARS THIS WAY ON ORIGINAL

Clinical Response

Clinical response, determined by the sponsor, was based on the evaluation at visit 4. The clinical response was based primarily on the global evaluations made by the investigator at the end of study visit who classified the clinical response of the subject as:

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Cure: Complete resolution of signs and symptoms

Improvement: Incomplete resolution of signs and symptoms

Failure: No apparent response or progression of signs and symptoms

The occurrence of any of the following conditions was to supersede the investigator's assessment:

- If the investigator-defined clinical response was failure at any visit, then the sponsor-defined clinical response was failure at all subsequent visits.
- If a subject was given a concomitant antibiotic at any time for incomplete clinical response or failure, then the sponsor-defined clinical response was failure at that visit or the prior visit if within 1 day of the concomitant antibiotic dosing and all subsequent visits.

However, subjects who were given a concomitant antibiotic prior to the evaluation timepoint were classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.

APPEARS THIS WAY ON ORIGINAL

Medical reviewer comments:

The reviewer accepted these definitions of clinical and bacteriologic responses.

APPEARS THIS WAY ON ORIGINAL

SAFETY

Adverse events were monitored up to visit 3 and serious adverse events were monitored throughout the study and for 30 days after the last dose of the study drug. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing illnesses, and objective test findings (e.g., abnormal laboratory test results) that result in a change in study drug dosage were to be recorded and followed-up until resolved or stabilized.

Serious adverse events included any experience that suggested a significant hazard, such as events which were fatal, life threatening, resulted in permanent disability, required inpatient hospitalization or prolongation of a hospital stay, or involved cancer, a congenital anomaly, or drug overdose.

Clinical laboratory tests (hematology, biochemistry, and urinalysis) were performed at baseline and at visit 2. Additional tests were done at visit 3 and 4 if clinically indicated or if a clinically significant abnormality was present at visit 2 or 3.

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STATISTICAL CONSIDERATIONS

Methods of analysis (from the protocol)

There were no planned interim analyses for this study. All statistical tests of significance were performed as two-sided tests (unless otherwise specified). No adjustments were made to significant levels for multiple endpoints for the same data. The Cochran-Mantel-Haenzel test controlling for center was used to compare the treatments for clinical and bacteriological response.

Also, 95% confidence intervals were produced for the difference between effects for cure and eradication rates. (For the confidence interval calculations, cure indicated cured or improved).

Baseline comparability of the treatment group was assessed for gender, age, race, and weight.

Clinical analyses were performed by comparing clinical outcomes at visit 4, based primarily on the global assessment made by the investigator. Subjects with no clinical information after baseline were considered as clinical treatment failure.

Bacteriological analyses was performed by comparing bacteriological outcomes at visit 4.

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PROTOCOL DEVIATIONS (from study report)

Significant deviations from protocol were noted for 19 subjects:

- 5 subjects became pregnant during the study and one subject was pregnant at baseline;
- 13 subjects were randomized into the incorrect strata: 12 females were intentionally assigned male randomization numbers due to shortages of female drug supply and one male was inadvertently randomized to a female randomization number);
- 2 subjects took only the tablet or capsule portion of their assigned study drug.

APPEARS THIS WAY ON ORIGINAL

RESULTS

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PATIENT ENROLLMENT AND DISPOSITION

Table 123.1 Patients enrolled and bacteriologically evaluable by center (modified by reviewer from applicant's table 1.3)

center ID	randomized	Trovafloracin 200mg qd x 7 days			Doxycycline 100mg bid x 5 days		
		enrolled	evaluabe	% evaluabe	enrolled	evaluabe	% evaluabe
5003	2	2	0	0	0	0	0
5012	95	47	25	53	48	26	54
5039	67	34	22	65	33	18	55
5068	39	20	12	60	19	10	53
5069	71	36	22	61	35	23	66
5078	3	2	0	0	1	0	0
5154	12	7	1	14	5	0	0
5162	27	13	8	62	14	3	21
5164	25	13	3	23	12	3	25
5166	156	78	45	58	78	39	50
5472	26	13	8	62	13	9	69
5473	12	6	2	33	6	2	33
5474	24	12	6	50	12	6	50
5506	46	24	11	46	22	10	45
5522	8	4	1	25	4	2	50
5649	8	5	4	80	3	1	33
5650	26	14	2	14	12	2	17
5680	26	12	6	50	14	7	50
5682	5	1	0	0	4	0	0
5683	13	6	4	67	7	2	29
5684	10	6	0	0	4	0	0
5685	24	11	4	36	13	8	62
5741	57	30	29	97	27	25	93
5762	9	5	1	20	4	1	25
5857	35	16	7	44	19	11	58
5858	20	10	5	50	10	7	70
5859	15	8	5	63	7	5	71
5989	25	13	10	77	12	8	75
6041	13	6	5	83	7	4	57
6109	16	8	3	38	8	5	63
6279	48	25	9	36	23	5	22
6282	3	2	2	100	1	1	100
6423	8	4	2	50	4	3	75
6449	3	2	1	50	1	0	0
total	977	495	265	54	482	246	51

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

Patients appeared to have been randomized evenly between the two treatment groups at each of the centers. In total, 41 sites participated and enrolled subjects; there was no site without enrollment. Seven sites had enrollment of 20 or more subjects (per arm) and accounted for about 55% of the enrollments (per arm). At site 5741, greater than 90% of the randomized subjects were evaluable in both arms, while the other 6/7 sites had (b)(4) evaluable subjects from those randomized. There was an average of 6.5 subjects enrolled per site. Of the 977 randomized patients, 569 completed the treatment and study while 511 were evaluable bacteriologically based on the applicant's results.

Table 123.2 Discontinuations from Study—Treated Subjects (from applicant's table 4.3.2)

	Trovaflaxacin 200 mg qd	Doxycycline 100 mg b. i. d.
Number of Treated Subjects	489(100%)	481(100%)
Discontinued Subjects	187(38%)	205(43%)
Related to Study Drug	3(< 1%)	2(< 1%)
ADVERSE EVENT	2(< 1%)	1(< 1%)
INSUFFICIENT RESPONSE	1(< 1%)	1(< 1%)
Not Related to Study Drug	184(38%)	203 (42%)
ADVERSE EVENT	0	1(< 1%)
DOES NOT MEET RANDOMIZATION CRITERIA	2(< 1%)	0
LOST TO FOLLOW- UP	41(8%)	44(9%)
OTHER	130(27%)	148(31%)
PROTOCOL VIOLATION	5(1%)	6(1%)
WITHDRAWN CONSENT	6(1%)	4(< 1%)

Percents are based on the number of treated subjects in each treatment group.

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

The case report forms for subjects discontinued from the study were reviewed and the reviewer agrees with the applicant regarding their disposition.

APPEARS THIS WAY ON ORIGINAL

Table 123.3 Subject disposition for enrolled subjects (from applicant's table 1.1, 1.2.1, 1.2.2)

	Trovaflaxacin 200 mg qd	Doxycycline 100 mg b.i.d.
Randomized	495	482
Treated	489	481
Withdrawn During Treatment	28	37
Completed Treatment	462	444
Withdrawn from study	187	205
Withdrawn During Treatment and Study	25	31
Withdrawn During Follow-up	162	174
Completed Study	303	276
Completed Treatment and Study	299	270
Negative Baseline Culture	163	181
Bacteriological Intent-to-Treat	332	301
Bacteriologically Evaluable	265	246
Clinically Evaluable	181	179
Analyzed for Safety (a)		
Adverse Events	489	481
Laboratory Data	366	381

(a) Based on number of treated subjects

APPEARS THIS WAY ON ORIGINAL

Medical Reviewer's comments:

The reviewer notes that in the trovaflaxacin arm, 489 were treated and 462 completed treatment; therefore the number who withdrew during treatment is 27.

Table 123.4 Study Evaluation Groups--Randomized Male and Female Subjects (from applicant's tables 1.2.1, 1.2.2)

	Males		Females	
	Trovafloracin	Doxycycline	Trovafloracin	Doxycycline
All Randomized Subjects	203	203	292	279
All Treated Subjects	200	203	289	278
Negative Baseline Culture	77	80	86	101
Inappropriate Baseline Diagnosis	0	1	3	1
Subjects with No Baseline				
Clinical Signs and Symptoms	31	29	61	50
Bacteriological Intent-to-Treat	126	123	206	178
Bacteriologically Evaluable	100	102	165	144
Bacteriologically Not Evaluable	26	21	41	34
Randomized, Not Treated	2	0	1	0
No post- baseline cultures	19	21	36	30
Insufficient therapy	6	7	6	9
Concomitant antibiotics	6	2	11	6
Clinical Intent- to- Treat	95	93	142	127
Clinically Evaluable	72	79	109	100
Clinically Not Evaluable	28	23	56	44
No post- baseline clinical assessments	21	15	50	38
No baseline clinical signs and symptoms	26	21	51	41
Analyzed for Safety (a)				
Adverse Events	200	203	289	278
Laboratory Data	146	164	220	217

(a) Based on number of treated subjects

BEST POSSIBLE

APPEARS THIS WAY ON ORIGINAL

NDA 20-759

DEMOGRAPHICS

Table 123.5 Demographic Characteristics—Treated Subjects (applicant's Table 2.1.1)

	Trovafoxacin (200 mg)			Doxycycline (100 mg b.i.d.)		
	Male	Female	Total	Male	Female	Total
Number of Subjects	200	289	489	203	278	481
Age (yr)						
<16	0	0	0	0	1 (<1%)	1 (<1%)
16-44	194 (97%)	285 (99%)	479 (98%)	198 (98%)	272 (98%)	470 (98%)
45-64	6 (3%)	4 (1%)	10 (2%)	5 (2%)	5 (2%)	10 (2%)
Mean	27.4	23.5	25.1	26.4	24.2	25.1
Minimum	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Maximum	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Race						
AMERICAN INDIAN/ALASKAN	1	0	1	0	0	0
ARABIAN	2 (1%)	1 (<1%)	3 (<1%)	1 (<1%)	0	1 (<1%)
ASIAN	1 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)	3 (1%)	4 (<1%)
BLACK	124 (62%)	169 (58%)	293 (60%)	119 (59%)	173 (62%)	292 (61%)
EAST INDIAN	0	0	0	1 (<1%)	0	1 (<1%)
HISPANIC	4 (2%)	8 (3%)	12 (2%)	8 (4%)	4 (1%)	12 (2%)
JAPANESE	1 (<1%)	0	1	0	0	0
LATINO	0	0	0	0	1	1
MIXED (WHITE + ASIAN)	0	1 (<1%)	1 (<1%)	0	0	0
NATIVE AMERICAN	0	1 (<1%)	1 (<1%)	0	0	0
PALESTINIAN	0	0	0	0	1 (<1%)	1 (<1%)
PHILIPINO	0	0	0	0	95 (34%)	168 (35%)
WHITE	67 (34%)	105 (36%)	172 (35%)	73 (36%)	1 (<1%)	1 (<1%)
WHITE/HISPANIC	0	1 (<1%)	1 (<1%)	0	0	0
Weight (kg)						
Mean	78.3	66.9	72.6	78.4	66.1	72.2
Minimum	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Maximum	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

Medical reviewer's comments:
 More women than men were treated in the study and less than 5% of the subjects were 45 years and older. Overall, the groups appeared comparable for age, race and weight.

APPEARS THIS WAY ON ORIGINAL

Table 123.6 Demographic Characteristics of Clinically Evaluable Subjects (modified by reviewer from applicant's table 2.1.2)

	Males		Females	
	Trovafoxacin	Doxycycline	Trovafoxacin	Doxycycline
Number of Subjects	100	102	165	144
Age (yrs)				
<16	0	0	0	1
16-44	98	100	163	143
45-64	2	2	2	0
Mean	26.6	25.5	22.7	23.0
Range	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Race				
ARAB	1	0	1	0
ASIAN	0	1	0	2
BLACK	61	56	90	85
HISPANIC	0	5	4	2
PALESTINIAN	0	0	1	0
WHITE	38	40	68	55
WHITE/HISPANIC	0	0	1	0
Weight (kg)				
Mean	78.4	79.1	66.3	66.3
Minimum	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Maximum	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Missing	0	0	1	0

There were no marked differences between subjects in the trovafloxacin and doxycycline groups with respect to medical history at baseline.

Medical reviewer's comments:

These results are similar to those in table 123.5. Most of the evaluable patients were between (b)(4) years of age, black and female. Within gender, the groups were similar with respect to age range, mean age, weight and racial distribution.

APPEARS THIS WAY ON ORIGINAL

APPLICANT'S EFFICACY RESULTS

Microbiological efficacy

Table 123.7 Bacteriological Response Rates in Bacteriologically Evaluable Subjects at EOS (from Applicant's Tables 5.1.1 and 5.1.4)

	Trovafloxacin 200 mg qd		Doxycycline 100 mg BID		95% CI
	Number (%) of Subjects				
Males					
# Subjects	100	(100%)	102	(100%)	
Eradication ^a	89	(89%)	101	(> 99%)	(- 16.4, -3.6)
Persistence	11	(11%)	1	(< 1%)	
Females					
# Subjects	165	(100%)	143	(100%)	
Eradication ^a	157	(95%)	138	(97%)	(- 5.8, 3.1)
Persistence	8	(5%)	5	(3%)	
Overall					
Subjects	265	(100%)	245	(100%)	
Eradication ^a	246	(93%)	239	(98%)	(- 8.4, -1.1)
Persistence	19	(7%)	6	(2%)	

CI= confidence interval, based on normal approximation.

^a Eradication = the number of subjects with outcome of eradication of *C. trachomatis* divided by the number of subjects in subset with *C. trachomatis* identified at baseline.

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

The 95% confidence intervals with continuity correction are:

Males: (-17.4%, -2.6%)

Females: (-6.5%, 3.8%)

APPEARS THIS WAY ON ORIGINAL

The lower bound of -10% for the 95% CI, when the higher of the cure rates is 90% or greater, was exceeded for males; therefore, equivalence of trovafloxacin to doxycycline for the treatment of chlamydial urethritis in males was not demonstrated. However, equivalence of trovafloxacin to doxycycline was demonstrated for the treatment of chlamydia cervicitis.

The results for pathogen outcome for bacteriologically evaluable patients and those for clinical response in clinically evaluable subjects summarized in the tables below (tables 123.8 and 123.9) are similar to those in table 123.7.

APPEARS THIS WAY ON ORIGINAL

Table 123.8 Defined Pathogen Outcome. By Gender for Bacteriologically Evaluable Subjects (Modified from Applicant's Tables 5.3.1, 5.3.3 and table E)

Sex	Pathogen	Source	Trovafoxacin (200 mg)			Doxycycline (100 mg b. i. d.)				95% CI
			E	P	Total Eradicated	E	P	NA	Total Eradicated	
MALE										
	C. trachomatis	URETHRA	86	10	86/96	96	1	0	96/97	(- 15.8, -3.0)
	N. gonorrhoeae/ C. trachomatis	URETHRA	3	1	3/4	5	0	0	5/5	
FEMALE										
	C. trachomatis	URETHRA	1	0	1/1	2	0	0	2/2	
		CERVIX	152	7	152/159	127	4	1	127/131	
		BOTH	153	7	153/160	129	4	1	129/133	(- 5.7, 2.9)
	N. gonorrhoeae/ C. trachomatis	CERVIX	4	1	4/5	9	1	0	9/10	
OVERALL										
	C. trachomatis	URETHRA	87	10	87/97	98	1	0	98/99	
		CERVIX	152	7	152/159	127	4	1	127/131	
		BOTH	239	17	239/256	225	5	1	225/230	(- 8.1, -0.9)
	N. gonorrhoeae/ C. trachomatis	URETHRA	3	1	3/4	5	0	0	5/5	
		CERVIX	4	1	4/5	9	1	0	9/10	

E= eradicated, P= persistence, NA= not assessable CI= confidence interval
 a Eradication Rate = the number of subjects with outcome of eradication of *C. trachomatis* divided by the number of subjects with *C. trachomatis* identified at baseline.

Of the 19 evaluable trovafloxacin subjects and 8 evaluable doxycycline subjects with a bacteriological response and pathogen outcome of persistence, 8 trovafloxacin subjects (5 males; 3 females) and 1 female doxycycline subject had baseline and post-treatment cultures for which serovars could be determined by immunotyping. Two female and 1 male trovafloxacin subjects had a different serovar post-treatment from that at baseline. The other 6 subjects had the same serovar post-treatment as at baseline.

In the other 10 cases, either the investigator failed to save the isolates as requested or the isolates could not be regrown.

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

All patients with interval unprotected sexual contact were considered non-evaluable by the reviewer because of their indeterminate status.

One patient (58581372) defined with persistent infection by the applicant had no sexual contact between visits 2-4 and was culture negative for chlamydia for the same period; this patient was considered a cure by the reviewer.

APPEARS THIS WAY ON ORIGINAL

Clinical efficacy

Table 123.9 Summary of Sponsor- Defined Clinical Response Rates at the End of Study Visit for Clinically Evaluable Subjects (from applicant's tables 5.5.1 and 5.5.3)

	Trovafloxacin 200 mg qd	Doxycycline 100 mg BID	95% CI
	Number (%) of Subjects		
Males			
Number of Subjects Assessed	72	79	
Success (Cure + Improvement)	68 (94%)	79 (100%)	(- 10.8, -0.3)
Cure	62 (86%)	79 (100%)	
Improvement	6	0	
Failure	4	0	
Females			
Number of Subjects Assessed	109	100	
Success (Cure + Improvement)	105 (96%)	94 (94%)	(- 3.5, 8.2)
Cure	100 (92%)	89 (89%)	
Improvement	5	5	
Failure	4	6	
Overall			
Number of Subjects Assessed	181	179	
Success (Cure + Improvement)	173 (96%)	173 (97%)	(- 5.1, 2.9)
Cure	162 (90%)	168 (94%)	
Improvement	11	5	
Failure	8	6	

CI= confidence interval

APPEARS THIS WAY ON ORIGINAL

Five (2 males; 3 females) of the eight trovafloxacin and 5/6 doxycycline female subjects designated as clinical failures had repeat cultures that showed eradication of *C. trachomatis* at the end of study.

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

After review of the CRF, the reviewer is in agreement with the applicant's assessment of outcome for these 14 failures.

APPEARS THIS WAY ON ORIGINAL

MEDICAL REVIEWER'S EFFICACY RESULTS

Consistent with the sponsor's criteria wherein it states that "the use of a condom is essential for the determination for evaluability", the reviewer's evaluable population excluded patients with unprotected sexual exposure during the study.

The reviewer examined the case report forms for patients classified as nonevaluable by the sponsor and for the most part was in agreement with the applicant regarding the classification of these subjects. However, the reviewer considered 3 subjects in the trovafloxacin arm (50683210, 550612801, and 64492169) and 1 subject in the doxycycline group (51641049) evaluable.

Subject 61091258, a 15 year old female patient in the doxycycline arm (protocol violation for age eligibility) was included in the sponsor evaluable group; this subject was considered evaluable for bacteriologic and clinical efficacy by the reviewer because this was not inconsistent with the IDSA/FDA guidelines which state that patients (b)(4) can participate in these trials, with consent.

Other differences in subject evaluability between the applicant and the medical reviewer are summarized below:

APPEARS THIS WAY ON ORIGINAL

Trovafoxacin

Males

51660212

urethra discharge unresolved missed visit 3, 4 no sexual contact between visits 1 and 2; culture negative for chlamydia at visit2

Sponsor assessment: non evaluable MO assessment: CLINICALLY EVALUABLE—FAILURE

55060305

new onset urethral discharge at visit3, culture positive for chlamydia at visit3, culture negative for chlamydia visits 2 and 4; no history of sexual contact at visit 2. no sexual exposure history done at visits 3 and 4

Sponsor assessment: evaluable, persistent infection MO assessment: NONEVALUABLE

APPEARS THIS WAY ON ORIGINAL

58590388

new onset symptoms at visit3, culture positive for chlamydia at visit4 , no sexual contact

Sponsor: Cure Persistent

MO comment: this subject should be a failure clinically and with persistent infection

APPEARS THIS WAY ON ORIGINAL

Females

58581372

cultures negative for chlamydia at visits 2-4, no sexual contact

sponsor assessment: persistent infection MO assessment: ERADICATED

APPEARS THIS WAY ON ORIGINAL

50393038

new onset discharge at visit 3, protected sexual contact; missed visit 4, culture negative for chlamydia at visit 2, 3 no culture at visit 4

Sponsor assessment: bacteriologically non evaluable

MO assessment: EVALUABLE-PERSISTENT INFECTION

APPEARS THIS WAY ON ORIGINAL

50683210

patient had protected sex contact throughout study, baseline symptoms had resolved at visit 2; symptomatic between visit 2 and 3 but culture negative for chlamydia throughout after baseline culture; given concomitant antibiotics for cervicitis

Sponsor assessment: bacteriologically non evaluable

MO assessment: EVALUABLE-PERSISTENT INFECTION

APPEARS THIS WAY ON ORIGINAL

Doxycycline

Males

56850243

asymptomatic; culture negative for chlamydia visit 2-4; treated with doxycycline for NGU beginning day 37

Sponsor assessment: bacteriologically evaluable, eradication

MO assessment: Bacteriologically Evaluable-PERSISTENT INFECTION.

APPEARS THIS WAY ON ORIGINAL

Table 123.10 Bacteriological Response Rates in Bacteriologically Evaluable Subjects at the End of Study Visit (MO's table)

	Trovafoxacin 200 mg qd Number (%) of Subjects	Doxycycline 100 mg BID Number (%) of Subjects	95% CI
Males			
# Subjects	85	94	
Eradication	79 (93%)	93 (99%)	(-12.9, 1.0)
Persistence	6	1	
Females			
# Subjects	150	123	
Eradication ^a	144 (96%)	118 (96%)	(-5.4, 5.5)
Persistence	6	5	

a Eradication = the number of subjects with outcome of eradication of *C. trachomatis* divided by the number of subjects in subset with *C. trachomatis* identified at baseline.

APPEARS THIS WAY ON ORIGINAL

Medical reviewer's comments:

Similar to the applicant's results, the lower bound of the 95% confidence interval for the eradication rates was below -10% for males; thus the equivalence of trovafloxacin with doxycycline for the treatment of NGU was not demonstrated. Trovafloxacin appears to be less effective than doxycycline in males as evidenced by the number of failures in males. In this trial, males had greater failure rates than women; treatment failures after successful completion of a regimen of doxycycline are uncommon with failure rates of (b)(4) men and (b)(4) women [CDC guidelines: MMWR Sept 24, 1993;42(RR-14):51]. This result appears to be different from that which would be expected in the treatment of uncomplicated chlamydial infections in men and women; there is however, no obvious explanation for why this was observed in this study.

APPEARS THIS WAY ON ORIGINAL

Table 123.11 Pathogen Outcome. By Gender of Bacteriologically Evaluable Subjects (MO table)

Sex	Pathogen	Source	Trovafoxacin (200 mg)			Doxycycline (100 mg b. i. d.)		
			E	P	Total Eradicated	E	P	Total Eradicated
MALE								
	<i>C. trachomatis</i>	URETHRA	76	5	76/81(94%)	88	1	88/89(99%)
	<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	URETHRA	3	1	3/4	5	0	5/5
FEMALE								
	<i>C. trachomatis</i>	URETHRA/ CERVIX	140	5	140/145(97%)	111	4	111/115(97%)
	<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	CERVIX	4	1	4/5	7	1	7/8

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Medical reviewer's comments:

The results of eradication based on pathogen outcome and culture site are similar to those of the bacteriologic response seen above. The dose of trovafloxacin studied by the sponsor for the treatment of uncomplicated gonorrhea is 100 mg in a single dose. The dose of 200 mg q day for 5 days for the treatment of chlamydia is 10x that sought by the sponsor to treat gonorrhea, which should be adequate to treat gonorrheal co-infections. Of the 3 co-infected patients with

persistence of the chlamydial infection, patients 50390131 and 50681224 both treated with trovafloxacin eradicated gonococcus while the third patient, 61091126, in the doxycycline arm did not. Overall, the results from the FDA analysis are similar to those of the applicant.

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Table 123.12 Summary of Clinical Response Rates at the End of Study Visit for Clinically Evaluable Subjects (MO Table)

	Trovafloxacin 200 mg Number (%) of Subjects	Doxycycline 100 mg BID	95% CI
Males			
Number of Subjects Assessed	73	79	
Success (Cure + Improvement)	67 (92%)	79 (100%)	(-15.8, -0.6)
Distribution of Clinical Response			
Cure	61 (84%)	79 (100%)	
Improvement	6	0	
Failure	6	0	
Females			
Number of Subjects Assessed	109	100	
Success (Cure + Improvement)	104 (95%)	94 (94%)	(-5.6, 8.5)
Distribution of Clinical Response			
Cure	99 (91%)	89 (89%)	
Improvement	5	5	
Failure	5	6	

CI= confidence interval

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Medical reviewer's comments:

These results are consistent with those of the microbiologic response in that equivalence of trovafloxacin with doxycycline was demonstrated for females but not males.

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SAFETY

Table 123.13 Summary of Adverse Events: All Causality; Treated Subjects (modified from applicant's Table 6.1)

	Trovafloxacin 200 mg	Doxycycline 100 mg b. i. d.
Number of Subjects Treated	489 (100%)	481 (100%)
Analyzed for Safety		
Adverse Events	489	481
Laboratory Data	366	381
Subjects With At Least One Event	222 (45%)	185 (38%)
Number of Adverse Events	394	268
Subjects with Serious Adverse Events	0	1 (< 1%)
Subjects with Severe Adverse Events	19 (4%)	11 (2%)
Subjects Discontinued Due to Adverse Events	11 (2%)	13 (3%)

Includes data up to seven days after last dose of active study medication.

No subject had the study medication dose reduced or was discontinued temporarily from treatment owing to adverse effects of the medication. There were no deaths among the patients during the conduct of the study. One patient was reported with a serious adverse event. This patient's information is summarized below:

Patient ID: 55061269
 Location: UK
 Female 32 years of age
 Race: other
 Weight: 52.0 kg
 Treatment: Doxycycline 200.00 mg
 Event onset: day 7
 Treatment stopped: day 7 permanently
 Event: Acute appendicitis-- hospitalized
 Outcome: resolved

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Table 123.14 (from applicant's study report)

Table A. Summary of the Most Commonly Reported Adverse Events ^{a,b} by Body System - All Causalities (All Treated Subjects)		
APPEARS THIS WAY ON ORIGINAL	Trovafloxacin 200 mg (N= 489)	Doxycycline 100 mg BID (N= 481)
Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event	222 (45%)	185 (38%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	141 (29%)	47 (10%)
Dizziness	105 (21%)	17 (4%)
Headache	55 (11%)	29 (6%)
GASTROINTESTINAL SYSTEM	95 (19%)	117 (24%)
Abdominal Pain	8 (2%)	10 (2%)
Diarrhea	14 (3%)	6 (1%)
Nausea	69 (14%)	78 (16%)
Vomiting	11 (2%)	39 (8%)
PSYCHIATRIC	11 (2%)	11 (2%)
Somnolence	8 (2%)	5 (1%)
REPRODUCTIVE	27 (6%)	13 (3%)
Vaginitis ^c	15 (5%)	10 (4%)
SPECIAL SENSES	13 (3%)	5 (1%)
Eye Pain	8 (2%)	0

a ≥ 2 % of subjects in either treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Preferred term is gender specific; therefore, the percentages are based on the number of females appropriately.
 Ref.: Tables 6.2 and 6.4

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Laboratory Abnormalities

Applicant's note: Clinically significant post-baseline laboratory abnormalities were observed for 14% (51/ 366) of subjects in the trovafloxacin group and 15% (58/ 381) of subjects in the doxycycline group. These abnormalities were observed at comparable incidence rates in both treatment groups.

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Medical reviewer's comments:

The most common adverse events were central nervous system (CNS) related (dizziness and headache) and gastrointestinal (nausea, diarrhea and vomiting). CNS problems, particularly

dizziness, occurred with greater frequency in the trovafloxacin group. The frequency of gastrointestinal events appeared comparable in the two groups. Changes in laboratory abnormalities appeared to have occurred with equal frequency in both arms.

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Conclusions

Based on the reviewer's evaluable population, the bacteriologic efficacy at the end of the study (test of cure visit) for males was 79/85 (93%) for trovafloxacin and 93/94 (99%) for doxycycline, with the lower bound of the 95% confidence interval exceeding -10%. The bacteriologic efficacy for females was 144/150 (96%) for trovafloxacin and 118/123 (96%) for the doxycycline group, with the lower bound of the 95% confidence interval greater than -10% and the upper bound above 0. Clinical efficacy results were similar.

Dizziness and headache were noted with greater frequency in the trovafloxacin group than in the doxycycline population and the difference was statistically significant.

Based on the results of this study, the reviewer recommends approval for the use of trovafloxacin in the treatment of chlamydial cervicitis/urethritis in females but not for the treatment of chlamydial urethritis in males.

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Study 154-105

Title: "An open, randomized, non-comparative, two-center dose-ranging study of trovafloxacin in the treatment of uncomplicated chlamydial urethritis/cervicitis."

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Objective

To assess the safety and efficacy at four different multiple doses in the treatment of uncomplicated chlamydia urethritis/cervicitis, with or without gonorrhea co-infection.

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Study design (copied from protocol)

This was an open, randomized, non-comparative, dose-ranging study of CP-99,219 in the treatment of uncomplicated genital chlamydial infections.

Participants in this study were subjects with chlamydial urethritis and/or cervicitis. Up to a total of 40 evaluable subjects (one-half of whom must have been females) were to be assigned to one of four multiple-dose regimens at each of the two centers as follows:

- Group 1 - 200 mg qd x 7 days
- Group 2 - 200 mg qd x 5 days
- Group 3 - 100 mg qd x 7 days
- Group 4 - 50 mg qd x 7 days

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Ten subjects (five males, five females) were to be assigned to each regimen at each center. Prior to proceeding to a regimen of shorter duration or lesser dose, eradication of *C. trachomatis* at the previous dosage regimen was to be present in at least 80% of the evaluable subjects enrolled at that dose at that center. Clinical and microbiological evaluations were performed at baseline and at one, two, and four weeks following completion of therapy.

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The following table summarizes the design for study 154-105:

Location	USA; 2 sites
Study dates	August 10, 1994-February 6, 1996
Patient ages	18 years and older
Structure	dose ranging, stepwise
Study dose and duration	outlined above; no concurrent control
Blinding	third party blind
Method of assignment	1:1; Stratification by gender
Efficacy variables	clinical, microbiologic
Safety variables	clinical signs and symptoms, laboratory results
Therapy evaluation, days (window)	
Baseline	1 (within 48 hours)
End of treatment-EOT	10 (9-11)
Post	21 (19-23)
Test of cure-TOC (end of study-EOS)	35 (31-39)
Number of subjects randomized	130

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STUDY POPULATION

Up to 40 evaluable subjects, 50% of which were required to be female, were to be enrolled in the study at each of the two centers.

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Inclusion criteria

Same as those for study 123 with the exception of the age criterion--patients had to be at least 18 years of age.

Exclusion criteria

Same as those for study 123.

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STUDY VISITS

At the **baseline visit (visit 1, day 1)**, subjects with a clinical diagnosis of genital chlamydial infection were eligible for randomization; these subjects had informed consent obtained, and it was confirmed that all of the inclusion and none of the exclusion criteria, applied. Women of childbearing potential had a serum or urine gonadotropin pregnancy test performed. A standard panel of blood and urine tests was performed and serologic test for syphilis (FTA or RPR) was also obtained.

The presumptive diagnosis of genital chlamydial infection was made on the basis of a positive nonculture chlamydia test, whether or not the subject was symptomatic.

A urethral swab from males and a cervical (or urethral) swab from females were cultured for *Chlamydia trachomatis* and *N. gonorrhoeae*.

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1. Anorectal cultures were necessary only if the male subject's history indicated rectal sexual exposure.
2. In females who lacked cervixes (e.g. those who have undergone hysterectomy), the urethra was cultured.

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Patients with Gram stain evidence of gonococcal urethritis and/or cervicitis received a single 125 mg IM dose of ceftriaxone.

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All subjects with culture-confirmed chlamydial infection had urethral/cervical cultures for chlamydia repeated at one week (5-9 days), two weeks (12-18 days), and four weeks (25-35 days) following completion of therapy (Note that for Group 2, these follow-up visits were two days sooner than for Groups 1, 3, and 4 because of the five-day vs. seven-day duration of therapy). In addition, follow-up cultures for

PROTOCOL OVERVIEW

SCHEDULE OF STUDY VISITS AND PROCEDURES (excerpted from the study protocol)

STUDY DAYS

d)	weeks	Treatment	STUDY DAYS							Post-treatment Follow-ups (5-9 d) ^a	(12-18 d)	(25-35)
			Baseline Day	1	2	3	4	5	6			
		Groups 1, 3, 4 ^b	X	X	X	X	X	X	X			
		Group 2 ^c	X	X	X	X	X	X				
		History and Physical Assessments	X									
		Clinical	X									
		Laboratory										
		1. FTA or RPR	X									
		2. Hematology	X									
		abn ^d										
		3. Serum Chemistry	X									
		4. Urinalysis	X									
		5. Gram stain ^e	X									
		6. Cultures for <i>C. trachomatis</i>	X									
		7. Cultures for <i>N. gonorrhoeae</i>	X									
		8. Pregnancy Test ^f	X									
		Adverse Events	X									

^aWindow for follow-up visit

^bGroup 1 - 200 mg qd x 7 days; Group 3 - 100 mg qd x 7 days; Group 4 - 50 mg qd x 7 days

^cGroup 2 - 200 mg qd x 5 days

^dOnly for clinically significant abnormalities present at previous visit

^{ee}Where feasible (i.e., presence of urethral or cervical discharge)

^fFor women of childbearing potential

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N. gonorrhoeae were obtained from all sites cultured at entry into the study, regardless of whether this infection was documented at enrollment or at previous follow-up visits. Also at each follow-up visit, the standard panel of blood and urine tests was repeated. **APPEARS THIS WAY ON ORIGINAL**

During the study, subjects could not be treated with another systemic antibiotic with potential anti-chlamydial activity. If such anti-infective medication was required during a subject's course of treatment, the subject discontinued from the study and another subject was entered to replace the discontinued subject. A subject with a positive serologic test for syphilis at entry was evaluated, received appropriate treatment and was discontinued from the study and replaced with another subject. **APPEARS THIS WAY ON ORIGINAL**

Subjects could not donate blood during, and for six weeks following, administration of study drug. Subjects were to abstain from sexual activity at least through the first follow-up visit. Thereafter, sexual intercourse with the use of a condom was permissible. (If unable to abstain from sexual activity until the first follow-up visit, the use of a condom was essential for the determination of evaluability). **APPEARS THIS WAY ON ORIGINAL**

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PROCEDURES

Drug Administration

All four regimens of CP-99,219 were administered, in an open fashion, as multiple oral doses. The first dose of study drug was administered in the clinic under direct observation, and all doses could be given without regard to meals. **APPEARS THIS WAY ON ORIGINAL**

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Microbiologic Methods

Susceptibility to CP-99,219 was determined by minimum inhibitory concentrations (MICs) for all isolates of *N. gonorrhoeae*, whether at baseline or at follow-up. For *C. trachomatis*, MICs were determined for two baseline isolates from each of the four dosage groups (at each center) and for all treatment failures. Criteria for determining susceptibility to CP-99,219 are summarized below:

	MIC*	
CRITERIA	(ug/ml)	
SUSCEPTIBILITY	≤2	APPEARS THIS WAY ON ORIGINAL
INTERMEDIATE	4	
RESISTANT	≥8	

*Tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing. **APPEARS THIS WAY ON ORIGINAL**

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EVALUABILITY CRITERIA AND EFFICACY ENDPOINTS

The criteria for evaluability and efficacy endpoints were the same as those used by the applicant in study 123. **APPEARS THIS WAY ON ORIGINAL**

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Medical reviewer's comments:

These criteria were not outlined in the study protocol but were included in the study report text.

SAFETY

The same safety evaluations done in study 123 were done in this study.

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STATISTICAL CONSIDERATIONS

The methods of analysis were those used in study 123.

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PROTOCOL DEVIATIONS

No significant protocol deviations were noted during this study.

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STUDY RESULTS

Study sites and Investigators

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
Robert Jones, M.D.	Nancy Hobson, N.P. Paula Linnemeier, N.P. Judy Roush, N.P. Sara Smith, N.P. Sue Waddell, R.N.	Department of Medicine Room 435, Emerson Hall 545 Barnhill Drive Indianapolis, IN 46202-5124
David Martin, M.D.	Barbara Armentor, R.N. Richard DiCarlo, M.D. Tomasz Mroczkowski, M.D.	Louisiana State University Medical School Section of Infectious Diseases Department of Infectious Diseases 1542 Tulane Avenue New Orleans, LA 70122-2822

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PATIENT ENROLLMENT AND DISPOSITION

Table 105.1 (from study report)

Table B. Summary of Study Evaluation Groups for Males and Females								
Randomized Subjects								
	Trovafoxacin (200 mg x 7 Days)		Trovafoxacin (200 mg x 5 Days)		Trovafoxacin (100 mg x 7 Days)		Trovafoxacin (50 mg x 7 Days)	
	Number of Subjects							
	Male	Female	Male	Female	Male	Female	Male	Female
Randomized	16	15	19	15	13	15	16	21
Treated	16	15	19	15	13	15	16	21
Negative Baseline Culture	3	2	7	4	2	2	2	5
Bacteriologically Intent-to-Treat	13	13	12	11	11	13	14	16
Bacteriologically Evaluable	9	11	9	9	6	8	11	10
Clinically Intent-to-Treat	12	13	11	11	7	13	12	13
Clinically Evaluable	8	11	8	9	4	8	10	9
Analyzed for Safety								
Adverse Events	16	15	19	15	13	15	16	21
Laboratory Analysis	9	11	12	5	5	4	8	9

Ref.: Tables 1.2.1 and 1.2.2

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Demographics

**Table 105.2 Demographic Characteristics for Treated Subjects
(applicant's table 2.1.1)**

Trovafoxacin 200 mg x 7 days			Trovafoxacin 200 mg x 5 days			Trovafoxacin 100 mg x 7 days			Trovafoxacin 50 mg x 7 days		
Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects											
16	15	31	19	15	34	13	15	28	16	21	37
Age (yr)											
16- 44											
16	15	31	18	15	33	13	15	28	16	21	37
0 45- 64											
0	0	0	1	0	1	0	0	0	0	0	0
Mean											
25.1	25.3	25.2	24.0	22.4	23.3	23.5	22.9	23.2	24.3	23.3	23.7

(b)(4)

Race											
BLACK											
15	12	27	16	13	29	13	13	26	14	16	30
HISPANIC											
0	1	1	0	0	0	0	0	0	0	1	1
WHITE											
1	2	3	3	2	5	0	2	2	2	4	6
Weight (kg)											
Mean											
76.6	69.0		83.1	65.5			74.7	71.4		80.7	63.1

(b)(4)

Medical reviewer's comments:
The groups were comparable with respect to mean age, racial distribution; the majority of subjects were black, and the gender distribution was essentially 50% of each.

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EFFICACY

Table 105.3 (from study report)

Table C. Summary Subjects with Bacteriological Response of Persistence (Bacteriologically Evaluable Subjects) and/or Clinical Response of Failure (Clinically Evaluable Subjects)							
Subject Number	Baseline Pathogen	Days of Treatment	Study Visit	Study Drug MIC (µg/mL)	Subject Bacteriological Response	Pathogen Outcome	Subject Clinical Response
Trovafoxacin 200 mg Daily for 7 Days							
Females							
5068-2004	<i>C. trachomatis</i> ^a	7	BL EOS	ND ND	Persistent	Persistent	Cure
Trovafoxacin 100 mg Daily for 7 Days							
Males							
5069-1225	<i>C. trachomatis</i> ^b	7	BL EOS	ND ND	Persistent	Persistent	Cure
Females							
5068-2201†	<i>C. trachomatis</i> ^a	7	BL EOS	0.031 ND	Persistent	Persistent	Cure
Trovafoxacin 50 mg Daily for 7 Days							
Males							
5068-1304	<i>C. trachomatis</i> ^b	7	BL EOS	0.063 ND	Persistent	Persistent	Cure
Females							
5068-2308	<i>C. trachomatis</i> ^{a,b}	7	BL EOS	0.25 ND	Eradication	Eradication	Failure
5069-2332	<i>C. trachomatis</i> ^a	7	BL EOS	ND ND	Eradication	Eradication	Failure
BL = Baseline; EOS = End of Study; MIC = Minimum Inhibitory Concentration; ND = Not Determined.							
a Pathogen isolated by cervical swab.							
b Pathogen isolated by urethral swab.							
† Subject received concomitant antibiotic for bacteriological failure during the study.							
Ref.: Appendix I, Table 8 and Appendix V, Table 16 and 18							

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Medical reviewer's comments:

The two female subjects (50682308, 50692332) in group 4, Trovafoxacin 50mg for 7 days, were bacteriologic failures.

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Table 105.4 Sponsor Defined Subject Bacteriological Response. By Gender for Bacteriologically Evaluable Subjects (applicant's table 5.1.1)

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	Trovafoxacin 200 mg x 7 days	Trovafoxacin 200 mg x 5 days	Trovafoxacin 100 mg x 7 days	Trovafoxacin 50 mg x 7 days
Male				
Total Number of Subjects	9	9	6	11
Number of Assessed Subjects	9 (100%)	9 (100%)	6 (100%)	11 (100%)
Eradication	9 (100%)	9 (100%)	5 (83%)	10 (91%)
Persistence	0	0	1 (17%)	1 (9%)
Female				
Total Number of Subjects	11	9	8	10
Number of Assessed Subjects	11 (100%)	9 (100%)	8 (100%)	10 (100%)
Eradication	10 (91%)	9 (100%)	7 (88%)	10 (100%)
Persistence	1 (9%)	0	1 (13%)	0

Medical reviewer's comments:

The reviewer accepted the applicant's evaluable population for this study. Because two of 10 female subjects in group 4, Trovafloxacin 50mg for 7 days, were bacteriologic failures, the eradication rate at this dose is 80%.

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Table 105.5 Investigator Defined Subject Clinical Response. By Gender for Clinically Evaluable Subjects (Sponsor Table 5.5.1)

	Trovafloxacin 200 mg x 7 days	Trovafloxacin 200 mg x 5 days	Trovafloxacin 100 mg x 7 days	Trovafloxacin 50 mg x 7 days
Male				
Total Number of Subjects	8	8	4	10
Number of Assessed Subjects	8	8	4	10
Success (Cure + Improvement)	8	8	4	10
Cure	7	8	4	10
Improvement	1	0	0	0
Female				
Total Number of Subjects	11	9	8	9
Number of Assessed Subjects	11	9	7	9
Success (Cure + Improvement)	11	9	7	8
Cure	11	8	7	8
Improvement	0	1	0	0
Failure	0	0	0	1

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Medical Reviewer's comments:

This table should also show two failures at the lowest dose of trovafloxacin instead of the one currently indicated.

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SAFETY

Table 105.6 Discontinuations from Study Treated Subjects (sponsor table 4.2)

	Trovafloxacin 200 mg x 7 days	Trovafloxacin 200 mg x 5 days	Trovafloxacin 100 mg x 7 days	Trovafloxacin 50 mg x 7 days
Number of Treated Subjects	31	34	28	37
Discontinued Subjects	10	12	9	13
Related to Study Drug	0	1	1	0
INSUFFICIENT BACTERIOLOGICAL RESPONSE	0	0	1	0
INSUFFICIENT CLINICAL RESPONSE	0	1	0	0
Not Related to Study Drug	10	11	8	13
LOST TO FOLLOW- UP	5	4	5	7
NO PATHOGEN ISOLATED FROM PRETREATMENT SPECIMEN	4	7	3	4
PROTOCOL VIOLATION	0	0	0	2
WITHDRAWN CONSENT	1	0	0	0

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Table 105.7 Summary of the Number and Percentage of Subjects with Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafoxacin (200 mg x 7 Days) (N= 31)	Trovafoxacin (200 mg x 5 Days) (N= 34)	Trovafoxacin (100 mg x 7 Days) (N= 28)	Trovafoxacin (50 mg x 7 Days) (N= 37)
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	5/ 31 (16%)	6/ 34 (18%)	6/ 28 (21%)	5/ 37 (14%)
Treatment- Related Adverse Events	1/ 31 (3%)	5/ 34 (15%)	3/ 28 (11%)	3/ 37 (8%)
Discontinuations Due to an Adverse Event	0	0	0	0
Clinically Significant Laboratory Abnormalities	4/ 20 (20%)	2/ 17 (12%)	2/ 9 (22%)	1/ 17 (6%)

There were no subjects with serious or severe adverse events and no subjects were discontinued for adverse events. Overall, the most commonly reported adverse event was dizziness. The overall percentage of adverse events was 16% in the trovafoxacin 200 mg x 7 days group, 18% in the trovafoxacin 200 mg x 5 days group, 21% in the trovafoxacin 100 mg x 7 days group, and 14% in the trovafoxacin 50 mg x 7 days group.

Clinically significant post-baseline abnormalities were observed for 20% (4/20) of subjects in the trovafoxacin 200 mg x 7 days group, 12% (2/17) of subjects in the trovafoxacin 200 mg x 5 days group, 22% (2/9) of subjects in the trovafoxacin 100 mg x 7 days group, and 6% (1/17) of subjects in the trovafoxacin 50 mg x 7 days group.

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Table 105.8 (from the study report)

Table D. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)				
	Trovafoxacin 200 mg x 7 Days (N=31)	Trovafoxacin 200 mg x 5 Days (N=34)	Trovafoxacin 100 mg x 7 Days (N=28)	Trovafoxacin 50 mg x 7 Days (N=37)
	Number of Incidents			
Number of Subjects With at Least One Adverse Event ^c	5 (16%)	6 (18%)	6 (21%)	5 (14%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM				
Dizziness	1	5	2	0
GASTROINTESTINAL SYSTEM				
Nausea	1	3	1	1
	1	2	1	0

a ≥2 incidents in any treatment group.
 b Includes data up to 7 days after last dose of active study medication
 c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

Ref.: Tables 6.2 and 6.4

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Medical reviewer's comments and conclusions

Group 2 subjects who received Trovafloxacin 200mg q day for 5 days appear to have had the greatest frequency of adverse events, except clinically significant laboratory abnormalities. As noted above, at the lowest dose evaluated, trovafloxacin 50mg for 7 days, bacteriologic persistence was found in 2/10 female subjects, the highest rate for all the groups studied. Based on the efficacy and safety results of the dose-ranging study, the sponsor chose to study trovafloxacin 200mg x 5 days for the treatment of chlamydial infections in men and women in the pivotal study 123 reviewed above.

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CONCLUSIONS

The lower efficacy of trovafloxacin in males compared to doxycycline in study 123 was consistently shown in the applicant's and the medical officer's bacteriologically evaluable populations. Therefore, equivalence of trovafloxacin to doxycycline was demonstrated in women but not in men.

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Adverse events were comparable in both groups except for dizziness and headache which occurred more frequently in the trovafloxacin treated patients. Laboratory abnormalities occurred with equal frequency in both treatment groups.

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RECOMMENDATION

Based on the results of study 123, it is the recommendation of the reviewer that trovafloxacin be approved for the treatment of chlamydial cervicitis but not chlamydial urethritis. Additionally, cautionary language to indicate that trovafloxacin had lower efficacy in males when compared to doxycycline should be included in the label.

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/s/ [Redacted Signature]

Mamodikoe K. Makhene, M.D.

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cc:

- IND (b)(4)
- IND [Redacted]
- NDA 20-759
- HFD-590/ Deputy Div Director/Albrecht
- HFD-590/Medical TL/Leissa/s/ [Redacted]
- HFD-344/DSI/Thomas
- HFD-520/PharmTox/Ellis
- HFD-520/Chemistry/Shetty
- HFD-520/Microbiology/Altaie
- HFD-590/Biopharm/Colangelo
- HFD-590/CSO/Anderson
- mkm/11/17/98
- HFD-520/MO/MAKHENE

concurrency only:
HFD-590/Division Director/Goldberge /s/ [Redacted]

APPEARS THIS WAY ON ORIGINAL

Medical Officer's Review of NDAs 20-759 and 20-760

Complicated Intra-abdominal Infections

- 1.1 NDAs : 20-759 (oral tablets) and 20-760 (injection)
- 1.2 Applicant identification
 - 1.2.1 Pfizer Central Research
 - 1.2.2 Address and telephone number:
Eastern Point Road
Groton, CT 06340
- 1.3 Submission/review dates
 - 1.3.1 Date of submission : 27 December 1996
 - 1.3.2 CDER stamp date : 30 December 1996
 - 1.3.3 Date submission received by reviewer : 6 January 1997
 - 1.3.4 Date review begun : 4 June 1998
 - 1.3.5 Date review completed : 12 December 1997
- 1.4 Drug identification
 - 1.4.1 Generic name : trovafloxacin mesylate (tablets)
alatrofloxacin mesylate (solution for injection)
 - 1.4.2 Proposed trade name : **TROVAN™**
 - 1.4.3 Other names used during development: 99,219 (tablet)
116,517 (IV)
- 1.5 Pharmacologic Category : fluoronaphthyridone
- 1.6 Dosage form : See 1.1 above
- 1.7 Route of Administration : intravenous (20-760) and oral (20-759)
- 1.8 Proposed Indication & Usage section :

COMPLICATED INTRA-ABDOMINAL INFECTIONS, including post-surgical infections caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus viridans*, *Bacteroides thetaiotaomicron*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Staphylococcus aureus*, *Beta Streptococcus* Group B, *Peptostreptococcus* species, *Prevotella* species, *Enterobacter* species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

1.9 Proposed Dosage and Administration section :

300 mg I.V. followed by 200 mg oral for a total of 7-14 days.

NOTE: Where the BernhardMod BT font is used in this document, this represents text copied from the applicant's submission.

1.10 Related Drugs : See 1.4.3 above.

1.11 Material Reviewed : NDAs and amendments

1.12 Regulatory Background

A) Anti-Infective Drug Products Approved For This Indication

The following products are approved for "INTRA-ABDOMINAL INFECTIONS" (NOTE: some labels specify "including peritonitis"):

amikacin, aztreonam, cefoperazone, cefotaxime, cefoxitin, ceftazidime, clindamycin, imipenem/cilastatin (PRIMAXIN®), metronidazole, mezlocillin, netilmicin, ticarcillin, ticarcillin/clavulanate (TIMENTIN®), tobramycin,

Piperacillin/tazobactam (ZOSYN) is approved for "**Appendicitis (complicated by rupture or abscess) and peritonitis** caused by piperacillin resistant, beta-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group; *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, Or *B. vulgatus*. The individual members of this group were studied in less than 10 cases."

Parenteral ciprofloxacin (CIPRO) is approved for "**Complicated Intra-Abdominal Infections** (used in conjunction with metronidazole) caused by *E. coli*, *P. aeruginosa*, *P. mirabilis*, *K. pneumoniae*, or *B. fragilis*" at a dose of 400 mg q12 hrs.

B) Regulatory Guidance

1992 DAIDP "Points to Consider" document (PTC)

The PTC states that for the treatment indication "complicated intra-abdominal infections" (CIAI):

- only a single study is needed
- only patients that require surgical intervention, including penetrating and blunt trauma should be studied.
- at least 80% of clinically evaluable patients should be microbiologically evaluable
- for an anaerobic claim, the drug product under review needs to establish effectiveness in either at least one other infection (with anaerobes) or establish in-vitro susceptibility and animal data effectiveness.

- need a reasonable mix of intra-abdominal infections – if not, a labeling restriction may be necessary
- it is expected for this indication to be granted, that efficacy also must be established in gynecologic infections at the same dosing and duration.
- tissue distribution studies are expected. (PK/PD)

IDSA/FDA Guidelines (*Clinical Infectious Diseases*; 15, Suppl. 1; Nov. 1992)

The guidelines make the following points about CIAI:

- Appropriate diseases for CIAI: where surgical intervention is needed (including percutaneous drainage), viscous perforation frequently resulting in peritonitis and/or abscess (including liver, pancreas, & spleen), periappendiceal abscess, perforated appendicitis, following emergency or elective operation with associated problems noted above.
- Inappropriate diseases for CIAI: diverticulitis, acute cholecystitis, non-operative management of acute appendicitis, Crohn's, ulcerative colitis (NOTE: w/o perforation), postoperative abdominal wound infections, spontaneous bacterial peritonitis, and CAPD-associated peritonitis perinephric infections, female genital tract infections, acute appendicitis, suppurative appendicitis

The IDSA/FDA Guidelines go on to comment on specific CIAIs:

- Acute gastric and duodenal perforations: if perforation occurs <24 hours prior to surgery, mostly gram-positive organisms and cultures only reflect intraluminal flora and therefore NOT appropriate for CIAI. However, if >24 hours, then gram-negative facultative and obligate anaerobes are present and culture results should correlate well with the isolation of this organism as a true pathogen.
- Traumatic perforations and transmural necrosis of the intestine: appropriate to include in CIAI study if surgery occurs >12 hours after perforation.
- Infections arising from the distal small bowel, appendix, and colon/rectum: need abscess or peritoneal fluid with WBCs and isolation of organisms from the infected site.
- Infections that occur following emergency or elective operation: constitute approx. 25% of intra-abdominal infections. May include resistant pathogens due to the failure of prophylaxis. Activity against resistant bugs (e.g., *P. aeruginosa* and *Enterobacteriaceae*) is important here.

The Guidelines discuss the following miscellaneous points:

- Parenteral therapy is usually continued until the patient is afebrile, WBC $<12,500/\text{mm}^3$, and return of bowel function - generally after a 7-day course.
- Infection must be documented at the time of surgery or during radiographically-directed drainage procedure.
- Patients should not be enrolled if the APACHE score >35
- Minimum total treatment duration (IV + PO) is typically 5 days; maximum is 14 days. If patients require >14 days of treatment, they should be considered failures. The minimum parenteral therapy is typically 3 days prior to switching to oral therapy.
- Patients who receive additional antimicrobial agents for nosocomial infections outside of the abdomen ≥ 5 days into the trial should be evaluated on the day on which therapy these agents are initiated. If there is no evidence of intra-abdominal sepsis at this time and there is no evidence of recurrent intra-abdominal infection during the subsequent clinical course, the patients should be considered clinically cured.

Clinical evaluability summarized (per IDSA/FDA Guidelines)

- Appropriate diagnosis (abscess, peritonitis, etc.) - diagnosed and treated via laparotomy or radiographically-directed drainage procedure.
- Survive >48 hours
- APACHE score <35 at entry
- For gastric & duodenal perforations: Need >24 hours since perforation prior to defining surgery
- For traumatic perforation, need >12 hours since perforation prior to defining surgery

Microbiological evaluability summarized (per IDSA/FDA Guidelines)

- Clinically evaluable AND
- (+) culture within 24 hours of defining surgery -- blood and/or site culture

Clinical outcomes summarized (per IDSA/FDA Guidelines):

Cure

- Minimum duration of therapy to be considered a cure is 5 days (first 3 days of therapy should be IV)
- To be evaluable for cure, the patient needs a valid 4-6 week follow-up visit after study entry

Failure

- additional surgical procedures needed
- treatment prolonged >14 days

- Any modification of therapy
- 2. Table of Contents: not applicable
- 3. Chemistry/Manufacturing Controls: See chemist's review.
- 4. Animal Pharmacology/Toxicology: See pharmacologist's review.

99,219 was found efficacious in a rat abscess model relative to control animals and comparable in effect with animals treated with clindamycin/gentamicin.

The preliminary data from this study are presented in the following table. This experimental model of intra-abdominal sepsis has been shown to consist of two phases: early peritonitis and abscess development in surviving recipients of a fecal inoculum. During the early, acute peritonitis stage, *Escherichia coli* and other Gram-negative organisms are numerically dominant and appear to be responsible for mortality. The second and more chronic stage of the disease, abscess formation, requires the presence of obligate anaerobes, such as *Bacteroides fragilis*. Quinolones, such as ciprofloxacin, do not prevent abscess formation when used alone in this animal model. Thus, the finding of only 2 of a possible 17 abscess formations in animals treated with 99,219 is further evidence suggesting the potential of this agent as sole treatment of intra-abdominal infections.

	Control	99,219	Clindamycin-gentamicin
Mortality (%)	13/19 (68.4%)	1/18 (5.6%)	0/19 (0.0%)
Abscess (%)	6/6 (100%)	2/17 (12%)	3/19 (16%)
Organisms recovered	<i>E. coli</i> <i>Gr. D. Strept</i> <i>Lactobacillus</i> <i>C. perfringens</i> <i>B. fragilis</i> <i>Fusobacterium</i>	<i>E. coli</i> <i>Lactobacillus</i>	<i>E. coli</i> <i>Gr. D. Strept</i> <i>Lactobacillus</i>

Table : Preliminary data from rat abscess model treated with 99,219 (20 mg SC three times daily for 7 days), clindamycin (15 mg SC three times daily for 7 days) and gentamicin (2 mg IM three times daily for 7 days), or placebo (Control).

- 5. Microbiology: See microbiologist's review.

The MIC₉₀s of trovafloxacin for pathogens commonly associated with intra-abdominal infections are listed in the following table:

Pathogen	MIC ₉₀ range (µg/mL)	median MIC ₉₀ (µg/mL)
AEROBES		
Gram (+)		
<i>S. agalactiae</i>		0.25
<i>S. aureus</i> (MSSA + MRSA)		2.0
viridans group streptococci		0.25
<i>E. faecalis</i> (vanc S)		2.0
<i>E. faecalis</i> (vanc R)		8.0
<i>E. faecium</i> (vanc S)		2.0
<i>E. faecium</i> (vanc R)		8.0
Gram (-)		
<i>Acinetobacter baumannii</i>		>8
<i>C. freundii</i>		0.375
<i>E. coli</i>		0.06
<i>E. cloacae</i>		1.6
<i>K. pneumoniae</i>		0.12
<i>M. Morganii</i>		0.5
<i>Proteus mirabilis</i> (indole -)		0.5
<i>Proteus vulgaris</i> (indole +)		0.5
<i>Providencia stuartii</i>		2.0
<i>P. aeruginosa</i>		2.0
STRICT ANAEROBES		
<i>B. fragilis</i> group		
<i>B. fragilis</i>		0.5
<i>B. thetaiotaomicron</i>		1.0
<i>B. ovatus</i>		2.0
<i>B. distasonis</i>		1.0
<i>B. vulgatus</i>		4.0
<i>B. uniformis</i>		4.0
<i>Prevotella</i> spp.		
<i>P. bivia</i>		1.0
<i>P. intermedia</i>		1.0
<i>P. melaninogenica</i>		1.5
<i>C. perfringens</i>		0.25
<i>Peptostreptococcus</i> spp.		1.0
<i>Fusobacterium</i> spp.		
<i>F. nucleatum</i>		0.375

6. Human Pharmacokinetics/Pharmacodynamics: See biopharm review.

The peak blood level (C_{max}) of alatrofloxacin at the 300 mg intravenous dose (trovafloxacin equivalent dose) used for intra-abdominal infections is 4.4 µg/mL with a half-life of 10.8 hours. The fluid/serum concentration ratio of trovafloxacin in peritoneal fluid after IV administration of 200 mg alatrofloxacin was 0.39. Mean tissue/serum concentration ratios for gynecologic tissues (ovary, uterus, myometrium, cervix and fallopian tubes) ranged _____ after single or multiple doses of oral trovafloxacin 200 mg. Thus, based upon its pharmacokinetic profile, single daily intravenous doses of 300 mg alatrofloxacin will exceed the MIC₉₀ values of pathogens commonly involved in intra-abdominal and acute pelvic infections.

7. Human Clinical Experience: not applicable

8. Clinical Studies:

8.1 Protocol Overview:

Study: 154-124

Protocol Title: A Randomized, Double-Blind, Multicenter Trial Assessing The Safety and Efficacy of Intravenous 116,517 (alatrofloxacin) Followed by Oral -99,219 (trovafloxacin) Compared to Intravenous Imipenem/Cilastatin (PRIMAXIN®) Followed by Oral Amoxicillin/Clavulanic Acid (AUGMENTIN®) for the Treatment Of Complicated Intra-Abdominal Infections

Study Dates: 12 April 1995 - 20 June 1996

Study objective : To compare the safety and efficacy of alatrofloxacin (intravenous prodrug) followed by oral trovafloxacin with the combination of intravenous imipenem/cilastatin followed by oral amoxicillin/clavulanic acid in the treatment of subjects with complicated intra-abdominal infections.

Subjects with suspected complicated intra-abdominal infections were randomized in a double-blind fashion to receive either a regimen of intravenous alatrofloxacin and oral trovafloxacin (300 mg/day intravenously followed by 200 mg/day orally for a maximum of 14 days of total therapy) or a combined regimen of imipenem/cilastatin (maximum dose of 1 gram intravenously every 8 hours) followed by amoxicillin/clavulanic acid (500 mg orally every 8 hours). Switching from parenteral to oral medication was to be determined by the investigator when oral intake had been re-established.

Adequacy of comparator:

PRIMAXIN® (imipenem/cilastatin) is FDA-approved in the INDICATIONS AND USAGE section for the treatment of:

The DOSAGE AND ADMINISTRATION section of PRIMAXIN® labeling states:

INTRAVENOUS DOSAGE SCHEDULE
FOR ADULTS WITH
NORMAL RENAL FUNCTION
AND BODY WEIGHT ≥ 70 kg

Type or Severity of Infection	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of <i>P. Aeruginosa</i>
Mild	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g)
Moderate	500 mg q8h (TOTAL DAILY DOSE = 1.5g) or 500 mg q6h (TOTAL DAILY DOSE = 2.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g) or 1 g q8h (TOTAL DAILY DOSE = 3.0g)
Severe, life threatening only	500 mg q6h (TOTAL DAILY DOSE = 2.0g)	1 g q8h (TOTAL DAILY DOSE = 3.0g) or 1 g q6h (TOTAL DAILY DOSE = 4.0g)

MO Comment : PRIMAXIN® is an adequate comparator.

MO Comment : Pfizer's rationale to use AUGMENTIN® as the follow-up oral therapy to PRIMAXIN® is acceptable.

Sample size: A total of 300 subjects were to be enrolled in this study. Recruitment was to cease when 300 subjects had been enrolled, even if some centers had not reached their projected recruitment targets.

MO Comment : The applicant enrolled a total of 414 patients instead.

Noteworthy Inclusion Criteria :

- 1) Subjects who are found to have one of the following infections requiring anti-infective therapy and an operative procedure or percutaneous drainage. Subjects must have physical examination findings consistent with an intra-abdominal infection (e.g. signs of peritoneal irritation, mass) as well as systemic evidence of inflammation (for example, fever [body temperature ≥ 38.5 °C], WBC $> 12,500$ cells/mm³, hypotension [systolic blood pressure < 90 mmHg], etc.). Physical findings may also include clinically-documented serosal inflammation and/or presence of localized or diffuse abdominal wall rigidity, mass, or ileus. Where appropriate, imaging studies may support signs and symptoms of an intra-abdominal infection.
 - intra-abdominal abscesses
 - bacterial peritonitis
 - appendicitis with evidence of a perforation or abscess; duration of symptoms ≥ 24 hours
 - acute perforations of the stomach or duodenum only if not operated on within 24 hours of perforation
 - traumatic perforations of the small bowel (excluding duodenum) or large bowel only if not operated on within 12 hours of perforation
 - perforations unrelated to trauma of the small bowel (excluding duodenum) or large bowel
 - intra-abdominal infections related to previous intra-abdominal surgery
 - intra-abdominal infections following penetrating and blunt trauma.

MO Comment : The protocol specifies that "Findings at operation must confirm the presence of an intra-abdominal infection (e.g. presence of purulent exudate and inflamed or necrotic tissue)."

- 2) Duration of the treatment of the intra-abdominal infection is anticipated to be at least 3 days.
- 3) Subjects may be included into the study after receiving prior anti-infective therapy under the following conditions:
 - the previous anti-infective therapy was given for < 24 hours of therapy with a drug which requires ≥ 7 days duration of therapy
 - subjects with a known intra-abdominal abscess may be enrolled into the study despite receiving empirical therapy for several days if pre-treatment cultures at time of surgery or percutaneous drainage yield bacterial pathogens susceptible to the study drugs
 - subjects infected with an organism that is resistant *in vitro* to the anti-infective drug initially used, provided that the organism causing the infection is recovered within 24 to 48 hours before enrollment and is susceptible to the study drugs.

Noteworthy Exclusion Criteria :

- 1) Subjects with any of the following disease states:
 - perinephric infections
 - infections of the female genital tract (gynecological infections)
 - spontaneous bacterial peritonitis
 - peritonitis associated with chronic peritoneal dialysis
 - acute (< 24 hours) perforations of the stomach or duodenum
 - traumatic perforations of the small or large bowel and operated on within 12 hours of the perforation
 - transmural necrosis of the intestine due to acute embolic or thrombotic occlusion
 - acute cholecystitis with infection confined to the gallbladder
 - early acute or suppurative (nonperforated) appendicitis unless there is evidence of an abscess or free peritoneal fluid containing leukocytes and microorganisms suggestive of regional contamination
 - pancreatic and peripancreatic sepsis.

- 2) Baseline APACHE II score > 35 obtained within 48 hours prior to randomization into double-blind therapy.
- 3) Subjects who require "open abdomen" techniques for management. However, when clinically-indicated, temporary closure of the abdominal incision using _____ (or equivalent) with a subsequent, *planned* surgical procedure to close the abdomen within 72 hours of the initial surgical procedure will be allowed.
- 4) Subjects with any infections that require treatment with an anti-infective agent other than the study drugs. Subjects requiring antibiotic irrigation of the abdominal cavity or surgical wound are not suitable for entry.
- 5) Immunocompromised patients

MO Comment : The applicant's criteria are entirely consistent with the IDSA/FDA Guidelines. The MO agrees with the applicant's use of them.

Evaluation Visits :

Patients were to be evaluated at baseline (day 1; within 48 hours prior to the start of therapy), daily between days 1-14, at end of therapy (EOT), and long-term follow up (EOS; days 28-42). Clinical response to therapy was to be assessed by the investigator at the end of the double-blind treatment period as well as at follow-up (day 30).

MO Comment : From a practical standpoint, the applicant used EOS as ≥ 21 days of study. Although the IDSA Guidelines recommend a 4-6 weeks post-therapy test-of-cure follow up visit, the MO considers this visit window acceptable. Furthermore, MERREM was recently approved for this indication based on a minimum follow-up visit of 7 days post-therapy.

At entry into the study, based on the findings from the illness-defining procedure, the investigator was instructed to capture the following information on the CRF:

UNDERLYING DISEASE (check all that apply) :

- ◇ Appendicitis with perforation or abscess ≥ 24 hours
- ◇ Acute perforation of stomach or duodenum with surgery ≥ 24 hours
- ◇ Perforation (non-traumatic) of small or large bowel
- ◇ Traumatic perforation of small bowel or large bowel with surgery ≥ 12 hours
- ◇ Intra-abdominal infection following penetrating or blunt trauma
- ◇ Intra-abdominal infection related to previous intra-abdominal surgery
- ◇ Other (specify) _____

SITES OF INTRA-ABDOMINAL INFECTION (check all that apply):

- ◇ Distal esophagus/stomach/duodenum
- ◇ Appendix
- ◇ Pancreas

- ◇ Biliary tree
- ◇ Colon
- ◇ Proximal small bowel
- ◇ Liver
- ◇ Distal small bowel
- ◇ Spleen
- ◇ Other (specify) _____

TYPE OF INFECTION (check all that apply):

- ◇ Single abscess
- ◇ Multiple abscesses
- ◇ Peritonitis

Protocol Prohibitions

- Intraluminal use of antibiotics was not allowed during the study.

Microbiology

The protocol stipulated,

- pre-treatment blood and peritoneal fluid specimens for culture were to be obtained within 48 hours prior to initiation of therapy or, with peritoneal fluid samples, up to 12 hours after the initiation of therapy. Each probable pathogen was to be identified to the species level.”
- blood cultures (more than 1) must be obtained from all subjects.

The following susceptibility testing was employed for this study:

	GP-99219 ¹	Imipenem-cilastatin ¹		Amoxicillin-clavulanic acid ²	
Criteria	MIC µg/mL	Zone 10-µg disk	MIC µg/mL	Zone 30-µg disk	MIC µg/mL
Susceptible	≤ 2	≥ 16	≤ 4	≥ 18	≤ 8
Intermediate	4	14 - 16	8	14 - 17	16
Resistant	≥ 8	≤ 13	≥ 16	≤ 13	≥ 32

¹tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing

²NCCLS criteria

According to the protocol, subjects need not be discontinued from the study drug if they do not have a pathogen isolated at baseline or because the pathogen is

resistant to any of the study medications. Rather, the investigator could choose to continue the patient in the study if there was evidence of clinical improvement.

Outcome Definitions

Clinical response

APPEARS THIS WAY ON ORIGINAL

At each visit, clinical response was assessed for the presence or absence of intra-abdominal pain/tenderness, abdominal rigidity, swelling, induration, surgical wound discharge, mass, ileus, bowel sounds, formed bowel movements, flatulence, hypotension and leukocytosis on the CRF. The following clinical response definitions were used by the applicant.

Cure : Typically, a successful outcome may be characterised by resolution of signs and symptoms of an inflammatory response (e.g. fever [body temperature ≥ 38.5 °C], elevated white blood cell count [WBC $\geq 12,500$ cells/mm³], hypotension [systolic blood pressure < 90 mmHg]) and intra-abdominal distress (localized or diffuse abdominal wall rigidity and/or mass and/or ileus, pain/tenderness, abdominal swelling, discharge, induration, and lack/presence of bowel sounds).

MO Comment : As stated above, the IDSA/FDA Guidelines state that the minimum duration of therapy to be considered a cure is 5 days and that the first 3 days of therapy should usually be administered parenterally. The MO asked the applicant to identify "clinically evaluable" patients in both treatment arms who transitioned from IV to oral within 3 days of study onset. The applicant responded that for the "cure" rate was 3/6 (50%) and 9/12 (75%) for the TROVAN and PRIMAXIN→AUGMENTIN treatment arms, respectively.

APPEARS THIS WAY
ON ORIGINAL

Improvement : Resolution of some but not all intra-abdominal symptoms and no requirement for additional antibiotic. The investigator will determine if the subject is improved from baseline, rather than cured or failed antibiotic therapy.

Failure will be defined by one or all of the following conditions:

- lack of resolution of all signs and symptoms of an intra-abdominal infection (as defined above).
- the need for additional antibacterial therapy for the treatment of the intra-abdominal infection. The reason for additional antibiotic therapy must be documented in the subject's Case Report Form.
- the need for greater than 14 days of antibiotic therapy.
- the need for more than one surgical procedure (with the exclusion of replacement of peritoneal drainage tubes). However, if assessed independently

by a blinded panel of investigators and the sponsor that the initial surgical procedure is considered inadequate, then the subject should be considered non-evaluable (see below). Subjects who require temporary closure of the abdominal incision using _____ (or equivalent) with a subsequent, *planned* surgical procedure to close the abdomen within 72 hours of the initial surgical procedure will be considered as having a single surgical procedure. Thus, this delayed closure procedure will not be considered a treatment failure.

The occurrence of any of the following conditions will supersede the evaluation of response as cure, improvement, or failure and will result in the reassignment of outcome by the sponsor as follows:

- for subjects who were previously assessed as failures, the outcome will always be failure at subsequent time points.
- for subjects who were given a concomitant systemic antibiotic prior to an evaluation time point, response will be classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.

According to an August 1995 protocol amendment: For subjects who stopped double-blind therapy because of no apparent response, response will be classified as failure.

According to a November 1995 protocol amendment : Clinical response will also be determined at initiation of concomitant antibiotic therapy. Patients who receive additional antimicrobial agents for any infections outside of the abdomen ≥ 5 days into the study must be evaluated on the day on which therapy with these agents is initiated.

MO Comment : The MO asked the applicant to identify patients in the clinically evaluable population considered "successes" (cure or improvement) who received a systemic anti-infective drug product ≥ 5 days into the study considered "unrelated" to the intra-abdominal infection. The applicant noted 19 and 14 patients in the TROVAN and PRIMAXIN→AUGMENTIN treatment arms, respectively, who met these criteria. Example reasons included pneumonia, UTI, wound suppuration, tooth abscess, change in therapy due to the development of an adverse event, and "prophylaxis".

Bacteriologic Response

APPEARS THIS WAY ON ORIGINAL

Bacteriologic response was usually presumptively determined based on the subject's clinical outcome. Possible responses included : **eradication**, **presumed eradication**, **persistence**, **superinfection** (new pathogen during therapy), and **presumed microbiological persistence**.

MO Comment : The MO agrees with the applicant's outcome definitions.

Evaluability Definitions

(1) Evaluable population

To be considered fully evaluable for clinical response, a subject must have :

- a. an intra-abdominal focus of established infection documented by operative intervention or by a radiographically-controlled drainage procedure
- b. signs and symptoms of an intra-abdominal infection

An indeterminate *clinical* outcome assessment was made (i.e., made nonevaluable), if the subject fulfilled any of the following criteria:

- a. Insufficient therapy: received < 5 days of double-blind therapy unless considered a failure
- b. inapplicable diagnosis (i.e. subject did not meet entry criteria for intra-abdominal infection).
- c. Concomitant systemic antibacterials given for intercurrent illness. However, if a subject receives additional antimicrobial agents for nosocomial infections outside the abdomen $\geq$ 5 days into the trial, the reason should be documented by the principal investigator or his designate and noted on the subject's Case Report Form. If no evidence of an intra-abdominal infection, nor evidence of a recurrent intra-abdominal infection during the subsequent clinical course exists, then this subject may be considered evaluable and, accordingly, a clinical cure.³
- d. Missing post-baseline clinical assessments: no visit at evaluation point unless subject was previously designated as a treatment failure.
- e. Inadequate initial operative procedure. An operation is considered inadequate if not all communications between the gastrointestinal tract and the peritoneal cavity are closed and/or if necrotic intestine is left and/or if an infected collection was missed at the initial drainage. Prior to the blind being broken, a panel of investigators and the sponsor will consider those cases which have questionable evaluability. Operative notes or percutaneous drainage notes will be reviewed and a decision will be rendered on the evaluability of these subjects.
- f. Death: subjects who die within 48 hours after initiation of double-blind therapy.
- g. if appropriate, other criteria may be added.

An indeterminate *bacteriologic* outcome assessment was made (i.e., made nonevaluable), if the subject fulfilled any of the following criteria:

³Solomkin JS, Hemsell DL, Sweet R, Tally F, Bartlett J. Evaluation of new anti-infective drugs for the treatment of intra-abdominal infections. *Clin Infect Dis* 1992; 15(Suppl 1):S33-S42.

- a. relevant post-baseline cultures are not obtained, unless it is a result of the absence of adequate purulent culture material (to be considered presumptive microbiologic eradication as defined below) or concomitant antibiotic use due to bacteriologic persistence
- b. concomitant antibiotic use for treatment of an intercurrent illness
- c. the subject was not considered clinically evaluable.

(2) Modified Intent-to-Treat population (protocol defined)
To be evaluable for the MITT analysis,

**APPEARS THIS WAY
ON ORIGINAL**

Subjects with inappropriate primary diagnoses (e.g., no clinical signs or symptoms at baseline, or having entered the study more than once) will be excluded. Otherwise, all randomized subjects will be included in the modified ITT analysis. Subjects with no clinical information after the baseline evaluation will be considered as clinical treatment failures.

Clinical Intent-to-Treat Subjects (from study summary)

**APPEARS THIS WAY
ON ORIGINAL**

The clinical intent-to-treat subjects subset included those subjects in the all randomized subjects subset who had confirmed intra-abdominal infection and underwent surgery or percutaneous drainage at baseline. Some subjects in this subset may never have received any study medication.

Bacteriological Intent-to-Treat Subjects (from study summary)

**APPEARS THIS WAY
ON ORIGINAL**

The bacteriological intent-to-treat subjects subset included those subjects in the clinical intent-to-treat subjects subset with at least one pathogen identified at baseline in either peritoneal fluid or blood culture. Subjects in this subset may never have received any study medication.

Efficacy Analyses

**APPEARS THIS WAY
ON ORIGINAL**

According to a November 1995 protocol amendment, the primary efficacy parameter:

will be *sponsor-defined* clinical response at follow-up (day 30).

**APPEARS THIS WAY
ON ORIGINAL**

The same amendment states :

The following secondary efficacy outcome parameters will be tabulated and compared between treatment groups:

- *sponsor-defined* clinical response at end of double-blind therapy
- *investigator-defined clinical response at the end of double-blind therapy and at follow-up*
- *sponsor-defined organism outcome at end of treatment and at follow-up*
- changes in baseline APACHE score on days 4, 7, 10, and 14 after start of double-blind therapy
- time post-operatively spent in the hospital (days)
- time of post-operative fever (days)
- time to recovery (days)
- duration of intravenous therapy (days)
- proportion of subjects with nosocomial infection
- proportion of subjects receiving additional antibiotics

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Schedule of Study Evaluations

Study day	Day 1	Day 4	Day 14 ^a	Day 30
Allowable Window:	-48 hours	Day 3-5	Day 10-14	Day 28-42
Treatment Period	Day 1 to Day 14 ^a			
Follow-up period	Day 15 to Day 42			
Informed consent	X			
Demographic information	X			
Physical examination of the abdomen ^b	X-----X		X	X
Maximum body temperature ^b	X-----X		X	X
Vital signs	X	X	X	X
Concomitant medication	X	X	X	X
APACHE scoring	X	X ^c	X	
Dosing record		X	X	
Clinical signs & symptoms ^b	X-----X		X	X
Assessment of bowel function ^b	X-----X		X	X
Microbiology culture & sensitivity				
• blood	X	X ^d	X ^d	X ^d
• peritoneal	X ^e			
Safety laboratory tests				
• hematology	X	X	X	abn
• biochemistry	X	X	X	abn
• urinalysis	X	X	X	abn
• pregnancy test ^f	X			
Adverse events	X-----X			X
Investigator's assessment of clinical response ^g			X	X
Time of recovery	X-----X		X	X
Health care resource utilization	X-----X		X	X

^aor end of double-blind therapy if sooner

^bperformed daily during the hospitalization period

^crecorded also on days 7 and 10

^donly if clinically indicated (e.g., time of discontinuation or previously positive culture)

^eor up to a 12-hour period after start of therapy

^fto be done locally for women of child bearing potential

^gand to be done at the time of discontinuation, if applicable

abn=to be done only if abnormal at previous visit or clinically significant adverse event

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8.3 Study Results

MO Comment : The Medical Officer reviewed the applicant's patient data and, in general, agreed with their assignment of patients to populations and outcome responses. Therefore, for the purposes of this review, the MO's and applicant's efficacy and safety populations are the same.

INVESTIGATORS:

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5133	Dennis Mikolich, MD
	5204	Stanley Klein, MD
	5229	Michael Neill, MD
	5429	John Yatsu, MD
	5431	Steven Mintz, MD
	5486	David Borgstrom, MD
	5495	George Mueller, MD
	5497	Joseph Wentzky, Jr, MD
	5524	C. Gene Cayten, MD
	5525	David Smith, MD
	5526	Gene Coppa, MD
	5529	Vinod Dhawan, MD
	5530	Philip Donahue, MD
	5532	Blaine Enderson, MD
	5533	Michael Esser, MD
	5534	Richard Greenberg, MD
	5535	David Longworth, MD
	5537	Luis Jauregui, MD
	5542	Carey Page, MD / Ronald Stewart MD
	5545	Robert Martindale, MD
	5549	Michael Metzler, MD
	5550	Ronald Simon, MD
	5552	John Oropello, MD
	5553	Russell Postier, MD
	5557	William Stahl, MD
	5560	Richard Wait, MD
	5562	Bienvenido Yangco, MD
5563	Thomas Berne, MD	
	Albert Yellin, MD	
	Jefferson Stowers, MD	
5599	Robert Gainer, II, MD	
5606	Lawrence Nastro, MD	
5608	Jon White, MD	
5610	Peter Krumpke, MD	
5613	Amir Neshat, MD	
5614	Kathaleen Porter, MD	
5615	David Redfield, MD	
5616		

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States (continued)	5617	Joseph Solomkin, MD
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	5739	James Wagner, MD
	5761	John Mazuski, MD
	5910	Joseph Portoghese, MD
	5931	Carol Kemper, MD
	5970	Alan Sugar, MD
	5998	Kenneth Courington, MD
	6006	Richard Kohler, MD
	6012	Corrado Marini, MD
	6044	Alexander Robbins, MD
	6046	E. Robert Harris, MD
	6047	Joseph Scoma, MD
	6048	Mark Sherman, MD
	6052	Craig Schaefer, MD
	6053	Ronald Nichols, MD
	6055	Jan Elston, MD
	6067	Larry Danziger, PharmD
	6068	Leon Smith, MD
	6069	Judith Wolf, MD
	6090	Burke Cunha, MD
	6099	Manuel Ramirez, MD
	6100	Vinod Rustgi, MD
	6107	Dana Edwards, MD
	6151	Gregory Timberlake, MD
	6155	Ellis Caplan, MD
	6170	Eduardo Gonzales, MD
	6246	Michael Hellinger, MD
	6287	Nicholas Price, MD
	6344	William O'Riordan, MD
	6367	Del Dehart, MD
	6380	John Dawson, MD
	6381	Bruce Harris, MD
6382	Jay Harviel, MD	
6383	Carol Leitner, MD	
6395	Gaylord Kavlie, MD	
6398	Patrick White, MD	
6409	Ronald Jackson, DO	
6424	H. Scott Bjerke, MD	
6425	Edward Condon, MD	
6431	Martin Schrieber, MD	
6498	Thomas Lawson, Jr., MD	
6499	Robert Cohen, MD	
France	5187	Dr. Didier Grange
	5199	Dr. Paul Teniere
	5990	Dr. Francois Fraisse
	6013	Dr. Georges Goursot
	6014	Dr. Francis Bur

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
France (continued)	6016	Dr. Jean Dupeyron
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	6018	Dr. Luc Guyot
	6019	Dr. Claude Jacquot
	6020	Dr. Patrick De Rohan Chabot
	6095	Dr. G. Kohlmann
	6311	Dr. Patrick Cougard
	6436	Dr. Ghassan Ferzli
	6437	Dr. Fariborz Hakami
	6439	Dr. Jean-Michel Kerrenneur
	6440	Dr. Michel Ossart
	6441	Dr. Jean-Claude Otteni
	6442	Dr. Philippe Lallemant
6444	Dr. Christian Virenque	
Canada	5155	Sylvie Trottier, MD
	5598	Frederick Brenneman, MD
	5921	Frank Baillie, MD
	6365	Marvin Gerson, MD
	6384	Jean Ledoux, MD
	6451	Claude Lemieux, MD
	6465	Jean-Francois Bellemare, MD
	6467	Vivian Mcalister, MD
6468	Murray Girotti, MD	
Poland	6517	Dr. Otmar Gedliczka
	6518	Dr. Zygmunt Mackiewicz
	6521	Dr. Bogdan Lazarkiewicz
	6522	Dr. Bruno Szczygiel
	6523	Dr. Andrzej Karwowski
	6524	Dr. Wojciech Noszczyk
Belgium	6092	Dr. Bernard Broze
	6093	Dr. Claude Chastel
	6496	Dr. Yves Van Laethem
United Kingdom	6255	Dr. Roger Leicester
	6256	Dr. Eric Taylor
	6258	Dr. Peter Donaldson

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The study was conducted in several countries and many centers were enlisted (120 total centers: 80 USA, 9 Canada, and 31 Europe).

Number of Patients Evaluated in Each Group		
	Alatrofloxacin ↓ Trovafoxacin	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid
Randomized	204	210
Randomized, not treated	3	3
All Treated	201 (100%)	207 (100%)
Completed Treatment	167 (83%)	170 (82%)
Completed Study	181 (90%)	184 (89%)
Evaluated for Efficacy ^a		
Clinical Intent-to-Treat	200 (98%)	199 (95%)
Clinical Intent-to-Treat with Abscesses	118 (58%)	102 (49%)
Clinical Intent-to-Treat with Peritonitis	111 (54%)	115 (55%)
Clinically Evaluable ^b	156 (76%)	152 (72%)
Clinically Evaluable with Abscesses	96 (47%)	82 (39%)
Clinically Evaluable with Peritonitis	87 (43%)	85 (40%)
Bacteriologically Intent-to-Treat	171 (84%)	164 (78%)
Bacteriologically Evaluable	135 (66%)	131 (62%)
Assessed for Safety		
Adverse Events	201 (100%)	207 (100%)
Laboratory Tests	198 (99%)	205 (>99%)
a	Based on the number of randomized subjects.	
b	Evaluability determined at the end of study.	

A total of 414 patients (204 Trovan vs. 210 Primaxin → Augmentin) were randomized into the study. There was no significant difference between treatment arms in the proportion represented in the various study populations.

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Summary of Baseline Demographic Characteristics		
	Alatrofloxacin ↓ Trovfloxacin	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid
Baseline Demographic Characteristic	Number and Percentage (%) of Subjects	
	(N=156 ^a)	(N=152 ^a)
Gender		
Male	114 (73%)	95 (63%)
Female	42 (27%)	57 (27%)
Race		
Black	20 (13%)	15 (10%)
White	87 (56%)	94 (62%)
Other (primarily hispanic)	49 (31%)	43 (28%)
Weight (kg)		
males (mean)	77.1	79.6
females (mean)	68.9	67.9
Age (years)		
Mean	42.6	45.4
Minimum		
Maximum		
16-44	94 (60%)	78 (51%)
45-64	39 (25%)	45 (30%)
≥65	23 (15%)	29 (19%)
Diseases/Syndromes at Baseline ^b	(N=201 ^c)	(N=207 ^c)
COPD	13 (6%)	20 (10%)
Diabetes Mellitus	13 (6%)	14 (7%)
Hepatic Disease	7 (3%)	4 (2%)
Impaired Renal Function	6 (3%)	5 (2%)
Congestive Heart Failure	5 (2%)	7 (3%)
COPD = chronic obstructive pulmonary disease.		
a Clinically evaluable subjects.		
b Not all treated subjects were assessed for intercurrent disease/syndrome at study entry.		
c Treated subjects.		

Among the clinically evaluable study population, proportionally more males were studied in each arm. Otherwise, the two treatment arms appeared similar with regard to other demographic features.

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Summary of Baseline Risk Factors Associated with a Possible Unfavorable Outcome (Clinically Evaluable Subjects)		
	Alatrofloxacin ↓ Trovafoxacin (N=156)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)
Risk Factors	Number and Percentage (%) of Subjects	
Subjects with at Least One Risk Factor*	109 (70%)	91 (60%)
APACHE score		
Mean	6.4	7.0
Median		
Maximum		
Type of Infection		
Abscess only	69 (44%)	67 (44%)
Peritonitis only	60 (38%)	70 (46%)
<i>Abscess and Peritonitis</i>	27 (17%)	15 (10%)
Site of Infection		
<i>Multiple</i>	19 (12%)	18 (12%)
Underlying Disease		
Appendiceal rupture	81 (51%)	71 (47%)
Peptic ulcer perforation	32 (21%)	32 (21%)
<i>Post/op abscess or perforation</i>	32 (21%)	30 (20%)
Extreme Age		
>75	6 (4%)	12 (8%)
Health Insurance		
None	53 (34%)	47 (31%)

* *italicized* titles listed above represent "risk factors" (according to the applicant)

For the clinically-evaluable population, risk factors were similarly distributed between the two treatment groups at baseline with the exception of the infection type "abscess and peritonitis" being higher in the Trovan arm. (17% vs. 10%)

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Summary of Premature Discontinuations From Treatment				
(All-Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=201)		Imipenem/Cilastatin ↓ Amoxicillin/Clavulanac Acid (N=207)	
	Number and Percentage (%) of Subjects			
Total Discontinued	34	(17%)	37	(18%)
Discontinuations Related to Study Drug:	21	(10%)	14	(7%)
Adverse Event	13	(6%)	6	(3%)
Insufficient Response	7	(3%)	8	(4%)
Laboratory Abnormality	1	(<1%)	0	
Discontinuations Unrelated to Study Drug:	13	(6%)	23	(11%)
Adverse Event	5	(2%)	9	(4%)
Did Not Meet Randomization Criteria	1	(<1%)	1	(<1%)
Laboratory Abnormality	0		1	(<1%)
Lost to Follow-Up	0		2	(<1%)
Other	2	(<1%)	6	(3%)
Subject Died	3	(1%)	1	(<1%)
Protocol Violation	1	(<1%)	1	(<1%)
Withdrawn Consent	1	(<1%)	2	(<1%)

Reasons for premature discontinuation were comparable between study arms.

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Clinical Efficacy

Summary of Sponsor-Defined Clinical Response Rates					
at the End of Treatment and the End of Study					
(Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloxacin (N=156)		Imipenem/Cilastatin ↓ Amoxicillin/Clavulanic Acid (N=152)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	155	(100%)	142	(100%)	
Success (Cure + Improvement)	136	(88%)	122	(86%)	(-5.9, 9.5)
Distribution of Clinical Response:					
Cure	119	(77%)	104	(73%)	
Improvement	17	(11%)	18	(13%)	
Failure	19	(12%)	20	(14%)	
End of Study:					
Number of Subjects Assessed	156	(100%)	152	(100%)	
Success (Cure + Improvement)	129	(83%)	127	(84%)	(-9.2, 7.5)
Distribution of Clinical Response:					
Cure	128	(82%)	125	(82%)	
Improvement	1	(<1%)	2	(1%)	
Failure	27	(17%)	25	(16%)	

For the clinically-evaluable population, by the end of treatment and end of study visits, efficacy was similar between treatment arms. Similar results were seen for the clinical intent-to-treat population. (See next table.)

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A Summary of the Sponsor's-Assessment of Clinical Efficacy Results (Clinical Intent-to-Treat Subjects)				
	End of Treatment		End of Study	
	Alatrofloxacin ↓ Trovafoxacin (N=200)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=199)	Alatrofloxacin ↓ Trovafoxacin (N=200)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=199)
Number and Percentage (%) of Subjects				
Number of Subjects Assessed	198 (100%)	193 (100%)	200 (100%)	199 (100%)
Success (Cure + improvement)	168 (85%)	163 (84%)	161 (81%)	162 (81%)
Distribution of Clinical Response:				
Cure	146 (74%)	136 (70%)	157 (79%)	156 (78%)
Improvement	22 (11%)	27 (14%)	4 (2%)	6 (3%)
Failure	30 (15%)	30 (16%)	39 (20%)	37 (19%)

According to the applicant, "Comparisons of the difference between the two treatment groups in sponsor-defined clinical success rates (cure + improvement) supported equivalence of the two treatments in both the clinically evaluable and intent-to-treat analyses at the end of treatment (95% CI: -5.9%, 9.5% and -6.8%, 7.5%, respectively) and at the end of study (95% CI: -9.2%, 7.5% and -8.6%, 6.8%, respectively)."

Summary of Clinical Signs and Symptoms at Baseline, EOT, and EOS (Clinically Evaluable Subjects)						
Sign/Symptom ^a	Alatrofloxacin ↓ Trovafoxacin			Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid		
	Baseline	EOT	EOS	Baseline	EOT	EOS
Percentage of Subjects With Clinical Signs and Symptoms						
Intra-abdominal Pain/Tenderness	92%	12%	7%	92%	16%	7%
Abdominal Rigidity	36%	0%	<1%	33%	0%	0%
Swelling	38%	2%	2%	46%	3%	<1%
Induration	11%	1%	<1%	9%	2%	2%
Surgical Wound Discharge	16%	16%	10%	13%	16%	10%
Mass	7%	0%	<1%	12%	1%	0%
Ileus	40%	<1%	<1%	39%	2%	0%
Hypotension	4%	1%	<1%	5%	<1%	0%
Leukocytosis	77%	16%	14%	74%	24%	13%
Bowel Sounds	55%	94%	94%	49%	95%	95%
Formed Bowel Movements	17%	75%	86%	16%	78%	85%
Flatulence	26%	76%	78%	24%	77%	84%
Intra-abdominal Pain/Tenderness	92%	14%	8%	91%	18%	8%
Abdominal Rigidity	34%	3%	<1%	32%	0%	<1%
Swelling	36%	5%	2%	41%	5%	2%
Induration	11%	2%	<1%	7%	2%	2%
Surgical Wound Discharge	16%	17%	10%	15%	17%	10%
Mass	8%	<1%	<1%	12%	2%	<1%
Ileus	37%	2%	<1%	38%	2%	0%
Hypotension	5%	4%	1%	5%	1%	0%
Leukocytosis	76%	18%	14%	74%	24%	13%
Bowel Sounds	56%	92%	94%	51%	94%	95%
Formed Bowel Movements	19%	71%	85%	15%	75%	83%
Flatulence	27%	75%	80%	24%	79%	83%

EOT=End of Treatment; EOS = End of Study
a Not all subjects were evaluated for all signs/symptoms at all timepoints.

For the clinically evaluable subjects, intra-abdominal signs and symptoms were comparable between populations at baseline, end of treatment, and end of study.

Other Indirect Measurements of Clinical Success (Clinical Intent-to-Treat Subjects)		
	Alatrofloxacin ↓ Trovafloxacin (n=200)	Imipenem/Cilastatin ↓ Amoxicillin/Clavulanic Acid (n=199)
Time to recovery (days)	(n=179) 7.9 ± 5.8*	(n=189) 8.2 ± 6.9*
Duration of post-op fever (days)	(n=199) 3.3 ± 3*	(n=197) 3.2 ± 3*
Duration of post-op hospitalization (days)	(n=193) 14.3 ± 14.5*	(n=195) 14.0 ± 14.2*
Median duration of hospitalization (days)	9	9

* = mean ± SD

As shown above, time to recovery, duration of post-op fever, duration of post-op hospitalization, and median duration of hospitalization was comparable between the two treatment arms.

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Microbiologic Efficacy:

Summary of Clinical Success (cure + improved) Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens ^a (Clinically Evaluable Subjects)								
Pathogen	Alatrofloxacin ↓ Trovafoxacin (N=156)		Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)		Alatrofloxacin ↓ Trovafoxacin (N=156)		Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanic Acid (N=152)	
	Number of Subjects				End of Treatment		End of Study	
Gram Positive Aerobes								
Alpha-haemolytic streptococci	9/12		4/4		8/12		6/6	
Beta-hemolytic streptococci, Gp. B (= <i>S. agalactiae</i>)	0/1		1/1		0/1		0/1	
<i>S. viridans</i>	18/20 (90%)		19/23 (83%)		18/20 (90%)		18/23 (78%)	
<i>S. anginosus</i>	7/10		8/8		6/10		8/8	
<i>Streptococcus</i> sp.	27/30 (90%)		38/41 (93%)		26/30 (87%)		40/43 (93%)	
<i>E. faecium</i>	3/4		5/6		3/4		5/6	
<i>E. faecalis</i>	7/13		12/16 (75%)		6/13		12/17 (71%)	
<i>Enterococcus</i> sp.	7/10		13/18 (72%)		7/10		15/20 (75%)	
<i>S. aureus</i>	8/11		1/3		8/11		1/3	
Gram Negative Aerobes								
<i>E. coli</i>	72/77 (94%)		52/58 (90%)		66/77 (86%)		51/59 (86%)	
<i>E. aerogenes</i>	3/3		2/2		3/3		2/2	
<i>E. cloacae</i>	6/7		5/7		5/7		6/7	
<i>Enterobacter</i> sp.	2/3		1/1		2/3		1/1	
<i>K. pneumoniae</i>	12/15 (80%)		10/14		10/15 (67%)		10/14	
<i>P. aeruginosa</i>	15/16 (94%)		14/17 (82%)		14/16 (88%)		15/18 (83%)	
Gram Positive Anaerobes								
<i>Peptostreptococcus</i> sp.	12/14		7/8		11/14		6/8	
<i>Clostridium</i> sp.	4/5		8/9		4/5		9/10	
<i>Corynebacterium</i> sp.	3/3		5/5		3/3		6/6	
Gram Negative Anaerobes								
<i>Prevotella buccae</i>	1/2		1/2		1/2		1/2	
<i>Prevotella intermedia</i>	1/1		0		1/1		0/0	
<i>Prevotella</i> sp.	10/13		2/4		10/13		3/5	
<i>B. fragilis</i>	30/31 (97%)		28/34 (82%)		26/31 (84%)		27/36 (75%)	
<i>B. thetaiotaomicron</i>	14/18 (78%)		13/13		11/18 (61%)		12/13	
<i>B. uniformis</i>	7/7		9/10		5/7		9/10	
<i>B. vulgatus</i>	5/7		7/7		5/7		7/7	
<i>Bacteroides</i> sp.	7/9		11/12		7/9		11/13	
<i>F. necrophorum</i>	3/3		2/2		3/3		2/2	
<i>F. nucleatum</i>	1/2		1/1		1/2		1/1	
<i>Fusobacterium</i> sp.	6/7		2/2		6/7		2/2	

^a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Comparable bacteriologic efficacy (often presumptively determined based on clinical response) was observed in both treatment arms for the majority of pathogens isolated at the time of the defining surgery. However, TROVAN appeared (albeit small numbers) to have lower efficacy against *B. thetaiotaomicron* compared to the control arm. (11/18 vs. 12/13)

For those patients who received repeat cultures at follow up, the development of resistance to trovafloxacin was not seen.

Safety

Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Alatrofloxacin ↓ Trovafoxacin (N=201)	Imipenem/Cilastatin ↓ Amoxicillin/ Clavulanac Acid (N=207)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	128/201 (64%)	120/207 (58%)
Treatment-Related Adverse Events	29/201 (14%)	23/207 (11%)
Discontinuations from Treatment Due to an Adverse Event: All Causality	19/201 (9%)	19/207 (9%)
Discontinuations Due to a Treatment-Related Adverse Event	13/201 (6%)	6/207 (3%)
Clinically Significant Laboratory Abnormalities	142/198 (72%)	153/205 (75%)
Deaths*	11	11
Deaths during study period (entry → 30 days post-therapy)	7	5

Adverse event reporting (all causality and treatment-related) was similar between the two treatment groups.

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Deaths

Eleven (11) deaths were reported for both treatment groups. Seven and five patients, respectively, died during the study period (entry to 30 days post-therapy). Narrative summaries for these 12 patients are provided below.

Four subjects in the TROVAN group (Subjects 5525-0068, 5533-0110, 6256-0404 and 6524-0918) and two subjects in the comparator regimen (Subjects 5533-0086, and 6052-0806) died while receiving therapy. None of these deaths were considered by the investigator to be related to study drug.

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**NARRATIVES OF ALL REPORTED DEATHS
(On Therapy or Within 30 days Posttherapy)**

Phase II/III Studies - Complicated intra-abdominal infection

Alatrofloxacin/Trovafloxacin

Subject 154-124-5525-0068	This 63-year old white male underwent radiation therapy for treatment of anal carcinoma. He was admitted to a center in the US for surgical repair and treatment of radiation therapy-associated perforation of the small bowel with abscess formation. His previous medical history was significant for anal carcinoma and hypertension. The subject was maintained on erythropoietin for the treatment of underlying anemia at the time of hospital admission. The subject was treated successfully with a 7-day course of 300 mg alatrofloxacin daily. His clinical course improved and he was transferred on day 4 from the surgical intensive care unit (SICU). On day 6, his condition rapidly deteriorated following a cardiopulmonary/pulmonary arrest due to mucous plugging and anoxia, and he was transferred back to the SICU. The patient expired on day 8 secondary to complications resulting from the cardiopulmonary/pulmonary arrest.
Subject 154-124-5533-0110	This 79-year old white male presented to the Emergency Department at a center in the US with acute lower quadrant pain, low grade fever, and multiple episodes of nausea. The subject was found surgically to have an acute appendicitis with an inflamed terminal ileum and cecum requiring resection. He was randomized into study on day 1 and treated for 11 days with intravenous alatrofloxacin 300 mg daily; one dose was missed. No chronic medications were listed at screening nor was his previous medical history significant for cardiac disease. The subject suffered a cardiac arrest on day 7 which was considered to be due to a pulmonary embolism. The subject continued to deteriorate and multiple organ failure was diagnosed on day 10. The subject was made "do not resuscitate" on post-operative day 11, the family requested all medication to be discontinued including study drugs, life support was withdrawn, and the patient expired on the same day.
Subject 154-124-6151-0603	This 77-year old white female with a 6-month history of abdominal pain and 3-month progressive weight loss (15 lb.) underwent a left and sigmoid colectomy for perforated sigmoid colon with fecal peritonitis at a center in the US. Previous medical history was significant for angina, constipation, COPD, and peptic ulcer disease. She was treated with alatrofloxacin 300 mg IV daily for 4 days. Her hospital course was complicated by thrombocytopenia which was thought to be related to study drug, recurrent pleural effusions (starting on day 3) and hemorrhage from the right chest tube (day 22) secondary to diffuse metastatic lung carcinoma, and acute renal failure on day 21. The subject expired on day 23 from cardiorespiratory arrest secondary to chronic obstructive pulmonary disease, lung carcinoma, and coronary disease.
Subject 154-124-6256-0404	This 68-year old white male underwent a sigmoid colectomy and Hartmann's closure of the rectal stump for peritonitis resulting from a nontraumatic perforation of the sigmoid colon at a center in the UK. Previous medical history was not significant for any underlying diseases nor was the subject maintained on chronic therapy. However, his prognosis was poor with a baseline APACHE II score of 27. The subject was treated with alatrofloxacin 300 mg IV daily for 3 days. The subject experienced multiple organ failure secondary to the disease under study and expired on post-operative day 3.

**NARRATIVES OF ALL REPORTED DEATHS
(On Therapy or Within 30 days Posttherapy)**

Phase II/III Studies - Complicated intra-abdominal infection

Subject 154-124-6451-0721	This 64-year old white female with peritonitis underwent surgical repair of perforated small bowel felt secondary to amyloidosis at a center in Canada. Concurrent active medical conditions included COPD, congestive heart failure, angina, and hepatic disease. The subject was maintained on cardiac drugs at time of hospital admission. She was randomized into study and received 8 days of intravenous alatrofloxacin 300 mg daily. The subject experienced severe restrictive cardiomyopathy, amyloidosis, and acute pulmonary decompensation on day 3. Her clinical course further deteriorated and on day 14, she had a cardiac arrest that was considered secondary to the COPD, restrictive cardiomyopathy, congestive heart failure, and amyloidosis. She subsequently lapsed into unconsciousness and expired on the same day.
Subject 154-124-6518-0934	This 72-year old white male underwent surgery for a perforated gastric ulcer at a center in Poland. Two weeks post-operatively, the subject underwent further surgery for peritonitis and drainage of multiple abscesses related to an anastomotic leakage from the prior surgery. He was subsequently randomized into study and received 14 days of alatrofloxacin 300 mg IV daily. The subject was maintained on multiple concomitant medications, including gastrointestinal agents, blood transfusions, anticoagulants, cardiac drugs, and an antifungal agent (fluconazole). His clinical course improved until day 11 when signs and symptoms of peritonitis were again noted. Surgical cleaning of the wound was performed on day 14 and no further antibiotics were administered. The subject expired on day 20 of multiple organ failure due to the disease under study. Autopsy findings included anastomotic healing, fibrocaceous peritonitis, nephritis, partial necrosis of tissue surrounding the pancreas, advanced cerebral and peripheral atherosclerosis, and lung venostasis.
Subject 154-124-6524-0918	This 68-year old white female with peritonitis secondary to bowel perforation from rectal carcinoma underwent a Hartmann's procedure at a center in Poland. The subject was treated with alatrofloxacin 300 mg daily IV for 7 days. Previous medical history was significant for COPD, congestive heart failure, and ischemic heart disease which were maintained with respiratory and cardiac drugs. Prognosis was poor and the subject expired on day 7 due to multisystem failure.

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ON ORIGINAL**

Comparator

Subject 154-124-5533-0086	This 72-year old Hispanic female had motor vehicle accident-related multisystem trauma with upper extremity fractures, ileal perforation, and evolving sepsis. The ileal perforation was surgically repaired at a center in the US. She was treated with imipenem/cilastatin 1000 mg IV every 8 hours for 10 days. She had no significant previous medical history nor maintained on chronic drug therapy prior to hospitalization. During her hospital stay, she received concomitant medications consistent with the disease under study and the associated surgical procedure. Chest x-rays confirmed adult respiratory distress syndrome caused by evolving sepsis on day 6 and the subject continued on respiratory support throughout her hospitalization. Her clinical course worsened on day 9 with evidence of an abdominal site infection and sepsis; the antibiotic therapy was switched to ampicillin/sulbactam and metronidazole on day 10. She expired on day 13 due to complications associated with the motor vehicle accident.
Subject 154-124-5553-0695	This 64-year old white male underwent drainage of a retroperitoneal abscess which developed from a previous enterolysis for small bowel obstruction at a center in the US. Previous medical history was significant for COPD, asthma, bladder and prostate cancer, and metastatic carcinoma of the right lung and left retroperitoneum. His pre- and post-operative course was complicated by cardiac arrhythmias (supraventricular tachycardia, atrial flutter with atrioventricular block). He also had a proximal femoral vein deep venous thrombosis pre-randomization. He was treated with imipenem/cilastatin 1000 mg every 8 hours for 8 days. His clinical course deteriorated, the subject was ventilator-dependent, and he was hemodynamically stabilized on dopamine and hyperalimentation. Due to his deteriorating neurologic status and end-stage condition, all supportive measures were withdrawn on day 14. The subject expired due to cardiac arrest on day 17.
Subject 154-124-6018-0497	This 82-year old white male was hospitalized for digestive hemorrhage due to hiatal hernia at a center in France. He underwent a vagotomy with pyloroplasty and then developed post-operative acute respiratory failure. He subsequently developed peritonitis secondary to the previous abdominal surgery and was randomized into study. His APACHE II score at baseline was 32. He was treated with imipenem/cilastatin 500 mg IV every 6-8 hours for 14 days. His previous medical history was significant for COPD, coronary insufficiency, transient ischemic accidents, renal impairment, and an abdominal aortic aneurysm. His clinical course deteriorated with multiple surgeries for acute cholecystitis, fistulization of the pyloroplasty, and evisceration of the surgical abdominal wound. The subject developed worsening respiratory failure, renal failure, and cardiac failure, and expired on day 26 due to multisystem organ failure.
Subject 154-124-6052-0806	This 86-year old white male underwent appendectomy for a perforated appendix with diffuse peritonitis at a center in the US. Previous medical history was significant for stroke, hypertension, and urinary tract infection. The subject was treated with imipenem/cilastatin 250 mg every 6 hours for 13 days; one dose was missed on day 3. He was diagnosed with aspiration pneumonitis by chest x-ray on day 1 following surgery. On day 5, there was evidence of a new cerebrovascular accident confirmed clinically by seizure-like activity. The subject expired on day 13 due to the recurrent stroke.

Subject 154-124-6441-0525

This 79-year old white male underwent surgical repair of a perforated duodenal ulcer at a center in France. Previous medical history was significant for impaired renal function and an adrenal gland tumor which was diagnosed at time of randomization. The subject was treated with imipenem/cilastatin 1000 mg IV every 12 hours for 2 days, then 500 mg IV every 12 hours for 1 day, then 500 mg IV every 8 hours for 11 days. Abdominal cultures were positive for *Candida albicans* at baseline, and on days 3, 6, and 11; blood cultures were positive for *Candida albicans* on days 9, 10, 12 and 19. The subject was treated with fluconazole and amphotericin B. On day 19, his clinical course deteriorated and the subject was intubated for adult respiratory distress syndrome. The subject expired on day 23 from *Candida* septicemia and disease under study.

9. Conclusions:

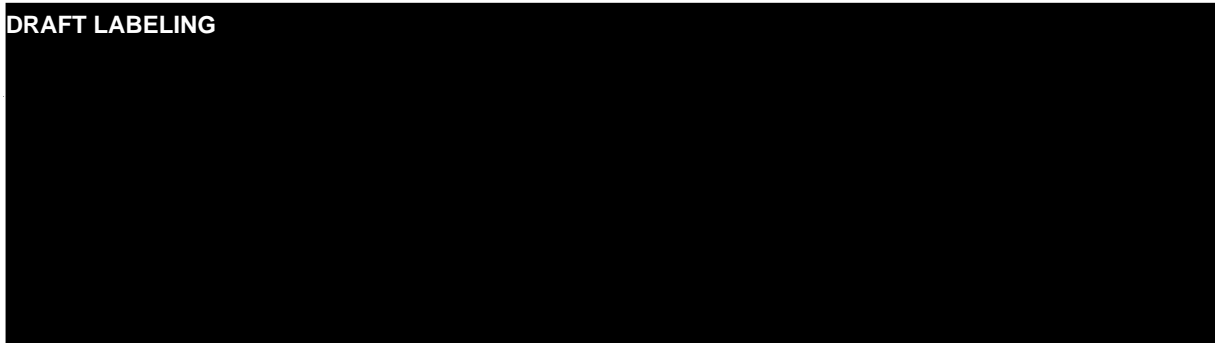
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Compared to Primaxin → Augmentin (an adequate comparator), the MO believes Pfizer has shown TROVAN to be safe and effective in the treatment of complicated intra-abdominal infections due to numerous pathogens.

In their proposed labeling, Pfizer requests the following be included in the INDICATIONS AND USAGE section:

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DRAFT LABELING



As discussed in the 1992 DAIDP Points-to-Consider document, to include an organism in a treatment indication, the following criteria are recommended:

- 1. the organism is generally considered pathogenic AND
- 2. the organism represents at least 10% of the evaluable cases OR
- 3. the organism represents 10 total (whichever is higher) AND
- 4. the eradication rate must be clinically acceptable.

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The PTC document goes on to discuss how one might include a pathogen in labeling where <10% of cases were associated with the "pathogen":

- 1. generally accepted to be a pathogen at the site of infection
- 2. in vitro activity is at least similar to that of other pathogens more substantially evaluated in clinical trials
- 3. the mechanism of resistance is similar to that of other pathogens more substantially evaluated in clinical trials

4. no scientific data exist suggesting differences in the management of infections due to these pathogens

Although not discussed in the PTC document, the following caveats should be considered in the approval of pathogens for treatment indications:

1. If this is the first time a pathogen is to be included in the INDICATIONS AND USAGE section of product labeling (i.e., no other label is approved for this pathogen), perhaps a higher standard of evidence may be appropriate.
2. All pathogens *should* be fully speciated for each treatment indication in the INDICATIONS AND USAGE section with the exception of viridans group streptococci and *Peptostreptococcus spp.* (e.g., *Bacteroides spp.* would be unacceptable because *in vitro* susceptibility can vary significantly between species of bacteroides within the genus).
3. It's feasible to use pathogen data from other treatment indications to support efficacy in the treatment indication under study as long as that extrapolation is appropriate and reasonable (clinically and pharmacodynamically). For example, anaerobes for complicated intra-abdominal infection and GYN infections could be combined in inferring a drug's *in vivo* efficacy against pathogens included in approved product labeling. However, for example, the extrapolation of *E. coli* efficacy from UTI studies to intra-abdominal infections would not be appropriate. (NOTE: Severity of treatment indication as well as dose and duration should be considered in making this extrapolation from one treatment indication to another.)

MO Comment : The MO does not believe that GYN/Pelvic infection efficacy data can be extrapolated to support the CIAI indication, because CIAI patients are often sicker (e.g., mortality is not rare in CIAI; it is rare in GYN/Pelvic infections).

The MO believes Pfizer has presented substantial evidence supporting approval for the following pathogens:

Escherichia coli, *Bacteroides fragilis*, *Streptococcus viridans*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Peptostreptococcus spp.*, and *Prevotella spp.*

MO Comment : Following discussion with the reviewing microbiologist, "viridans group streptococci" is the preferred collective name for *S. viridans* including other streptococci. e.g., *Streptococcus anginosus*.)

MO Comment : Following review of the NDA, the MO could not find convincing *in vitro* or clinical data suggesting that different prevotella species demonstrate variable susceptibility patterns or clinical outcomes to TROVAN. Therefore, the MO recommends approval of "*Prevotella* species" for this treatment indication.

The MO does not believe the following bacteria should be included in this treatment indication:

Bacteroides thetaiotaomicron : As noted previously, efficacy appears to be lower for this pathogen (relative to the comparator regimen) in the clinical study AND *in vitro* data show the MIC₉₀ for trovafloxacin to be high: 1.5 mcg/mL. Therefore, *in vitro* susceptibility testing support this clinical concern.

Staphylococcus aureus : Following the above discussion, there were 135 bacteriologically-evaluable TROVAN recipients. Ten percent of 135 is 14. Only 11 *S. aureus* were isolated. This number does not meet the points-to-consider guidance.

As already discussed above, the Agency has been reluctant to include genus information alone (without speciation) in the INDICATIONS AND USAGE section of product labeling, because susceptibility testing may differ for species within a genus. Therefore, unlike prevotella, the MO recommends the following unspciated pathogens/organisms not be included in product labeling:

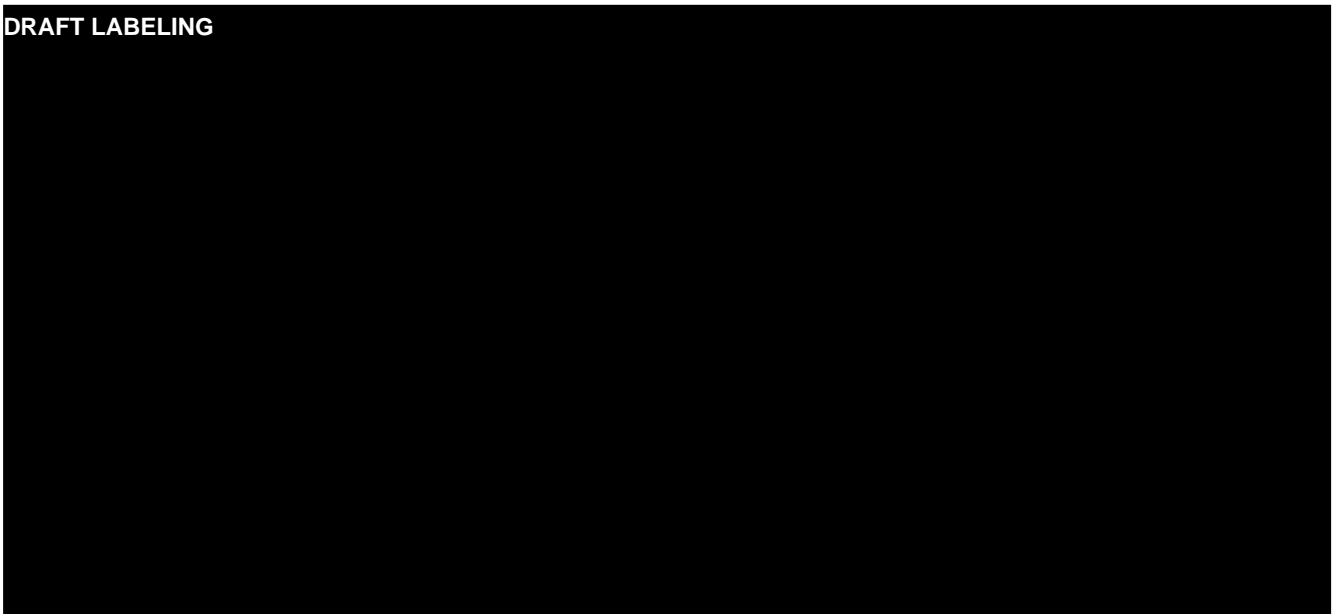
Enterobacter species, *Enterococcus* species, *Corynebacterium* species, *Fusobacterium* species, *Streptococcus* species or *Bacteroides* species.

Unfortunately, the applicant did not speciate these organisms during the trial and this information cannot be inferred.

10. Recommendations:

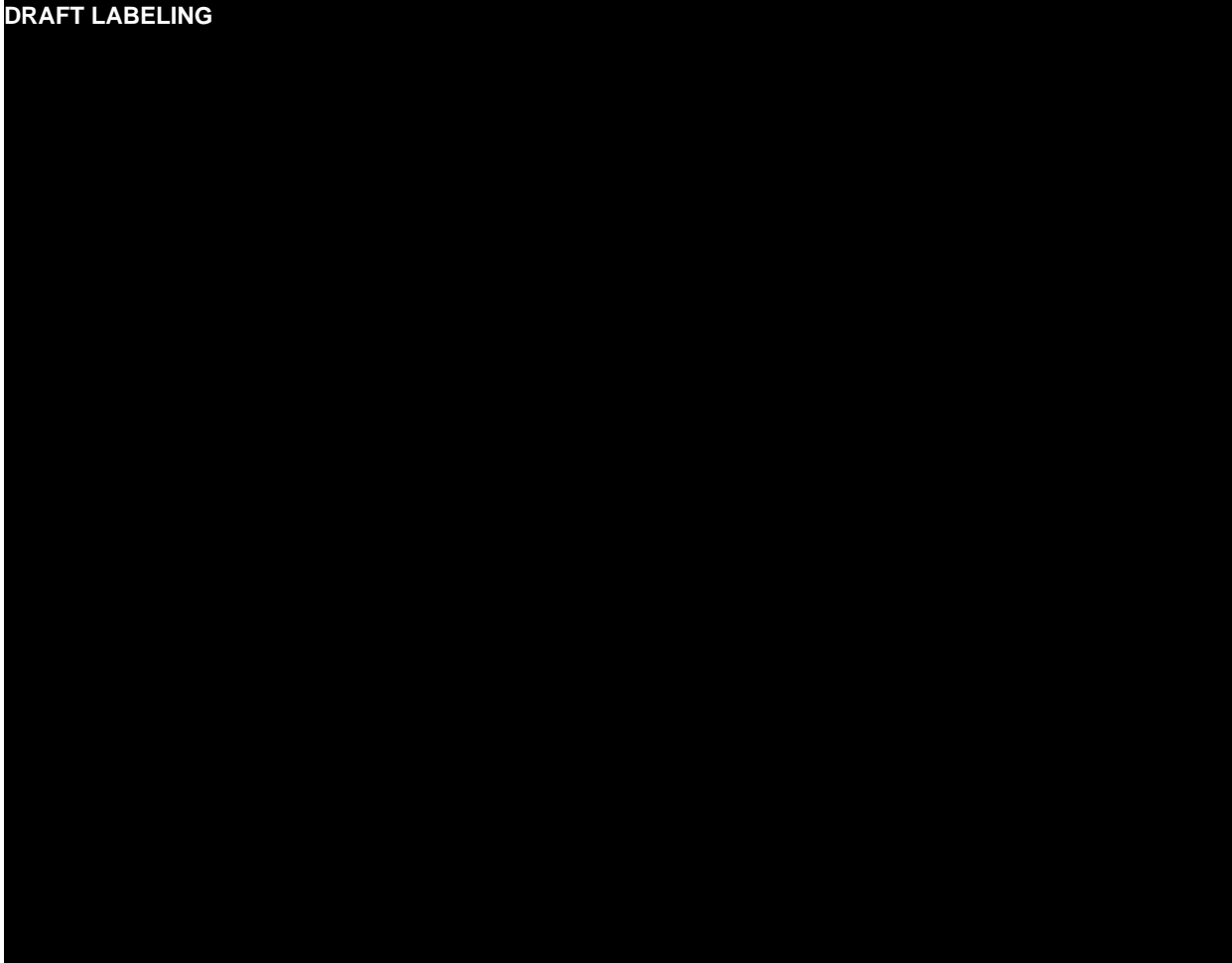
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DRAFT LABELING



In addition, the following should be included in the CLINICAL STUDIES section:

DRAFT LABELING



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/S/

Brad Leissa, MD
Medical Officer/HFD-590

cc: Orig. NDA
Division file
HFD-590/MO/Leissa
HFD-590/MO/Alivisatos
HFD-590/MO/Cox
HFD-590/CSO/Kimzey

Concurrence only: DivDir/Goldberger

/S/

11/4/98

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**Medical Officer's Review of
NDAs 20-759 and 20-760**

Surgical Prophylaxis

1.1 NDAs : 20-759 (oral tablets) and 20-760 (injection)

1.2 Applicant identification

1.2.1 Pfizer Central Research

1.2.2 Address and telephone number:

Eastern Point Road
Groton, CT 06340

**APPEARS THIS WAY
ON ORIGINAL**

1.3 Submission/review dates

1.3.1 Date of submission : 27 December 1996

1.3.2 CDER stamp date : 30 December 1996

1.3.3 Date submission received by reviewer : 6 January 1997

1.3.4 Date review begun : 4 June 1998

1.3.5 Date review completed : 12 December 1997

1.4 Drug identification

1.4.1 Generic name : trovafloxacin mesylate (tablets)
 alatrofloxacin mesylate (solution for injection)

1.4.2 Proposed trade name : **TROVANTM**

1.4.3 Other names used during development: CP-99,219 (tablet)
 CP-116,517 (IV)

1.5 Pharmacologic Category : fluoronaphthyridone

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1.6 Dosage form : See 1.1 above

1.7 Route of Administration : intravenous (20-760) and oral (20-759)

1.8 Proposed Indication & Usage section :

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**SURGICAL PROPHYLAXIS - PROPHYLAXIS OF INFECTION
ASSOCIATED WITH ELECTIVE SURGICAL PROCEDURES**, where there is
increased risk of postoperative infections (e.g., colorectal surgery, vaginal and
abdominal hysterectomy).

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1.9 Proposed Dosage and Administration section :

1.10 Related Drugs : See 1.4.3 above.

1.11 Material Reviewed : NDAs and amendments

1.12 Regulatory Background

A) Anti-Infective Drug Products Approved For This Indication

(1) The following drugs are specifically approved for "surgical prophylaxis":

CEFTRIAXONE (Rocephin)

SURGICAL PROPHYLAXIS: The preoperative administration of a single 1 gm dose of Rocephin may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as **contaminated or potentially contaminated** (eg, vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (eg, during coronary artery bypass surgery). Although Rocephin has been shown to have been as effective as cefazolin in the **prevention of infection following coronary artery bypass surgery**, no placebo-controlled

trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

When administered prior to surgical procedures for which it is indicated, a single 1 gm dose of Rocephin provides protection from most infections due to susceptible organisms throughout the course of the procedure.

Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

DOSAGE AND ADMINISTRATION:

For preoperative use (surgical prophylaxis), a single dose of 1 gram administered intravenously 1/2 to 2 hours before surgery is recommended.

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CEFONICID

SURGICAL PROPHYLAXIS : Administration of a single 1 gram dose of Monocid before surgery may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., colorectal surgery, vaginal hysterectomy, or cholecystectomy in high-risk patients), or in patients in whom infection at the operative site would present a serious risk (e.g., prosthetic arthroplasty, open heart surgery). Although cefonicid has been shown to be as effective as cefazolin in prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery or prosthetic heart valve replacement.

DOSAGE AND ADMINISTRATION:

When administered 1 hour prior to appropriate surgical procedures (see INDICATIONS AND USAGE), a 1 gram dose of Monocid provides protection from most infections due to susceptible organisms throughout the course of the procedure. Intraoperative and/or postoperative administrations of Monocid are not necessary. Daily doses of Monocid may be administered for 2 additional days in patients undergoing prosthetic arthroplasty or open heart surgery.

(2) Other drugs labeled for "pre-" or "peri-operative" prophylaxis: **APPEARS THIS WAY
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CEFUROXIME (Zinacef, Cefurox)

PREVENTION: The preoperative prophylactic administration of ZINACEF may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. ZINACEF should usually be given one-half to 1 hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

DOSAGE AND ADMINISTRATION:

For preventive use for clean-contaminated or potentially contaminated surgical

procedures, a 1.5-gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged. For preventive use during open heart surgery, a 1.5-gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

CEFOTAXIME (Claforan)

The administration of Claforan(R) preoperatively reduces the incidence of certain infections in patients undergoing surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.

DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in contaminated or potentially contaminated surgery, the recommended dose is a single 1 gram IM or IV administered 30 to 90 minutes prior to start of surgery.

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CEFAZOLIN (Ancef, Kefzol)

Perioperative Prophylaxis : The prophylactic administration of Kefzol preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (eg, vaginal hysterectomy or cholecystectomy in high-risk patients such as those over 70 years of age who have acute cholecystitis, obstructive jaundice, or common-bile-duct stones).

The prophylactic administration of Kefzol should usually be discontinued within a 24-hour period after the surgical procedure. For surgery in which the occurrence of infection may be particularly devastating (eg, open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Kefzol may be continued for 3 to 5 days following the completion of surgery. If there are signs of infection, specimens for culture should be obtained for the identification of the causative organism so that appropriate therapy may be instituted (See DOSAGE AND ADMINISTRATION).

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DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

- a) 1 gram I.V. or I.M. administered 1/2 hour to 1 hour prior to the start of surgery.
- b) For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram I.V. or I.M. during surgery (administration modified depending on the duration of the operative procedure).
- c) 500 mg to 1 gram I.V. or I.M. every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (1/2 to 1 hour) prior to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision; and (2) Ancef be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Ancef (sterile cefazolin sodium) may be continued for 3 to 5 days following the completion of surgery.

CEFAMANDOLE (Mandol)

Preventive Therapy : The administration of Mandol preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (eg, gastrointestinal surgery, cesarean section, vaginal hysterectomy, or cholecystectomy in high-risk patients such as those with acute cholecystitis, obstructive jaundice, or common-bile-duct stones).

If signs of infection occur, specimens for culture should be obtained for identification of the causative organism so that appropriate antibiotic therapy may be instituted.

DOSAGE AND ADMINISTRATION:

For perioperative use of Mandol, the following dosages (for adults) are recommended: 1 or 2 g intravenously or intramuscularly 1/2 to 1 hour prior to the surgical incision followed by 1 or 2 g every 6 hours for 24 to 48 hours.

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MEZLOCILLIN (Mezlin)

PREVENTION : The administration of MEZLIN(R) perioperatively (preoperatively, intraoperatively, and postoperatively) may reduce the incidence of infections in patients undergoing surgical procedures (e.g. vaginal hysterectomy and colorectal surgery) that may be classified as contaminated or potentially contaminated. Effective perioperative use for surgery depends on the time of administration. To achieve effective tissue levels, MEZLIN(R) should be given 1/2 hour to 1 1/2 hours before surgery.

For patients undergoing colorectal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g. neomycin) is recommended.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in contaminated or potentially contaminated surgery, the following doses are recommended: 4g IV given 1/2 hour to 1 1/2 hours prior to the start of surgery. 4g IV given 6 hours and 12 hours later.

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METRONIDAZOLE (Flagyl)

PROPHYLAXIS : The prophylactic administration of Flagyl I.V. or Flagyl I.V. RTU preoperatively, intra-operatively, and post-operatively may reduce the incidence of postoperative infection in patients undergoing elective colorectal surgery which is classified as contaminated or potentially contaminated.

Prophylactic use of Flagyl I.V. or Flagyl I.V. RTU should be discontinued within 12 hours after surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given (see Dosage And Administration).

DOSAGE AND ADMINISTRATION:

For surgical prophylactic use, to prevent postoperative infection in contaminated or potentially contaminated colorectal surgery, the recommended dosage schedule for adults is:

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- a) 15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery; followed by
 b) 7.5 mg/kg infused over 30 to 60 minutes at 6 and 12 hours after the initial dose.

It is important that (1) administration of the initial preoperative dose be completed approximately one hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision, and (2) Flagyl I.V. or Flagyl I.V. RTU be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Flagyl I.V. or Flagyl I.V. RTU should be limited to the day of surgery only, following the above guidelines:

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CEFOTETAN (Cefotan)

The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (e.g., cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery). If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

DOSAGE AND ADMINISTRATION:

To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery.

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CEFOXITIN (Mefoxin)

indicated for the prophylaxis of infection in patients undergoing uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section. If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate treatment may be instituted.

Effective prophylactic use depends on the time of administration. MEFOXIN usually should be given one-half to one hour before the operation, which is sufficient time to achieve effective levels in the wound during the procedure. Prophylactic administration should usually be stopped within 24 hours since continuing administration of any antibiotic increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.

DOSAGE AND ADMINISTRATION:

For prophylactic use in uncontaminated gastrointestinal surgery, vaginal hysterectomy, or abdominal hysterectomy, the following doses (for adults) are recommended:

2 grams administered intravenously just prior to surgery (approximately one-half to one hour before the initial incision) followed by 2 grams every 6 hours after the first dose for no more than 24 hours.

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B) Regulatory Guidance

1992 DAIDP "Points to Consider" document (PTC)

No guidance is provided in the PTC for this indication.

IDSA/FDA Guidelines (*Clinical Infectious Diseases*; 15, Suppl. 1; Nov. 1992)

The IDSA/FDA Guidelines discuss colorectal surgical prophylaxis but do not discuss hysterectomy surgical prophylaxis.

The guidelines distinguish between the prophylactic (within 12 hours of surgery) versus treatment (>12 hours from the time of surgery after the development of signs of serious infection, such as septic shock, abscess formation, or diffuse peritonitis) use of an anti-infective drug product.

Three different surgical conditions exist when one considers the need for anti-infective prophylaxis:

1. "contaminated or dirty" operations : gun-shot wound, perforation of the gastrointestinal tract (ruptured appendix, perforated diverticulum)
2. "clean-contaminated" operations : vaginal hysterectomy and colorectal operations
3. "clean" operations where prophylaxis is not justified : mastectomy, inguinal hernia repair

Prophylaxis is indicated for "dirty/contaminated" and "clean-contaminated" (colorectal & hysterectomy) procedures, but NOT "clean" (e.g., hernia repair) except where vascular grafts and prosthetic devices are present.

According to the guidance, an anti-infective drug product under development for surgical prophylaxis should meet the following objectives:

- prevent postoperative infectious morbidity and mortality;
- reduce the length and cost of hospital care;
- be the cause of minimal side effects (e.g., cause minimal *C. difficile* colonization leading to antibiotic-associated diarrhea & pseudomembranous colitis);
- give rise to minimal adverse effects on the microbial flora of the patient or hospital. (e.g., the promotion of antimicrobial resistance)

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Furthermore, the Guidelines continue, in addition to a product achieving the above objectives, an anti-infective drug should be:

- active against the pathogens most likely to contaminate the wound;
- given in appropriate doses, and at a time that ensures adequate concentrations at the incision site during the potential contamination;
- safe; and
- administered for the shortest effective period in order to minimize cost and adverse drug effects.

General Surgical Prophylaxis Points Discussed in the Guideline:

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- Additional measures to reduce infection such as pre-operative skin antisepsis, wound irrigation (preferably without antibiotics), prophylactic drainage, or variations in surgical technique should be clearly identified in the protocol, should be standardized insofar as possible, and should be recorded in the course of the study.
- In general, the first dose of a parenterally-administered antibiotic should be selected to achieve peak target concentrations in the primary surgical site at the time of the initial incision.
- Although not required for evaluability, it is highly desirable to record antimicrobial resistance patterns of infecting pathogens in both treatment and control groups in order to analyze for evidence of "emergence" of resistance.
- Duration of follow-up should be clearly defined and appropriate to the surgical procedure. Ordinarily, a 4-week follow-up is sufficient.

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Specific Colorectal Surgical Prophylaxis Points Discussed in the Guideline:

Approximately 43% of patients on a placebo treatment arm developed post-operative wound infections (vs. _____ in the active-control, oral treatment group). Subsequent studies have identified wound infection rates of _____ when an oral antimicrobial bowel preparation, such as neomycin, was used. When single-dose cefotetan prophylaxis was studied, the infection rate was 14% compared with 11% for cefoxitin q6h. Therefore, the IDSA authors for this chapter express their concern that parenteral cephalosporin prophylaxis may be less (>9% infection rate) effective than oral antimicrobial bowel preparation

MO Comment : The IDSA guidelines express concern that cephalosporin may not be the best comparator agents where clinical trials are designed to assess the activity of a new anti-infective drug product in preventing post-operative surgical infections.

Risk factors for postoperative infection in colorectal operations include the following:

- Rectal resections (abdominal-perineal resections) are associated with higher rates of infection than intra-peritoneal resections.
- Operations lasting more than 3½ or 4 hours are associated with more infections than those of shorter duration.
- Inadequate bowel preparation (e.g., isotonic lavage solution)
- Emergency surgical procedures

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Failure of Prophylaxis (as defined in the IDSA/FDA Guidelines):

- Postoperative infection within the primary operative incision and/or the peritoneal cavity, including peritonitis and abscess formation.
 - Infection developing in the **primary operative incision(s)** should be classified as failure of antimicrobial prophylaxis.
 - Infection developing in a **distant site** (e.g., urinary tract, respiratory tract, IV catheter, etc.) should be reported but not included as a criterion of success or failure of prophylaxis.
- Any unexplained use of anti-infective agents in the 4-week period following the primary operation.
- Any drainage procedure at the operative site or in and around the peritoneal cavity for infection.
- The development of an anastomotic leak.

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The Guidelines note, "A minimum of 50 evaluable patients per participating site center is required."

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2. Table of Contents: not applicable
3. Chemistry/Manufacturing Controls: See chemist's review.
4. Animal Pharmacology/Toxicology: See pharmacologist's review.
5. Microbiology: See microbiologist's review.
6. Human Pharmacokinetics/Pharmacodynamics: See biopharm review.

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The peak blood level (C_{max}) of alatrofloxacin at the 300 mg intravenous dose (trovafloxacin equivalent dose) used for intra-abdominal infections is 4.4 µg/mL with a half-life of 10.8 hours. The fluid/serum concentration ratio of trovafloxacin in peritoneal fluid after IV administration of 200 mg alatrofloxacin was 0.39. Mean tissue/serum concentration ratios for gynecologic tissues (ovary, uterus, myometrium, cervix and fallopian tubes) after single or multiple doses of oral trovafloxacin 200 mg. Thus, based upon its pharmacokinetic profile, single daily intravenous doses of

300 mg alatrofloxacin will exceed the MIC₉₀ values of pathogens commonly involved in intra-abdominal and acute pelvic infections.

MO Comment : The applicant requests approval of the 200 mg dose.

7. Human Clinical Experience: not applicable

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8. Clinical Studies:

Summary of the two studies (significant differences between the two studies are highlighted in bold lettering):

	STUDY 154-128	STUDY 154-146
	Colorectal	Hysterectomy (abdominal & vaginal)
Study design	Randomized, double-blind, double-dummy, comparative, multicenter	same
Study dates	April 1995 - March 1996	January - June 1996
Gender/age	Males/females; ≥18 yo	Females; ≥18 yo
Location	US, Canada	US
Trovan dosing (NOTE: T _{max} of PO = 1-2 hrs T _{max} of IV = end of 60' infusion)	200 mg IV within 2 hours of surgery and infused over 1 hour	200 mg PO trovafloxacin was given 30-60 mins. prior to surgery
Comparator	2g cefotetan IV was given 30-60 mins. prior to surgery and infused over 3-5 minutes	2g cefoxitin IV was administered up to 30 minutes prior to the surgery (and to be infused over 5-15 minutes). Cefoxitin could be given as a 2 nd dose if the surgical procedure lasted >4 hrs OR there was >1500 mL of blood loss)
Target enrollment	TROVAN = 200 CEFOTAN = 200	TROVAN = 175 MEFOXIN = 175
Target evaluability	not specified	TROVAN = 143 MEFOXIN = 143
How many received prophylaxis?	TROVAN = 256 CEFOTAN = 236	TROVAN = 188 MEFOXIN = 175
Visits	- Pre-surgery (-48h) - Once daily while hospitalized - Days 28-35 of study	- Pre-surgery (-72h) - Once daily while hospitalized - Days 24-36 of study
Primary efficacy parameter	Incidence of primary site infections at EOS, including: - Surgical site infection - Intraabdominal infection - Bacteremia (if no "distant site") - Unexplained fever	Incidence of primary site infections at EOS, including: - Surgical site infection - Pelvic cellulitis - Pelvic abscess - Infected pelvic hematoma
Secondary efficacy parameters	Distant site infections (e.g., pneumonia, UTI, IV catheter infection, etc.) NOTE: Could include bacteremia if not believed related to the colorectal procedure	Distant site infections (e.g., pneumonia, UTI, IV catheter infection, etc.)
Inclusion criteria	- Elective surgery of colon/rectum - Time to complete preoperative bowel preparation (GoLYTELY)	Elective abdominal or vaginal hysterectomies for non-malignant disease processes (e.g., dysplasia, abnormal bleeding, uterine prolapse, leiomyomas)

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Exclusion criteria APPEARS THIS WAY ON ORIGINAL	• Emergency colorectal operations • Decompensated intestinal obstruction • Active inflammatory bowel disease involving the colon • Revision of a previous operation that has involved large bowel resection (e.g. revision of a colostomy and ileorectal anastomosis). • Subjects with a bacterial infection at the time of surgery or who were administered an antibiotic within 1 week prior to surgery.	• Emergency hysterectomy • Hysterectomy for malignancy • Outpatient surgical hysterectomy • Subjects with a bacterial infection at the time of surgery or who were administered an antibiotic within 1 week prior to surgery. APPEARS THIS WAY ON ORIGINAL
Definition of failure APPEARS THIS WAY ON ORIGINAL	• Development of infection in the primary operative incision(s). • Development of an unexplained fever requiring systemic antibiotic intervention. • Use of any systemic anti-infective drug during the 30-day post-operative period for treatment of infection (suspected or confirmed) at the primary site. • Any unexplained use of anti-infective agents in the 30-day period following the primary operation. • Missing post-baseline assessment • Any drainage procedure at the operative site or in and around the peritoneal cavity for infection. • Need for more than one surgical procedure. However, if an independent reviewer considers the initial surgical procedure inadequate, and a subsequent operation is required to correct or reverse the first surgical procedure, then the subject should be considered nonevaluable.	• Concomitant antibiotic at any time for primary surgical site infection or unexplained use • Missing post-baseline assessment • Significant drainage procedure at the operative site or in and around the pelvic cavity for infection APPEARS THIS WAY ON ORIGINAL
Applicant's reasons for clinical non-evaluability (of special note) APPEARS THIS WAY ON ORIGINAL	• A documented preoperative infection exists that requires antibiotic therapy following surgery (e.g. pre-operative positive urine culture) • Requiring delayed primary closure • Antiseptic peritoneal lavage • Initial surgery inadequate (post hoc)	• Concomitant antibiotics administered to treat a distant site infection • Requiring delayed primary closure • Antiseptic peritoneal lavage*

*According to the applicant (12/9/97 e-mail): In the 154-146 study, three subjects received neomycin bowel prep and two subjects were administered triple-sulfa vaginal cream as a packing. All were subsequently rendered not clinically evaluable (App V Table 21.1) during our double-blind review of the evaluability listings. We allowed povidone-iodine or alcohol scrubs, but not as bowel preps or lavages.

8.1 Study 154-128

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Protocol Title: "A randomized, double-blind, multicenter trial assessing the safety and efficacy of a single intravenous dose of ALATROFLOXACIN (CP-116,517) compared with cefotetan for the prophylaxis of infection following elective colorectal surgery."

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8.1.1 Protocol Overview:

Study objective: To compare the safety and efficacy of CP-116,517 (intravenous prodrug of CP-99,219) with cefotetan in the prophylaxis of primary site infection after elective colo-rectal surgery.

Study dates: April 10, 1995 - March 12, 1996

Study Design: Study 154-128 was a randomized, double-blind, double-dummy, comparative, multicenter trial of alatrofloxacin (200 mg within 2 hours of surgery and infused over 1 hour), administered intravenously, versus cefotetan (2000 mg within 30-60 minutes of surgical incision and infused over 3-5 minutes), administered intravenously, for the prophylaxis of infection following elective colo-rectal surgery. (NOTE: alatrofloxacin or placebo was infused first followed by the cefotetan or placebo.)

A total of 400 subjects will be enrolled in this study. Each study site should attempt to enroll at least 15 subjects.

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As explained in the protocol introduction to justify the use of TROVAN in this study: In CP-99,219 distributed well into murine gastric tissue after intravenous administration (tissue to serum ratios of 2.9 for gastric mucosa and 1.7 for gastric tissue), suggesting that CP-99,219 will be available for treatment of intra-abdominal infections.¹

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Noteworthy Inclusion criteria :

An "elective" surgery of the colon and/or rectum was defined in the protocol as : those scheduled in advance and those for which there is time to complete preoperative bowel preparation.

Noteworthy Exclusion criteria :

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1. Subjects with any coexisting conditions that will require anti-infective therapy during the course of the study.

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2. The following conditions are excluded:

- **emergency** colo-rectal operations (unscheduled and/or insufficient time for bowel preparation as described in this study)
- decompensated intestinal obstruction
- active inflammatory bowel disease involving the colon
- revision of a previous operation that has involved large bowel resection (e.g. revision of a colostomy and ileorectal anastomosis).

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¹Polzer RJ, Potchoiba MJ, Renouf DN, West M, Liston TE. Distribution of [¹⁴C]CP-99,219 into gastric tissue of Long-Evans rats and Swiss-Webster mice following intravenous administration. ICAAC 1994, Orlando, FL.

- 3. Subjects with a bacterial infection at the time of surgery or who have been administered an antibiotic within 1 week prior to surgery.

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At study entry, investigators were asked to fill out the following information in the Case Report Form for each study subject:

UNDERLYING DISEASE (check all that apply):

- Diverticulitis
- Cancer
- Polyposis
- Other (specify) _____

- INDICATE TYPE OF SURGERY (check all that apply):

- Ileocecal resection
- Colic resection
- Hemicolectomy
- Colostomy
- Anterior resection of the rectum
- Total colectomy with reconstruction
- Esophagocoloplasty
- Hartman resection
- Miles amputation
- Palliative by-pass
- Polyp removal by laparotomy
- Other (specify) _____

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Prior to the surgical operation, patients were administered an iso-osmotic oral bowel preparatory, such as GoLYTELY. There was no attempt by the applicant to standardize operative technique among surgeons. However, each study site was asked to standardize the skin preparation method. In addition, Investigators were asked to record whether staples or suture were used for skin closure.

As shown in the following chart, patients were assessed at entry, on each day of hospitalization, and study day 30

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Schedule of Study Evaluations
(Copied from the protocol for Study 154-128)

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Study day	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-48 hours		Day 28-35
Informed consent	X		
Demographic information	X		
Physical examination of the abdomen	X	X ²	X
Maximum body temperature	X	X ²	X
Vital signs	X	X ³	X
Concomitant medication	X	X	X
Bowel preparation	X ⁴		
Dosing record	X		
Safety laboratory tests			
• hematology	X	X ⁵	abn ⁶
• biochemistry	X	X ⁵	abn ⁶
• urinalysis	X	X ⁵	abn ⁶
• pregnancy test ⁷	X		
Adverse events	X	X	X
Investigator's report of infection history/presence		X ⁵	X
Health care resource utilization			X

During the surgery, No antibiotic or antiseptic peritoneal lavage is allowed.

The following post-surgical infection definitions were used:

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(A) Primary wound infections

1. Primary surgical site infection diagnosed by purulent exudate (as defined microscopically (≥ 10 PMN/hpf) or by gross inspection), cellulitis requiring antibiotics, or the need to re-open the closed wound. Infection severity will be graded as minor (erythema extends at least 2 cm from the wound in any direction, with or without purulent discharge) or major (a wound with erythema and drainage, a wound with purulent drainage, or a wound that was opened and not re-closed).
2. Intra-abdominal infection defined as an intraperitoneal or a pelvic collection of pus or gastrointestinal contents diagnosed by an imaging study, confirmed by laparotomy, spontaneous discharge (including fistulae), or percutaneous drainage.

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² once daily

³ upon hospital discharge only

⁴ GoLYTELY (Appendix B) or equivalent

⁵ at 48 hours post-surgery and upon hospital discharge

⁶ abn = abnormal at previous visit or clinically-significant adverse event

⁷ to be done locally for women of child-bearing potential

The investigator should record whether an anastomotic leak or a staple/suture leak has occurred.

(B) Distant site infections

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1. Pneumonia diagnosed by a new infiltrate on the chest x-ray and presence of at least one of the following signs and symptoms: fever (defined as body temperature $\geq 38\text{ }^{\circ}\text{C}$), leukocytosis greater than $12,500\text{ cells/mm}^3$, increased sputum production with numerous leukocytes, and a predominant bacterial species.
2. Urinary tract infection diagnosed by signs and symptoms of a urinary tract infection and a urine culture with $\geq 100,000\text{ colonies/mL}$ (or $\geq 10,000\text{ colonies/mL}$ if the same bacterial species was isolated from two urine samples at different times).
3. Intravenous catheter infection defined by erythema, swelling, tenderness, and/or the presence of purulent material at the catheter site.
4. Other distant site infections which are clearly unrelated to the primary

(C) Bacteremia

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Bacteremia diagnosed by presence of a spiking fever associated with a positive blood culture (at least 2 cultures) of a pathogenic organism. If, in the opinion of the investigator, the source of the bacteremia is known and not associated with the surgical procedure, then the finding of bacteremia in this subject will be considered a distant site infection. Otherwise, if the source of the bacteremia is unknown, or there is clinical suspicion that the source is related to the colo-rectal procedure, bacteremia will be considered a primary wound infection.

(D) Unexplained Fever

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Subjects presenting with fever, defined as body temperatures $\geq 38\text{ }^{\circ}\text{C}$ on at least 2 repeated times within an interval of greater than 6 hours, with no immediate explanation will be thoroughly evaluated for an infectious origin. This evaluation will include cultures and a complete physical examination. If, by the follow-up visit (day 30), the fever remains unexplained and a systemic antibiotic for treatment of this fever was administered, the subject will be considered a failure to prophylaxis.

Surgical prophylaxis success was defined as:

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No signs or symptoms of infection at the surgical site (primary site infection). Infection in a distant site (e.g. urinary tract infection, respiratory tract, intravenous catheter) is not included as a criterion for success or failure of prophylaxis.

Surgical prophylaxis **failure** was defined as the occurrence of any of the following during the study period:

- development of infection in the primary operative incision(s).
- development of an unexplained fever requiring systemic antibiotic intervention.
- use of any systemic anti-infective drug during the 30-day post-operative period for treatment of infection (suspected or confirmed) at the primary site.
- any *unexplained* use of anti-infective agents in the 30-day period following the primary operation.
- any drainage procedure at the operative site or in and around the peritoneal cavity for infection.
- need for more than one surgical procedures. However, if the initial surgical procedure is considered inadequate by an independent reviewer, and a subsequent operation is required to correct or reverse the first surgical procedure, then the subject should be considered nonevaluable.

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Nonevaluability:

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Study subjects were considered nonevaluable if :

- a. subjects received less than complete dose of double-blind prophylaxis for reasons other than an adverse event (e.g. administration error, pump failure). Included also will be those situations where the preoperative dose of study drug or control drug is not given, or not given prior to incision, or given not according to protocol
- b. subjects received concomitant systemic antibiotic for intercurrent illness or other prophylactic use of an anti-infective agent, not allowed in the protocol (e.g. antibiotics in the lavage procedure)
- c. a documented preoperative infection exists that requires antibiotic therapy following surgery (e.g. pre-operative positive urine culture)
- d. subjects requiring delayed primary closure

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Statistical Considerations

As stated in the protocol : Assuming the response rate of the reference drug is 90% (i.e. a failure rate of 10%), the number of subjects for each treatment group required to ensure with 80% probability that the lower limit of the 95% Confidence Interval for the true difference in efficacy is greater than -10% is 142 subjects per treatment group.

Hence, the planned enrollment of 400 subjects is sufficient to detect differences in equivalence.

Investigators for Study 154-128

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5064	Daniel Buffington, PharmD
	5133	Dennis Mikolich, MD
	5204	Stanley Klein, MD
	5229	Michael Neill, MD
	5429	John Yatsu, MD
	5486	David Borgstrom, MD
	5487	David Canal, MD
	5490	William Friend, MD
	5491	Richard Howerton, MD
	5493	Rama Jager, MD
	5495	George Mueller, MD
	5497	Joseph Wentzky, Jr., MD
	5498	Christine White, MD
	5524	C. Gene Cayten, MD
	5525	David Smith, MD
	5526	Gene Coppa, MD
	5527	John Cunningham, MD
	5529	Vinod Dhawan, MD
	5530	Philip Donahue, MD
	5532	Blaine Enderson, MD
	5533	Michael Esser, MD
	5534	Richard Greenberg, MD
	5537	Luis Jauregui, MD
	5538	Jeffrey Milsom, MD
	5542	Carey Page, MD
	5545	Robert Martindale, MD
	5550	Ronald Simon, MD
	5553	Russell Postier, MD
	5557	William Stahl, MD
	5558	Stephen Vogel, MD
	5559	Jesse Thompson, MD
	5560	Richard Wait, MD
5563	Robert Beart, MD	
	Albert Yellin, MD	

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States (continued)	5599	Jefferson Stowers, MD
	5603	John Eggenberger, MD
	5608	Lawrence Nastro, MD
	5610	Jon White, MD
	5611	Paul Harrison, MD
	5612	Leon Josephs, MD
	5613	Peter Krumpe, MD
	5614	Amir Neshat, MD
	5615	Kathaleen Porter, MD
	5616	David Redfield, MD
	5617	Joseph Solomkin, MD
	5742	Yang Chen, MD
	5761	John Mazuski, MD
	5782	Robert Rosser, MD
	5910	Joseph Portoghese, MD
	5931	Carol Kemper, MD
	6005	Marvin Corman, MD
	6012	Corrado Marini, MD
	6044	Alexander Robbins, MD
	6045	Arnold Luterman, MD
	6046	E. Robert Harris, MD
	6047	Joseph Scoma, MD
	6048	Mark Sherman, MD
	6053	Ronald Nichols, MD
	6069	Judith Wolf, MD
	6090	Burke Cunha, MD
	6099	Manual Ramirez, MD
	6100	Vinod Rustgi, MD
	6107	Dana Edwards, MD
	6123	Mahmoud Kulaylat, MD
	6151	Gregory Timberlake, MD
	6170	Eduardo Gonzales, MD
	6246	Michael Hellinger, MD
6247	Steven Schechter, MD	
6310	Anthony Netterville Brannan, MD	
6317	Susan Galandiuk, MD	
6337	Darell Covington, MD	
6344	William O'Riordan, MD	
6367	Del Dehart, MD	
6369	Renu Sinha, MD	
6379	H. Randolph Bailey, MD	
6421	Raymond Staniunas, MD	
6499	Robert Cohen, MD	
Canada	5155	Sylvie Trottier, MD
	5466	Gary Garber, MD
	5826	John Bohnen, MD
	6365	Marvin Gerson, MD
	6368	David Grant, MD
	6384	Jean Ledoux, MD

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Summary of Subject Disposition Study 154-128				
	Alatrofloxacin		Cefotetan	
	Number and Percentage (%) of Subjects			
Randomized Subjects	269		249	
Randomized, Not Treated ^a	13		13	
All Treated Subjects	256	(100%)	236	(100%)
Withdrawn from Treatment ^b	7	(3%)	1	(<1%)
Completed Treatment	249	(97%)	235	(>99%)
Withdrawn from Study	10	(4%)	14	(6%)
Withdrawn during Treatment	1	(<1%)	0	
Withdrawn during Follow-Up	9	(4%)	14	(6%)
Completed Study	247	(96%)	223	(94%)
Completed Treatment and Study Evaluated for Efficacy	240	(94%)	221	(94%)
Clinical Intent-to-Treat	246	(91%)	236	(95%)
Clinically Evaluable ^c	161	(60%)	156	(63%)
Clinically Evaluable + Subjects Receiving Concomitant Antibiotics for Distant Site Infections	210	(78%)	204	(82%)
Assessed for Safety				
Adverse Events	256	(100%)	236	(100%)
Laboratory Tests	246	(96%)	231	(98%)

a One randomized, not treated subject in each treatment group completed study.
b Of the 7 alatrofloxacin subjects who were withdrawn from treatment, 6 completed study; the 1 cefotetan subject who was withdrawn from treatment completed study.
c Based on End of Study assessment.

Summary of Baseline Characteristics and Underlying Diseases and Syndromes at Baseline Study 154-128				
All Treated Subjects				
Baseline Characteristic	Alatrofloxacin 200 mg (N=256)		Cefotetan 2000 mg (N=236)	
	Number and Percentage (%) of Subjects			
Age (years)				
Mean	59.9		59.6	
16-44	38	(15%)	45	(19%)
45-64	116	(45%)	87	(37%)
≥65	102	(40%)	104	(44%)
COPD	27	(11%)	24	(10%)
Diabetes Mellitus	26	(10%)	34	(14%)
Hepatic Disease	10	(4%)	8	(3%)
Congestive Heart Failure	7	(3%)	13	(6%)
Impaired Renal Function	7	(3%)	7	(3%)

COPD = Chronic Obstructive Pulmonary Disease

MO Comment : Baseline populations and characteristics appear similar between the two treatment groups.

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Summary of High Risk Factors for Post-Operative Infection Study 154-128				
Number and Percentage (%) of Clinically Evaluable Subjects with High Risk Factors				
	Alatrofloxacin 200 mg (N=161)		Cefotetan 2000 mg (N=156)	
Subjects with ≥1 High Risk Factor	78	(48%)	67	(43%)
High Risk Factor				
Surgery Time >215 Minutes	20	(12%)	33	(21%)
Surgical Procedure Rectal	49	(30%)	37	(24%)
Age >75 Years	21	(13%)	19	(12%)

MO Comment : Cefotetan recipients appeared more likely to undergo prolonged surgery times compared to alatrofloxacin recipients.

Summary of Other Risk Factors Study 154-128				
Number and Percentage (%) of Clinically Evaluable Subjects with Other Risk Factors				
	Alatrofloxacin 200 mg (N=161)		Cefotetan 2000 mg (N=156)	
Other Risk Factors				
Type of Closure Other Than Stitches/Staples	5	(3%)	6	(4%)
Surgical Drain Present	48	(30%)	41	(26%)
Albumin ≤2 g/dL	0		0	
Diabetes Present	17	(11%)	21	(13%)
Health Insurance None	11	(7%)	10	(6%)

MO Comment : Other risk factors appeared comparable between treatment groups.

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PROPHYLACTIC EFFICACY:

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Summary of the Applicant's Assessment of Clinical Response					
Study 154-128					
Clinically-Evaluable Subjects					
	Hospital Discharge		End of Study		
	Alatrofloxacin 200 mg (N=161)	Cefotetan 2000 mg (N=156)	Alatrofloxacin 200 mg (N=161)	Cefotetan 2000 mg (N=156)	
	Number and Percentage (%) of Subjects				
Success ^a	127 (79%)	128 (82%)	116 (72%)	113 (72%)	
Failure	34 (21%)	28 (18%)	45 (28%)	43 (28%)	
Clinically-Evaluable Subjects Plus Subjects Receiving Concomitant Antibiotics for Distant Site Infection					
	Hospital Discharge		End of Study		
	Alatrofloxacin 200 mg (N=210)	Cefotetan 2000 mg (N=204)	Alatrofloxacin 200 mg (N=210)	Cefotetan 2000 mg (N=204)	
Success ^a	165 (79%)	158 (77%)	152 (72%)	139 (68%)	
Failure	45 (21%)	46 (23%)	58 (28%)	65 (32%)	

a No signs or symptoms of a primary infection.

Corrected 95% CI for clinically-evaluable population at EOS: (-11%, 10%)

Corrected 95% CI for clinically-evaluable population including those being treated for distant site infection at EOS: (-5%, 14%).

MO Comment : Alatrofloxacin demonstrates similar prophylactic efficacy relative to cefotetan.

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The IDSA Guidelines for colorectal prophylaxis imply that based on historical controls, one would expect infection rates of for parenteral cephalosporins -- which may be less effective than that for the typical oral bowel preparations

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In this study, the infection rate was >20% in the TROVAN arm (albeit comparable to the cefotetan arm); 21% at hospital discharge and 28% at EOS.

The applicant was asked to provide an explanation as to why the infection rate (for both study arms) was so much higher than that of historical controls, and therefore, why this should be considered adequate in light of the lower numbers seen with historical controls.

Pfizer Response (11/25/97 e-mail): "The overall infection rate of intestinal origin (28%) was somewhat higher than that found with historical controls. Because there was no difference in failure rate between treatment groups, the patient population, study design, and risk factors for failure were likely the causes of difference in outcome from previous studies. A significant proportion of patients (86/317, 27%) underwent surgical procedures associated with a higher risk of failure, i.e., abdomino-perineal resection and low anterior resection (1-3). Other studies with a similar profile of procedures had higher than typical failure rates). There was a 60%

increase in failure rate associated with these procedures compared with the remaining patient population. A surgical time in excess of 3.5 hours has also been identified as a risk factor for failure to prophylaxis (1,2). In the current study, 53 patients (53/317, 17%) had surgical times >215 minutes; these patients had a failure rate of 49% compared with an incidence rate of 23% in patients who had surgical times $\leq$ 215 minutes. Thus, approximately one-half of the patients in the current study had risk factors known to be associated with failure to prophylaxis (i.e., more difficult procedures, surgical time > 215 minutes) which may inflate the overall incidence of failure compared with literature values (3).

"The protocol also adopted a conservative approach to the definition of failure to prophylaxis. Culture-negative minor wound infections or inflammatory responses that were treated with an antibiotic were considered failures. If a subject was given a concomitant antibiotic for bacteremia from an unknown source, unexplained fever, or unexplained use, then the clinical response was considered failure to prophylaxis. If a subject had no post-baseline assessments, then the clinical response was considered failure to prophylaxis. Further, a subject was a failure to prophylaxis if he/she required any unplanned drainage procedure at the operative site or in and around the peritoneal cavity, whether for infection or exploratory. Intra-abdominal infections were also considered failures to prophylaxis. The incidence rate of intra-abdominal infections in this study (4%) is consistent with previous reports (7,8) and was not different between treatment groups.

"Nonetheless, the failure rate to prophylaxis of alatrofloxacin was equivalent when compared with the accepted prophylactic regimen of intravenous cefotetan given as a single preoperative 2-gram dose."

Pfizer referenced literature:

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2. Gorbach SL. Antimicrobial prophylaxis for appendectomy and colorectal surgery. *Rev Infect Dis* 1991;13(Suppl 10):S815-S820.
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7. Hershman MJ, Swift DTR, Logan WA, et al. Prospective comparative study of cefotetan with piperacillin for prophylaxis against infection in elective colorectal surgery. *J R Coll Surg Edinb* 1990;35:29-32.

8. Jensen LS, Anderson A, Fristrip SC, *et al.* Comparison of one dose *versus* three doses of prophylactic antibiotics, and the influence of blood transfusion, on infectious complications in acute and elective colorectal surgery. *Br J Surg* 1990;77:513-518.

During the NDA review, Pfizer was also asked to assess prophylaxis outcome for low versus high risk subjects. On 12/11/97, Pfizer responded via e-mail with the following analysis:

Colorectal Surgical Prophylaxis Outcome (Success Rate) and Risk Factors at EOS (Clinically Evaluable)		
	Alatrofloxacin	Cefotetan
Low Risk	110/124 (89%)	107/122 (88%)
High Risk	19/32 (59%)	20/30 (67%)

APPEARS THIS WAY ON ORIGINAL

MO Comment : Although prophylaxis efficacy may be less in the high risk population, numbers are too small to conclude this.

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Summary of the Most Common Primary Wound Infections ^a Study 154-128 (Investigator Assessment) (Clinically Intent-to-Treat Subjects)		
	Alatrofloxacin 200 mg (N=246)	Cefotetan 2000 mg (N=236)
Number and Percentage (%) of Subjects		
Hospital Discharge		
Primary Wound Infections	49 (20%)	41 (17%)
Primary Surgical Site Infection	42 (17%)	37 (16%)
Major	22 (9%)	21 (9%)
Minor	22 (9%)	14 (6%)
Wound Dehiscence	7 (3%)	12 (5%)
Intra-Abdominal Infection	5 (2%)	5 (2%)
Intraperitoneal Focus	5 (2%)	4 (2%)
Bacteremia	4 (2%)	5 (2%)
Unexplained Fever	7 (3%)	1 (<1%)
End of Study		
Primary Wound Infections	26 (11%)	30 (13%)
Primary Surgical Site Infection	22 (9%)	24 (10%)
Major	13 (5%)	12 (5%)
Minor	7 (3%)	11 (5%)
Wound Dehiscence	6 (2%)	7 (3%)
Intra-Abdominal Infection	4 (2%)	5 (2%)
Anastomotic Leak	2 (<1%)	4 (2%)

a ≥2% of subjects in either treatment group.

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MO Comment : The two treatment groups appeared similar.

Summary of the Most Common Distant Site Infections ^a Study 154-128				
(Investigator Assessment) (Clinically Intent-to-Treat Subjects)				
	Alatrofloxacin 200 mg (N=246)		Cefotetan 2000 mg (N=236)	
	Number and Percentage (%) of Subjects			
Hospital Discharge				
Distant Site Infections	19	(8%)	24	(10%)
Pneumonia	5	(2%)	7	(3%)
Urinary Tract Infection	11	(4%)	16	(7%)
End of Study				
Distant Site Infections	16	(7%)	12	(5%)
Urinary Tract Infection	11	(4%)	12	(5%)
Other Infection	5	(2%)	1	(<1%)

a ≥2% of subjects in either treatment group.

MO Comment : The two treatment groups appeared similar.

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Summary of the Most Common Pathogens Associated with Primary and Distant Site Infections ^a Study 154-128 (Clinically Intent-to-Treat Subjects)				
	Alatrofloxacin 200 mg (N=246)		Cefotetan 2000 mg (N=236)	
	Number and Percentage (%) of Subjects			
Number of Subjects with a Primary and/or Distant Site Infection and an Isolated Pathogen	93	(38%)	87	(37%)
Wound Site Pathogen				
Abdominal Wound <i>E. faecalis</i>	0		5	(2%)
Blood <i>P. aeruginosa</i>	4	(2%)	0	
Surgical Wound Discharge				
<i>B. fragilis</i>	5	(2%)	9	(4%)
<i>Bacteroides sp.</i>	3	(1%)	5	(2%)
<i>B. thetaiotaomicron</i>	1	(<1%)	4	(2%)
Coagulase-Negative <i>Staphylococcus</i>	8	(3%)	10	(4%)
<i>Corynebacterium sp.</i>	7	(3%)	3	(1%)
<i>E. faecalis</i>	2	(<1%)	6	(3%)
<i>Enterococcus sp.</i>	3	(1%)	8	(3%)
<i>E. coli</i>	2	(<1%)	8	(3%)
<i>Peptostreptococcus sp.</i>	4	(2%)	0	
<i>P. aeruginosa</i>	4	(2%)	4	(2%)
<i>S. aureus</i>	6	(2%)	2	(<1%)
<i>S. epidermidis</i>	6	(2%)	7	(3%)
<i>Staphylococcus sp.</i>	2	(<1%)	6	(3%)
<i>Streptococcus sp.</i>	1	(<1%)	4	(2%)
<i>S. viridans</i>	4	(2%)	6	(3%)
Urine				
<i>E. faecalis</i>	0		9	(4%)
<i>Enterococcus sp.</i>	6	(2%)	12	(5%)
<i>E. coli</i>	2	(<1%)	9	(4%)
<i>K. pneumoniae</i>	2	(<1%)	5	(2%)
<i>P. aeruginosa</i>	2	(<1%)	4	(2%)

^a ≥2% of subjects in either treatment group.

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MO Comment : For unknown reasons, more enterococcal infections (wound site and urinary tract) were seen in the cefotetan arm compared to alatrofloxacin.

perhaps a difference in spectrum. The cephalosporins are not very good for enterococci. I have not seen clear to me whether the trend in vitro is clinically useful.

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SAFETY:

Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically-Significant Laboratory Values Study 154-128 (According to applicant)				
	Alatrofloxacin 200 mg		Cefotetan 2000 mg	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	156/256	(61%)	135/236	(57%)
Treatment-Related Adverse Events	26/256	(10%)	6/236	(3%)
Discontinuations from Treatment Due to Adverse Events ^a	5/256	(2%)	0/236	
Clinically Significant Laboratory Abnormalities	191/246	(78%)	184/231	(80%)
a - All were treatment-related.				

MO Comment : Approximately three-times as many treatment-related adverse events were reported with alatrofloxacin compared with cefotetan. However, all causality AEs were comparable between treatment arms.

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A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities Study 154-128 (All Treated Subjects)				
	Alatrofloxacin 200 mg IV (N=256)		Cefotetan 2000 mg IV (N=236)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	156	(61%)	135	(57%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	66	(26%)	51	(22%)
Appl./Inj./Incision/Insert. Infection/Inflammation	30	(12%)	26	(11%)
Appl./Inj./Incision/Insertion Site Pain	10	(4%)	5	(2%)
Appl./Inj./Incision/Insertion Site Reaction	19	(7%)	5	(2%)
Appl./Inj./Incision/Insertion/Device Complication	20	(8%)	19	(8%)
CARDIOVASCULAR SYSTEM	29	(11%)	20	(8%)
Tachycardia	8	(3%)	4	(2%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	19	(7%)	15	(6%)
Confusion	7	(3%)	5	(2%)
Headache	8	(3%)	5	(2%)
GASTROINTESTINAL SYSTEM	49	(19%)	48	(20%)
Diarrhea	3	(1%)	6	(3%)
Ileus	7	(3%)	10	(4%)
Nausea	27	(11%)	27	(11%)
Vomiting	19	(7%)	14	(6%)
GENERAL	34	(13%)	24	(10%)
Fever	17	(7%)	13	(6%)
PSYCHIATRIC	15	(6%)	10	(4%)
Insomnia	7	(3%)	4	(2%)
RESPIRATORY SYSTEM	23	(9%)	31	(13%)
Atelectasis	7	(3%)	9	(4%)
Pneumonia	6	(2%)	6	(3%)
SKIN/APPENDAGES	24	(9%)	14	(6%)
Pruritus	13	(5%)	9	(4%)
URINARY SYSTEM	30	(12%)	38	(16%)
Urinary Retention	8	(3%)	9	(4%)
Urinary Tract Infection	11	(4%)	14	(6%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion/Site				
a ≥3 % of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				

MO Comment : Overall, causality safety was comparable between treatment groups. However, more insertion site reactions were reported with alatrofloxacin.

**APPEARS THIS WAY
ON ORIGINAL**

8.2 Study 154-146

Protocol Title: "A randomized, double-blind, multicenter trial of the efficacy and safety of a single oral dose of trovafloxacin (99,219) compared with intravenous cefoxitin for the prophylaxis of infection following elective abdominal or vaginal hysterectomy."

8.2.1 Protocol Overview:

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ON ORIGINAL

Study Objectives: To compare the safety and efficacy of a single oral dose of trovafloxacin with a single intravenous dose of cefoxitin in the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy.

Study Dates: 18 January 1996 - 11 June 1996

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Study Design: Study 154-146 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin, administered orally, versus cefoxitin administered intravenously, for the prophylaxis of infection following elective abdominal or vaginal hysterectomy.

Pre-operative Administration:

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Oral trovafloxacin or its matching placebo tablets are to be administered 45 (±15) minutes prior to the estimated time of surgical incision. Trovafloxacin should therefore not be administered less than 30 minutes, or more than 60 minutes, prior to the estimated time of the surgical procedure. Only a minimal volume of water (~50 mL) should be provided to assist administration.

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Trovafloxacin will not be available to subjects at the conclusion of the study.

Cefoxitin or its matching placebo I.V. solution is to be infused over 10 (±5) minutes. Completion of the infusion should occur no earlier than 30 minutes prior to, and no later than the time of, surgical incision. While intravenous cefoxitin or its matching placebo is being injected, it is advisable to temporarily discontinue administration of any other solutions at the same site.

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Second Administration Of I.V. Study Drug Regimen: Should the duration of surgery extend beyond four hours, or, if there is greater than a 1500 mL blood loss, a second dose should be provided as follows:

Placebo for cefoxitin (0.1 mL MVI in solution for injection) OR cefoxitin (2 grams in solution for injection)

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Second Dose Administration:

If a second dose is indicated, cefoxitin or its matching placebo I.V. solution is to be infused over 10 (±5) minutes. The infusion should be given within 4-6 hours of the initiation of surgery. While intravenous cefoxitin or its matching placebo is being injected, it is advisable to temporarily discontinue administration of any other solutions at the same site.

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Noteworthy Inclusion criteria:

Women scheduled to undergo elective abdominal or vaginal hysterectomy for non-malignant disease processes (e.g., dysplasia, abnormal bleeding, uterine prolapse, leiomyomas).

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Noteworthy Exclusion criteria:

1. Subjects undergoing emergency hysterectomy and/or hysterectomy for malignant disease processes.
2. Subjects with significant gastrointestinal or other conditions which may have affected study drug absorption; known acquired immunodeficiency syndrome (AIDS); neutropenia; or immunosuppressive therapy (including treatment with >10 mg per day of prednisone); prior history of seizure or epilepsy; significant renal impairment (Cr_s >2.5 mg/dL).
3. Subjects with any coexisting condition(s) that would require anti-infective therapy during the course of the study.
4. Subjects with signs and symptoms of infection at the time of surgery or subjects who had been administered an antibiotic within 1 week prior to surgery.

At study entry, investigators were asked to fill out the following information in the Case Report Form for each study subject:

PRIMARY REASON FOR HYSTERECTOMY (check one only):

- Leiomyomas
- Endometriosis
- Chronic pelvic pain
- Cervical dysplasia
- Recurrent dysfunctional uterine bleeding
- Other (specify) _____

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Definition of infections

Symptoms and physical findings of any infections found during the 30-day study period will be recorded on the case report form and cultures will be obtained as previously described. Upon verification of a positive culture in the local laboratory, all potentially pathogenic isolates will be sent to the central laboratory.

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Primary infections

1. Surgical site infection (Abdominal surgical wounds only). Diagnosed as present if any one or more of the following are present:

- purulent exudate (as defined microscopically (≥ 10 PMN/hpf) or by gross inspection) with or without positive culture, or
- non-purulent drainage from the wound with a positive culture and signs/symptoms of infection at the wound site (hyperemic, hyperthermic, indurated and/or the presence of tenderness/ pain), or
- cellulitis requiring antibiotic therapy, or
- the need to re-open the closed wound.

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2. Pelvic Cellulitis

General findings are infection in the extraperitoneal space extending to parametrial tissue with signs and symptoms of pelvic, back, and/or lower abdominal pain and tenderness on deep palpation in the lower abdominal wall. *Vaginal cuff should be tender to palpation: Tenderness into parametrial tissue and engorgement without masses present should be evident on bimanual examination. Purulent discharge from the vaginal incision may or may not be present. Specific criteria are as follows: a) body temperature $\geq 101^{\circ}$ F on a single occasion or $\geq 100.4^{\circ}$ F on two separate occasions at least 6 hours apart (following the initial 24 hour post-operative period) and b) one or more of the following: tachycardia ($bmp \geq 100$), leukocytosis ($WBC \geq 2 \times$ baseline or $>$ upper limit of normal), or left shift ($\geq 10\%$ bands).*

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3. Pelvic Abscess or Infected Hematoma. Palpation of a *new* mass in the parametrial or adnexal region in addition to signs and symptoms of generalized pelvic inflammation and tenderness specified in (2) above *or, supportive imaging studies*.

4. Severity Grading For Primary Infections⁸ (Abdominal surgical wounds only).

0=no erythema or discharge at surgical site

1=cellulitis present at surgical site without purulent exudate

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⁸ Jensen LS, Andersen A, Fistrup SC, Holme JB, Hvid HM, Kraglund K, Rasmussen PC, Toftgaard C. Comparison of one dose *versus* three doses of prophylactic antibiotics, and the influence of blood transfusion, on infectious complications in acute and elective colorectal surgery. *Br J Surg* 1990; 77:513-518.

- 2=cellulitis present at surgical site with purulent exudate
 3=infection throughout surgical site or evidence of pelvic cellulitis/abscess

Distant infections

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1. Pneumonia. Diagnosed by *an* infiltrate on chest x-ray and presence of at least one of the following signs and symptoms: fever (defined as body temperature $\geq 100.4^{\circ}$ F following the initial 24 hour post-operative period), leukocytosis ($WBC \geq 2 \times$ baseline or $>$ upper limit of normal), left shift ($\geq 10\%$ bands), increased sputum production with numerous leukocytes, or a predominant bacterial species on culture.
2. Urinary tract infection. Diagnosed by signs and symptoms of a urinary tract infection and a urine culture with $\geq 10^5$ colonies/mL (or $\geq 10^4$ colonies/mL if the same bacterial species was isolated from two urine samples at different times). Signs and symptoms of urinary tract infection include at least one of the following: dysuria, frequency, urgency or suprapubic pain.
3. Intravenous catheter infection. Diagnosed by the presence of erythema, swelling, tenderness, and/or the presence of purulent material at the catheter site.
4. Other distant site infection. Other infections with associated signs and symptoms that are not classified above and are clearly unrelated to the operative procedure. The case report form will specify the type of infection.

Febrile Morbidity

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Defined as subjects presenting with fever ($\geq 101^{\circ}$ F on a single occasion or $\geq 100.4^{\circ}$ F on two separate occasions at least 6 hours apart) following the first 24 hour post-operative period for whom there is neither clinical or microbiological evidence of infection as specified above.

Clinical Response

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For both evaluable and intent-to-treat subjects, sponsor-defined subject clinical response was based primarily on the investigator's documented evidence or history of infection.

1. Success: No signs or symptoms of a primary infection. Infection in a distant site alone (e.g., urinary tract infection, respiratory tract, or intravenous catheter) was not included as a criterion for success or failure of prophylaxis.
2. Failure: If the investigator's assessment was primary site infection at any time, then the sponsor-defined subject clinical response was failure at all subsequent visits.
3. Failure: If a subject was given a concomitant antibiotic at any time for primary surgical site infection or unexplained use, then the sponsor-defined subject clinical response was failure at all subsequent assessments.
4. Failure: If a subject had no post-baseline assessment, then the sponsor-defined clinical response was failure at both the Hospital Discharge and End of Study.

- 5. Failure: If a subject needed any significant drainage procedure at the operative site or in and around the pelvic cavity for infection, then the sponsor-defined subject clinical response was failure at all subsequent assessments.

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Statistical Considerations

As stated in the protocol: The definition of equivalence, as suggested by some regulatory agencies, is that the 95% confidence interval for the difference in response rates is within 10% when the true satisfactory response rate of the reference drug is 90% or better.

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Assuming the response rate of the reference drug is 90 to 95% (i.e., a failure rate of 5 to 10%), the number of subjects for each treatment group required to ensure with 80% probability that the lower limit of the 95% confidence interval for the true difference in efficacy is greater than -10% is _____; per treatment group (for 5% and 10% failure, respectively). Hence, the planned enrollment of 350 subjects is sufficient to detect differences in equivalence assuming 80% of subjects are evaluable.

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Schedule of Study Evaluations
(Copied from the protocol for Study 154-146)

Study day	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-72 hours		Day 24-36
Informed consent	X		
Demographic information	X		
History & Physical (including pelvic)	X		
Examination for signs and symptoms of infection			
with abdominal/perineal exam	X	X ^a	X
Oral body temperature	X	X ^b	X
Vital signs	X	X ^b	X
Concomitant medication	X	X	X
Dosing record	X		
Safety laboratory tests			
• hematology	X	X ^c	abn ^d
• biochemistry	X	X ^c	abn ^d
• urinalysis	X	X ^c	abn ^d
Adverse events	X	X	X
Investigator's assessment of infection		X	X
Health care resource utilization			X

^a once daily during post-op hospital course

^b q 4-6h

^c at 48 hours post-op or at hospital discharge (whichever is earlier)

^d only if clinically significant abnormality was present at time of most recent determination

**APPEARS THIS WAY
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Investigators for Study 154-146

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5238	Subir Roy, MD
	5601	James Mcgregor, MD
	5748	David Baker, MD
	5750	David Hemsell, MD
	5766	Sebastian Faro, MD
	5770	Joseph Pastorek, MD
	6003	John Larsen, Jr., MD
	6109	Mark Martens, MD
	6126	Todd Vanheest, MD
	6390	Lane Mercer, MD
	6470	David Godwin, MD
	6471	Stephen Gordon, MD
	6474	Maurizio Maccato, MD
	6475	Mark Pearlman, MD
	6476	Campbell Skokos, MD
	6478	David Soper, MD
	6479	Neil Wolfson, MD
6567	Nicholas Lindberg, MD	

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**Summary of Subject Disposition
Study 154-126**

	Trovafloxacin		Cefoxitin	
	Number and Percentage (%) of Subjects			
Randomized Subjects	196		191	
Randomized, Not Treated ^a	8		16	
All Treated Subjects	188	(100%)	175	(100%)
Withdrawn from Treatment ^b	5	(3%)	0	
Completed Treatment	183	(97%)	175	(100%)
Withdrawn from Study	6	(3%)	1	(<1%)
Withdrawn during Treatment	1	(<1%)	0	
Withdrawn during Follow-Up	5	(3%)	1	(<1%)
Completed Study ^c	185	(98%)	181	(103%) ^c
Completed Treatment and Study	178	(95%)	174	(>99%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	183	(93%)	185	(97%)
Clinically Evaluable	133	(68%)	127	(66%)
Clinically Evaluable + Subjects Receiving Concomitant Antibiotics for Distant Site Infections	163	(83%)	162	(85%)
Assessed for Safety				
Adverse Events	188	(100%)	175	(100%)
Laboratory Tests	179	(95%)	172	(98%)

a Three randomized, not treated subjects in the trovafloxacin group completed study and seven randomized, not treated in the cefoxitin group completed study. No subject received placebo.
b Of the five trovafloxacin subjects who were withdrawn from treatment, four completed study.
c Includes seven subjects who were randomized but not treated and who completed study.

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Summary of Baseline Characteristics and Underlying Diseases and Syndromes at Baseline Study 154-146				
All Treated Subjects				
	Trovafoxacin 200 mg (N=188)		Cefoxitin 2000 mg IV (N=175)	
Baseline Characteristic	Number and Percentage (%) of Subjects			
Age (years)				
Mean	42.9		42.5	
Minimum	(b)(4)			
Maximum				
16-44	107	(57%)	103	(59%)
45-64	75	(40%)	68	(39%)
≥65	6	(3%)	4	(2%)
Anemia	40	(21%)	26	(15%)
Hypertension	39	(21%)	33	(19%)
Diabetes Mellitus	14	(7%)	13	(7%)
COPD	3	(2%)	2	(1%)
Congestive Heart Failure	1	(<1%)	1	(<1%)
Hepatic Disease	0		1	(<1%)
Impaired Renal Function	1	(<1%)	0	

COPD = Chronic Obstructive Pulmonary Disease

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Summary of High Risk Factors Study 154-146				
Number and Percentage (%) of Clinically Evaluable Subjects with High Risk Factors				
	Trovafoxacin 200 mg (N=133)		Cefoxitin 2000 mg IV (N=127)	
Subjects with ≥1 High Risk Factor	89	(67%)	88	(69%)
High Risk Factor				
Abdominal Procedure	73	(55%)	73	(57%)
Age >50 Years	17	(13%)	14	(11%)

MO Comment : The two treatment arms appeared similar at baseline.

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PROPHYLACTIC EFFICACY:

Summary of the Applicant's Assessment of Clinical Response					
Study 154-146					
All Clinically Evaluable Subjects					
	Hospital Discharge		End of Study		
	Trovafloxacin 200 mg (N=133)	Cefoxitin 2000 mg IV (N=127)	Trovafloxacin 200 mg (N=133)	Cefoxitin 2000 mg IV (N=127)	
Number and Percentage (%) of Subjects					
Success ^a	128 (96%)	122 (96%)	111 (84%)	117 (92%)	
Failure	5 (4%)	5 (4%)	22 (16%)	10 (8%)	
Clinically Evaluable Subjects: Excluding Subjects who Received BICITRA®					
	Hospital Discharge		End of Study		
	Trovafloxacin 200 mg (N=103)	Cefoxitin 2000 mg IV (N=97)	Trovafloxacin 200 mg (N=103)	Cefoxitin 2000 mg IV (N=97)	
Number and Percentage (%) of Subjects					
Success ^a	99 (96%)	93 (96%)	91 (88%)	88 (91%)	
Failure	4 (4%)	4 (4%)	12 (12%)	9 (9%)	
Infection types of failures	APPEARS THIS WAY ON ORIGINAL		12	9	
			Surgical site	3	4
			Pelvic cellulitis	5	3
			Pelvic cellulitis, abscess or infected hematoma	2	2
			Vaginal cuff infection	1	0
Missing	1	0	1	0	
Subjects who failed requiring rehospitalization or prolonged hospitalization	APPEARS THIS WAY ON ORIGINAL		4	5	
Clinically Evaluable Subjects: Excluding Subjects who Received BICITRA® By Type of Hysterectomy					
			End of Study		
			Trovafloxacin 200 mg (N=103)	Cefoxitin 2000 mg IV (N=97)	
Number and Percentage (%) of Subjects					
Abdominal	APPEARS THIS WAY ON ORIGINAL		(n=55)	(n=59)	
			Success ^a	48 (87%)	53 (90%)
Failure	7 (13%)	6 (10%)			
Vaginal	APPEARS THIS WAY ON ORIGINAL		(n=48)	(n=38)	
			Success ^a	43 (90%)	35 (92%)
Failure	35 (10%)	3 (8%)			
Clinically Evaluable Subjects Plus Subjects Receiving Concomitant Antibiotics for Distant Site Infection: Excluding Subjects who Received BICITRA®					
	Hospital Discharge		End of Study		
	Trovafloxacin 200 mg (N=131)	Cefoxitin 2000 mg IV (N=130)	Trovafloxacin 200 mg (N=131)	Cefoxitin 2000 mg IV (N=130)	
Success ^a	123 (94%)	126 (97%)	112 (85%)	118 (91%)	
Failure	8 (6%)	4 (3%)	19 (15%)	12 (9%)	

a No signs or symptoms of a primary infection.

FDA 95% CI for ALL clinically-evaluable patients at EOS: (-17%, 0%)

FDA 95% CI for clinically-evaluable patients (excluding BICITRA® recipients) at EOS: (-12%, 7%)

FDA 95% CI for clinically-evaluable patients (including distant site infections BUT excluding BICITRA® recipients) at EOS: (-14% ,3%)

MO Comment : Trovafloxacin appeared to be less effective than cefoxitin in preventing surgical infections. However, in a *post hoc* analysis, Pfizer determined that if patients who received Bicitra orally were excluded, the treatment arms are comparable with regard to preventing surgical infections post hysterectomy. In addition, there efficacy was comparable for both abdominal or vaginal hysterectomy.

During the NDA review, Pfizer was also asked to assess prophylaxis outcome for low versus high-risk subjects. On 12/12/97, Pfizer responded via e-mail with the following analysis for hysterectomy:

"We did the analysis and the efficacy was not different between the "high risk" population (67 and 69% for Trovan and comparator, respectively - clinically evaluable with or without Bicitra) and those not considered at high risk by treatment arm."

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In addition, Pfizer submitted the following analysis on 12/15/97 by e-mail.

Hysterectomy Surgical Prophylaxis Outcome (Success Rate) with/without Risk Factors AND including/excluding Bicitra at EOS (Clinically Evaluable)		
	Trovafloxacin	Cefoxitin
Including Bicitra		
No risk factors	36/44 (82%)	36/39 (92%)
At least 1 risk factor	75/89 (84%)	81/88 (92%)
Excluding Bicitra		
No risk factors	32/35 (91%)	26/29 (90%)
At least 1 risk factor	59/68 (87%)	62/68 (91%)

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ON ORIGINAL

MO Comment : The MO is satisfied that prophylactic efficacy was comparable between the two treatment arms depending with no risk factors or with at least 1 risk factor (with or without Bicitra).

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Summary of Pathogens Associated With Primary Site Infection (Clinical Intent-to-Treat Subjects <u>Excluding</u> Subjects who Received BICITRA®) Study 154-146		
	Trovafloxacin 200 mg (N=149)	Cefoxitin 2000 mg (N=150)
Number of Subjects with a Primary Site Failure	19	17
Number of Subjects with a Primary Site Infection and an Isolated Pathogen	10	3
Gram Positive Aerobes		
<i>S. agalactiae</i>	4	1
<i>S. anginosus</i>	1	0
<i>S. mitis</i>	0	1
<i>Staphylococcus</i> sp.	4	1
Gram Negative Aerobes		
<i>E. coli</i>	0	1
<i>P. mirabilis</i>	1	1
<i>P. aeruginosa</i>	0	1
Gram Positive Anaerobes		
<i>Lactobacillus</i> sp.	1	0
<i>Peptostreptococcus</i> sp.	3	0
<i>Propionibacterium</i> sp.	1	0
Gram Negative Anaerobes		
<i>Bacteriodes</i> sp.	1	0
<i>Gardnerella vaginalis</i>	2	1
<i>Prevotella</i> sp.	2	0

MO Comment : Overall, the number of subjects with a primary site prophylaxis failure were similar between treatment groups. When a primary site failure occurred, more pathogens were isolated from trovafloxacin recipients.

APPEARS THIS WAY
ON ORIGINAL

SAFETY:

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values Study 154-146				
	Trovafloxacin 200 mg		Cefoxitin (2000 mg IV)	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	114/188	(61%)	97/175	(55%)
Treatment-Related Adverse Events	0/188		2/175	(1%)
Discontinuations From Treatment Due to an Adverse Event	1/188 ^a	(<1%)	0/175	
Clinically Significant Laboratory Abnormalities	110/179	(61%)	95/172	(55%)
a Rash developed during infusion of drug-free placebo (PID 5766-0177).				

MO Comment : All causality adverse events were similar between treatment groups. Unlike to colorectal prophylaxis study, no treatment-related AEs were reported with trovafloxacin.

APPEARS THIS WAY
ON ORIGINAL

A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities Study 154-146 (All Treated Subjects)			
APPEARS THIS WAY ON ORIGINAL			APPEARS THIS WAY ON ORIGINAL
APPEARS THIS WAY ON ORIGINAL	Trovafoxacin 200 mg (N=188)	Cefoxitin 2000 mg IV (N=175)	
Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	114	(61%)	97 (55%)
BODY SYSTEM			
WHO Term			
APPL./INJ./INCISION/INSERTION SITE	37	(20%)	23 (13%)
Appl./Inj./Incision/Insertion Site Infection	6	(3%)	3 (2%)
Inflammation	6	(3%)	1 (<1%)
Appl./Inj./Incision/Insertion Site Edema	9	(5%)	8 (5%)
Appl./Inj./Incision/Insertion Site Pain	16	(9%)	13 (7%)
Appl./Inj./Incision/Insertion/Device Complication			
CENTRAL AND PERIPHERAL NERVOUS	15	(8%)	13 (7%)
Dizziness	6	(3%)	4 (2%)
Headache	8	(4%)	8 (5%)
GASTROINTESTINAL	23	(12%)	21 (12%)
Constipation	1	(<1)	6 (3%)
Nausea	14	(7%)	10 (6%)
Vomiting	7	(4%)	4 (2%)
GENERAL	47	(25%)	38 (22%)
Cellulitis, other than Injection Site	7	(4%)	2 (1%)
Fever	32	(17%)	32 (18%)
PSYCHIATRIC	8	(4%)	7 (4%)
Insomnia	5	(3%)	5 (3%)
SKIN/APPENDAGES	20	(11%)	22 (13%)
Pruritus	14	(7%)	18 (10%)
URINARY SYSTEM	14	(7%)	17 (10%)
Urinary Tract Infection	8	(4%)	10 (6%)
a ≥3 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication			

MO Comment : When specific AEs are assessed, there appeared to be more injection site complications reported in the trovafoxacin arm (placebo, since trovafoxacin was administered orally) compared with cefoxitin.

Time of Drug Dosing for Optimal Surgical Prophylaxis

APPEARS THIS WAY
ON ORIGINAL

For effective surgical prophylaxis, the optimal dosing strategy is to time drug administration such that peak antimicrobial peak drug concentrations are present at the time of first surgical incision.

For oral TROVAN, the T_{max} is 1-2 hours. During the NDA review, Pfizer was asked to provide a rationale for why they chose a 30-60 minute oral dosing prior to surgical incision for the hysterectomy study.

APPEARS THIS WAY
ON ORIGINAL

Pfizer Response (11/25/97 e-mail): "The package insert for cefoxitin states that it must be administered 30-60 minutes before surgical incision. To preserve double-blinding, the protocol stated that both drugs (trovafloxacin and cefoxitin) would be administered at the same time. Further, standard surgical practice is such that prophylaxis drugs are administered within 30-60 minutes of the surgical incision. Other antibiotics approved for prophylaxis, such as cefoxitin and cefotetan, are administered intravenously such that the T_{max} is upon completion of the administration, and elimination half-lives are too short to permit a longer window for drug administration. We wanted to test trovafloxacin under the same standards of practice to be assured that it was effective if used according to the practices for other prophylactic antibiotics. According to its pharmacokinetics, there would be adequate concentrations when administered 30-60 minutes before surgical incision, and the long elimination half-life allows for delays in surgical start times as well as prolonged complicated cases."

APPEARS THIS WAY
ON ORIGINAL

In addition, Pfizer was asked to examine the impact of the start of infusion relative to the timing of surgical incision and its impact on effective colorectal prophylaxis in study 154-128. Although the protocol stipulated that prophylaxis be administered within 2 hours of surgery, Pfizer requested that a "Single dose within 4 hr before surgery" be included in the DOSAGE & ADMINISTRATION section of product labeling. Indeed, many patients received their first dose of alatrofloxacin ≥ 2 hours prior to incision.

APPEARS THIS WAY
ON ORIGINAL

Pfizer submitted the following analysis on 12/9/97:

Surgical Prophylaxis Success Rates Based on Time of Start of Infusion Relative to Time of Surgical Incision (154-128)			
Clinical ITT Population			
Hospital Discharge			
Timing of infusion start prior to surgical incision	Alatrofloxacin	Cefotetan	95% CI (w/ continuity correction)
≤2 hrs	102/130 (79%)	100/126 (79%)	-12%, 10%
>2 and <4 hrs.	77/97 (79%)	70/94 (75%)	-8%, 18%
<4 hrs	179/227 (79%)	170/220 (77%)	-7%, 10%
End of Study (EOS)			
≤2 hrs	93/130 (72%)	89/126 (71%)	-11%, 13%
>2 and <4 hrs.	72/97 (74%)	61/94 (65%)	-5%, 24%
<4 hrs	165/227 (73%)	150/220 (68%)	-4%, 13%

Surgical Prophylaxis Success Rates Based on Time of Start of Infusion Relative to Time of Surgical Incision (154-128)			
Clinically Evaluable Population			
End of Therapy (EOT)			
Timing of infusion start prior to surgical incision	Alatrofloxacin	Cefotetan	95% CI (w/ continuity correction)
≤2 hrs	75/94 (80%)	73/86 (85%)	-17%, 7%
>2 and <4 hrs.	52/67 (78%)	55/70 (79%)	-16%, 14%
<4 hrs	127/161 (79%)	128/156 (82%)	-13%, 6%
End of Study (EOS)			
≤2 hrs	67/94 (71%)	66/86 (77%)	-19%, 8%
>2 and <4 hrs.	49/67 (73%)	47/70 (67%)	-11%, 23%
<4 hrs	116/161 (72%)	113/156 (72%)	-11%, 10%

MO Comment : Alatrofloxacin appeared comparable to cefotetan when dosing began as long as 4 hours prior to surgical incision.

Pfizer also stated on 12/9/97:

APPEARS THIS WAY
ON ORIGINAL

"The protocol for the elective colorectal study (154-128) and the elective hysterectomy study (154-146) stipulated windows of 2 hours and 30-60 minutes, respectively, for TROVAN dosing. As with all studies, we reviewed the dosing window while still blinded to treatment during our review of the evaluability listings. Many subjects (approx. half the clinically evaluable subset in the 128 study but far fewer [<5] subjects in the 146 study) were rendered not clinically evaluable due to dosing occurring

outside the 2-hour window. Reasons for the noncompliance in adhering strictly to the dosing window were largely due to delays in surgery starts (OR scheduling conflicts, surgeon timetables, etc.). Since clinical outcome was not different when one looked at a 2-hour window or a 4-hour window, we applied the 4-hour window for clinical evaluability. In so doing, we are able to assess the drug in a clinically realistic environment (i.e., where operating room and surgical incision times are difficult to standardize).

"In summary, all 128 and 146 subjects who received study drug within 4 hours of the surgical incision were included in efficacy analysis." APPEARS THIS WAY ON ORIGINAL

The MO is satisfied that the phrase, "Single dose within 4 hr before surgery" may be included for both colorectal and hysterectomy prophylaxis.

9. Conclusions:

APPEARS THIS WAY ON ORIGINAL

TROVAN is safe and effective in preventing infections associated with elective colorectal and abdominal/vaginal hysterectomy.

The applicant has adequately demonstrated that TROVAN can be administered up to 4 hours prior to the surgical procedure. However, because the concept of attaining peak serum concentrations at the time of surgical incision remains important, TROVAN should not be administered any earlier than 30 minutes prior to incision. (This is consistent with labeling for other products.)

The applicant has adequately demonstrated that trovafloxacin should NOT be administered orally within 2 hours of Bicitra®. Bicitra® causes decreased bioavailability of oral trovafloxacin when the two are co-administered.

APPEARS THIS WAY ON ORIGINAL

10. Recommendations:

APPEARS THIS WAY
ON ORIGINAL

TROVAN should be approved with the following product labeling:

/s/

Brad Leissa, MD
Medical Officer/HFD-590

cc: Orig. NDA
Division file
HFD-590/MO/Leissa
HFD-590/MO/Alivisatos
HFD-590/MO/Cox
HFD-590/CSO/Kimzey

Concurrence only: DivDir/Goldberger

/s/

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020759/020760

CHEMISTRY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Katagene

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-760

CHEM. REVIEW #: 2

REVIEW DATE: 10/15/97

SUBMISSION/TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

AMENDMENT

10/3/97

NAME & ADDRESS OF APPLICANT:

Pfizer Central Research
Medical Research Laboratory
Eastern Point Road
Groton, Connecticut 06340

DRUG PRODUCT NAME

Proprietary:

Trovan I.V.

Nonproprietary/USAN:

Alatrofloxacin Mesylate,
Alatrofloxacin Injection

Code Names/#'s:

CP-116,517-27

Chemical Type:

1S

Therapeutic Class:

ANDA Suitability Petition/DESI/Patent Status:

N/A [if applicable]

APPROVED BY
GISHWILL

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: Aqueous Concentrate Injection

STRENGTHS: 5 mg/mL, 100 mg, 200 mg, and 300 mg

ROUTE OF ADMINISTRATION: Intravenous Infusion

DISPENSED:

Rx

OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Structural Formula:

The structural formula of alatrofloxacin mesylate is given below:

APPROVED BY
GISHWILL

Molecular Formulae and Weights

Molecular Formula of Alatrofloxacin Mesylate: $C_{26}H_{25}F_3N_6O_5 \cdot CH_3SO_3H$

Molecular Formula of Alatrofloxacin: $C_{26}H_{25}F_3N_6O_5$

Molecular Weight of Alatrofloxacin Mesylate: 654.62

Molecular Weight of Alatrofloxacin: 558.52

Nomenclature

Chemical Abstracts Services Name: (1 α , 5 α , 6 α)-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate

APPROPRIATE
ON SEP 11

Chemical Abstracts Services Number: [157605-25-9]

I.N.N.: alatrofloxacin

Proposed Proprietary or Trade Name: TROVAN® injection

U.S.A.N.: alatrofloxacin mesylate

W.H.O. or B.A.N.: alatrofloxacin mesylate

Laboratory Code

Pfizer Laboratory Code: CP-116,517-27

APPROPRIATE
ON SEP 11

8

PAGES REDACTED

**CONTAINED TRADE
SECRETS and/or
CONFIDENTIAL/
COMMERCIAL
INFORMATION**

APPEARS THIS WAY
ON ORIGINAL

CONCLUSION:

The NDA may be approved from the chemistry, manufacturing and control point of view. The following items are acceptable.

- NOTE:**
1. EER is acceptable
 2. Trade name approved
 3. EA-FONSI has been issued
 4. All chemistry deficiencies hve been answered satisfactorily
 6. Sterility review has been completed by HFD-805 and found acceptable, 7/3/97.

APPEARS THIS WAY
ON ORIGINAL

/S/

11/26/97

B. Vithal Shetty, Ph.D.
Review Chemist

- cc: Orig. NDA 20-760
HFD-520/Division File
HFD-520/BVShetty
HFD-590/MO/Alivisatos
HFD-590/Pharm/Hastings
HFD-590/Micro/Lard
HFD-590/CSO/Fogarty
HFD-520/DKatague
R/D Init by: DKatagu

**APPEARS THIS WAY
ON ORIGINAL**

/S/

11/26/97

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

AUG 28 1997

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-760

CHEM. REVIEW #: 1

REVIEW DATE: 7/1/97

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	12/27/96	1/02/97	6/27/97

NAME & ADDRESS OF APPLICANT: Pfizer Central Research
 Medical Research Laboratory
 Eastern Point Road
 Groton, Connecticut 06340

DRUG PRODUCT NAME

Proprietary: Trovan I.V.
Nonproprietary/USAN: Alatrofloxacin Mesylate,
 Alatrofloxacin Injection
Code Names/#'s: CP-116,517-27
Chemical Type: 1S
Therapeutic Class:

APPROVED FOR
 06/27/97

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOLOGICAL CATEGORY/INDICATION:

APPROVED FOR
 06/27/97

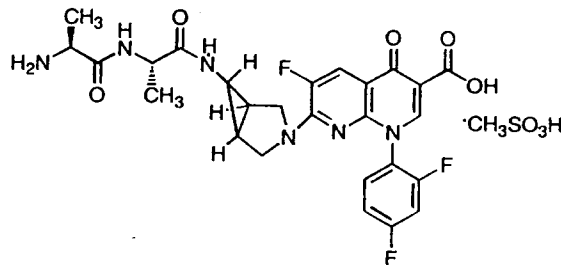
DOSAGE FORM: Aqueous Concentrate Injection
STRENGTHS: 5 mg/mL, 100 mg, 200 mg, and 300 mg
ROUTE OF ADMINISTRATION: Intravenous Infusion
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Structural Formula:

APPROVED FOR
 06/27/97

The structural formula of alatrofloxacin mesylate is given below:



APPROVED FOR
 06/27/97

Molecular Formulae and Weights

Molecular Formula of Alatrofloxacin Mesylate: $C_{26}H_{25}F_3N_6O_5 \cdot CH_3SO_3H$
Molecular Formula of Alatrofloxacin: $C_{26}H_{25}F_3N_6O_5$
Molecular Weight of Alatrofloxacin Mesylate: 654.62
Molecular Weight of Alatrofloxacin: 558.52

Nomenclature

Chemical Abstracts Services Name: (1 α , 5 α , 6 α)-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate
Chemical Abstracts Services Number: [157605-25-9]
I.N.N.: alatrofloxacin
Proposed Proprietary or Trade Name: TROVAN® injection
U.S.A.N.: alatrofloxacin mesylate
W.H.O. or B.A.N.: alatrofloxacin mesylate

Laboratory Code

Pfizer Laboratory Code: CP-116,517-27

SUPPORTING DOCUMENTS:

IND
IND

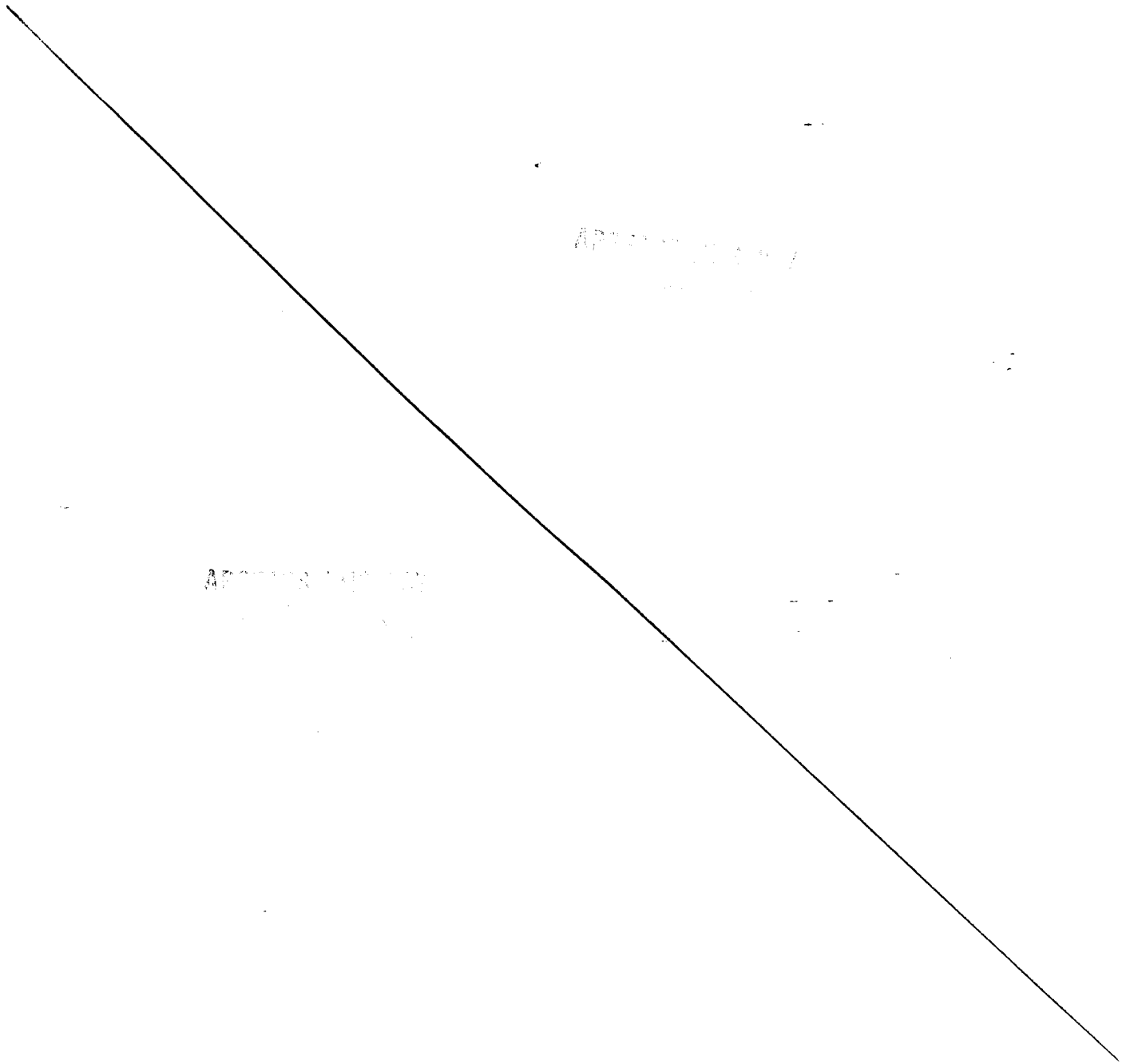
ADDITIONAL

APPROPRIATE
ON CHARTER

RELATED DOCUMENTS (if applicable):

NDA 20-759 (Trovafloracin Mesylate Tablet)

This NDA was submitted simultaneously with NDA 20-759. It is being reviewed at present.



CONSULTS:

1. Environmental Assessment

3. The trade name, TROVAN I.V., has already been approved.

5. EER - The EER dated 6/9/97 was found to be acceptable.

REMARKS/COMMENTS:

Alatrofloxacin is a fluoronaphthyridone derivative, structurally similar to, and with a comparable mechanism of action to the fluoroquinolone class of antibacterial agents.

APPROVED THIS WAY
BY ORIGINAL

APPROVED THIS WAY
BY ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 (or 507 for an antibiotic) of the Act.

131 /S/ 8/27/97

B. Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 20-760
HFD-520/Division File
HFD-520/BVShetty
HFD-520/MO/Alivisatos
HFD-520/Pharm/Hastings
HFD-520/Micro/Lard
HFD-520/CSO/Fogarty
HFD-520/DKatague
R/D Init by: DKatague/S/ 8/28/97

APPROVED FOR SIGNATURE
DATE

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

OCT 20 1997

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-759

CHEM. REVIEW #: 2

REVIEW DATE: 9/22/97

SUBMISSION/TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

AMENDMENT/AC

10/09/97

NAME & ADDRESS OF APPLICANT:

Pfizer Central Research
Eastern Point Road
Groton, Connecticut 06340

DRUG PRODUCT NAME

Proprietary:

Trovan

Nonproprietary/USAN:

Trovafloxacin Mesylate

Code Names/#'s:

CP-99,219-27

Chemical Type:

1S

Therapeutic Class:

Quinolone, antibacterial

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOLOGICAL CATEGORY/INDICATION:

APPROVED
ORIGINAL

DOSAGE FORM: Tablets

STRENGTHS: 100 and 200 mg

ROUTE OF ADMINISTRATION: Oral

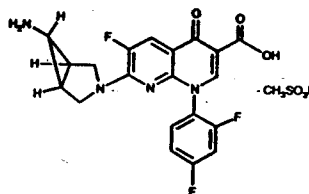
DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Structural Formula:

The structural formula of trovafloxacin mesylate is given below:



APPROVED
ORIGINAL

Molecular Formulae and Weights

Molecular Formula of Trovafloxacin Mesylate: $C_{20}H_{15}F_3N_4O_3 \cdot CH_3SO_3H$

Molecular Formula of Trovafloxacin: $C_{20}H_{15}F_3N_4O_3$

Molecular Weight of Trovafloxacin Mesylate: 512.46

Molecular Weight of Trovafloxacin: 416.36

APPROVED
ORIGINAL

7

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**CONTAINED TRADE
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CONFIDENTIAL/
COMMERCIAL
INFORMATION**

APPROVED
10/8/97

CONCLUSION:

The NDA may be approved from the chemistry, manufacturing and control point of view. The following items are acceptable.

NOTE:

1. EER is acceptable
2. FONSI has been issued
3. All chemistry deficiencies have been answered satisfactorily
4. Trade name has been approved.

APPROVED
10/8/97

PENDING:

APPROVED
10/8/97

/S/ 10/8/97

B.Vithal Shetty, Ph.D.
Review Chemist

- cc: Orig. NDA 20-795
HFD-590/Div. Files
HFD-520/Shetty
HFD-590/Albrecht
HFD-590/Alivisatos
HFD-590/Hastings
HFD-590/Schmuff
HFD-520/Katague
HFD-590/Lard
HFD-590/Fogarty
R/D Init by: DKatague

APPROVED
10/20/97

/S/ 10/20/97

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Dr. Shetty

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-759

CHEM. REVIEW #: 1

REVIEW DATE: 3/26/97

SUBMISSION/TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

ORIGINAL

12/27/96

1/02/97

1/7/97

NAME & ADDRESS OF APPLICANT: Pfizer Central Research
Eastern Point Road
Groton, Connecticut 06340

DRUG PRODUCT NAME

Proprietary: Trovan
Nonproprietary/USAN: Trovafloxacin Mesylate
Code Names/#'s: CP-99,219-27
Chemical Type: 1S
Therapeutic Class: Quinolone, antibacterial

ANDA Suitability Petition/DESI/Patent Status:

N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: Tablets

STRENGTHS: 100 and 200 mg

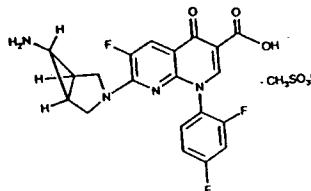
ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Structural Formula:

The structural formula of trovafloxacin mesylate is given below:



Molecular Formulae and Weights

Molecular Formula of Trovafloxacin Mesylate: C₂₀H₁₅F₃N₄O₃ · CH₃SO₃H

Molecular Formula of Trovafloxacin: C₂₀H₁₅F₃N₄O₃

Molecular Weight of Trovafloxacin Mesylate: 512.46

Molecular Weight of Trovafloxacin: 416.36

Nomenclature

<u>Chemical Abstracts Services Name:</u>	(1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate
<u>Chemical Abstracts Services Number:</u>	[147059-75-4]
<u>I.N.N.:</u>	trovafloxacin
<u>Proposed Proprietary or Trade Name:</u>	TROVAN®
<u>U.S.A.N.:</u>	trovafloxacin mesylate
<u>W.H.O. or B.N.F.:</u>	trovafloxacin mesylate

Laboratory Code

<u>Pfizer Laboratory Code:</u>	CP-99,219-27

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

NDA 20-760

CONSULTS:

3. Trade Name, TROVAN, already approved.
4. EER - Requested on January 29, 1997. It was found to be acceptable.

REMARKS/COMMENTS:

Trovafloxacin is a fluoronaphthyridone derivative similar to, and with a comparable mechanism of action to the fluoroquinolone class of antibacterial agents. The tablets are 100 and 200 mg in weight. The firm states that Trovan has demonstrated activity against certain resistant pathogens including penicillin-resistant streptococcus pneumonia and methicillin-resistant staphylococcus aureus. It is stated that this is the only antibacterial agent (trovan) to date that can be administered orally for the treatment of infections caused by these pathogens including serious infections of the respiratory tract, epidemic meningococcal meningitis in children and for the prophylaxis of infection following abdominal or vaginal hysterectomy.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 (or 507 for an antibiotic) of the Act. Specific items which are not approvable are identified under the

following headings: Synthesis, Controls, Drug Product, Stability, Environmental Assessment, Methods Validation, and Labeling.

1S/

7/21/97

B. Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 20-759
HFD-520/Division File
HFD-520/BVShetty
HFD-520/MO/ *Alvrisatos*
HFD-520/Pharm/ *Hastings*
HFD-520/Micro/ *David*
HFD-520/CSO/ *Fogarty*
HFD-520/DKatague
R/D Init by: DKatague

1S/ 8/11/97

APPROVED FOR
SUBMISSION

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20759/20760

PHARMACOLOGY REVIEW(S)

866.5
520

DEC 15 1997

NDA's 20,759-000 and 20,760-000/Trovan® Tablets and IV

1

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520**

NDA #s: 20,759-000 (trovafloxacin mesylate tablets) and 20,760-000 (alatrofloxacin mesylate injection)

SPONSOR: Pfizer Inc.
Eastern Point Road
Groton, CT 06340

ADP 12/15/97
12/15/97

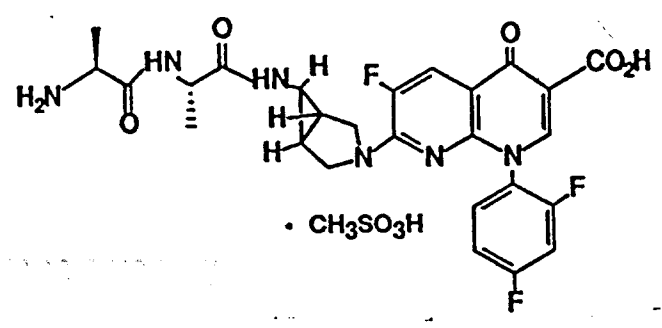
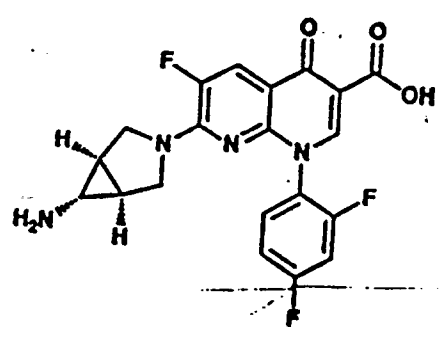
AUTHORIZED REPRESENTATIVE: Ronald I. Trust, Ph.D., M.B.A.
(860) 441-6991

DRUG NAMES: Trovan® Tablets: trovafloxacin mesylate; CP-99,219-27; (1 α ,5 α ,6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate

Trovan® I.V.: alatrofloxacin mesylate; CP-116,517-27; (1 α ,5 α ,6 α)-L-alanyl-N-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide monomethanesulfonate

CATEGORY: Fluoronaphthyridone anti-infective (structurally similar to fluoroquinolones and also an inhibitor of DNA gyrase)

STRUCTURAL FORMULAS:



Alatrofloxacin is the bis L-alanine prodrug of trovafloxacin.

RELATED SUBMISSIONS: IND

NUMBER OF VOLUMES: 203 total (18 for Pharm/Tox)

DATE CDER RECEIVED: 12/30/96

DATE ASSIGNED: 1/7/97

DATE REVIEW STARTED: 1/8/97

DATE 1ST DRAFT COMPLETED: 12/11/97

DATE REVIEW ACCEPTED BY TEAM LEADER: *December 15, 1997*

REVIEW OBJECTIVES: To ascertain whether the nonclinical studies submitted by the sponsor adequately demonstrate the potential toxicities of trovafloxacin and alatrofloxacin and to determine if these drug products meet safety standards allowing them to be approved for marketing.

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Trovafloxacin will be available as 100 and 200 mg tablets (based on weight of trovafloxacin free base) to be administered orally. Each tablet contains:

	100 mg tablet	200 mg tablet
Trovafloxacin Mesylate ^a		
Microcrystalline Cellulose ^b		
Magnesium Stearate		
coating		

^aWeight of drug substance will be adjusted based on actual potency of lot

^bWeight of microcrystalline cellulose will be adjusted depending on amount of trovafloxacin mesylate used in the batch in order to maintain constant tablet weights
tablet.

contains hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, polyethylene glycol, and FD&C blue #2 aluminum lake.

Alatrofloxacin will be available as aqueous 5 mg/ml concentrates in vials containing 100, 200, or 300 mg (all based on weight of trovafloxacin free base equivalent) to be diluted prior to intravenous administration.

The solution will be adjusted to pH of approximately 3.75 using HCl and NaOH as needed. For example, a 100 mg vial will contain 157.232 mg of alatrofloxacin mesylate in 20.06 ml of water.

REQUESTED CLINICAL INDICATIONS:

Indication	Daily Dose/Route	Treatment Duration
Adults		
Nosocomial Pneumonia	300 mg I.V followed by 200 mg oral	10-14 days
Community Acquired Pneumonia	200 mg oral or 200 mg I.V. followed by 200 mg oral	7-14 days
Acute Bacterial Exacerbation of Chronic Bronchitis	100 mg oral	7-10 days
Acute Sinusitis	200 mg oral	10 days
Complicated Intra- Abdominal Infections, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Gynecologic and Pelvic Infections, Complicated, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Surgical Prophylaxis- Elective Colorectal Surgery	200 mg I.V.	Single dose within 4 hours before surgery
Surgical Prophylaxis- Elective Abdominal and Vaginal Hysterectomy	200 mg oral	Single dose within 4 hours before surgery
Skin and Skin Structure Infections, Uncomplicated	100 mg oral	7-10 days
Skin and Skin Structure Infections, Complicated, including diabetic foot infections	200 mg oral or 200 mg I.V. followed by 200 mg oral	10-14 days
Uncomplicated Urinary Tract Infections, including cystitis	100 mg oral	3 days

Bacterial Prostatitis	200 mg oral	28 days
Acute, Uncomplicated Gonorrhea	100 mg oral	Single Dose
Non-Gonococcal Urethritis and Cervicitis	200 mg oral	5 days
Pelvic Inflammatory Disease	200 mg oral or 200 mg I.V. followed by 200 mg oral	14 days
Children		

INDEX OF NONCLINICAL STUDIES SUBMITTED TO THIS NDA
(and location of review):

Pharmacology Studies:

General Pharmacology of CP-99,219-27 Summary reports of studies investigating the general pharmacologic parameters of trovafloxacin are included here. *In vivo* experiments explored the effects of trovafloxacin on CNS activity in mice, canine cardiovascular system, renal excretion in conscious rats, blood gas measurements in rats, gastrointestinal transit time in rats, and gastric acid secretion in pylorus-ligated rats. *In vitro* experiments explored trovafloxacin-induced effects on ligand binding, isolated guinea pig aorta, ileum, and atria, and isolated rat uterus.

Reviewed below

General Pharmacology of CP-116,517 Summary reports of a study investigating the effects of alatrofloxacin on the cardiovascular system of conscious primates and an *in vitro* study of alatrofloxacin effects on receptor-specific ligand binding in bovine brain.

Reviewed below

Interaction of Trovafloxacin and Alatrofloxacin with a Non-Steroidal Anti-Inflammatory Drug in Mice Summary Study Report

Reviewed below

Toxicology Studies:

Single Dose Toxicity Studies:

Trovafloxacin:

Single Dose Oral and Intraperitoneal Toxicity Studies in Mice and Rats (91-783-14)

Alatrofloxacin:

Single Dose Intravenous Toxicity Studies in Mice and Rats (92-851-10)

Multiple Dose Acute Toxicity Studies:

Trovafloxacin:

14 Day Oral Gavage Exploratory Tolerant Study in Sprague-Dawley Rats at 0, 50, 100, or 200 mg/kg/day (91-783-06)

14 Day Oral Exploratory Tolerant Study in Beagle Dogs at 0, 12.5, 25, and 50 mg/kg/day (91-783-07)

Alatrofloxacin:

2 Week IV Exploratory Tolerant Study in Sprague-Dawley Rats (92-851-07)

Ten Day Intravenous Infusion Exploratory Tolerant Study in Beagle Dogs (92-851-08)

Subchronic/Chronic Toxicity Studies:

Trovafloxacin:

One Month Oral Toxicity Study in Beagle Dogs (91-783-09)

One Month Oral Toxicity Study in Sprague-Dawley Rats (91-738-10)

6 Month Gavage Study in Beagle Dogs (93-783-16)

6 Month Oral Gavage Study in Sprague-Dawley Rats (93-783-17)

Alatrofloxacin:

1 Month Intravenous Toxicity Study in Sprague-Dawley Rats at 6.5, 20, and 50 mg/kg (92-851-04)

1 Month Intravenous Toxicity Study in Beagle Dogs (92-851-05)

Special Toxicity Studies:

Trovafloxacin:

**Antigenicity Study in Guinea Pigs (94-01-81)
reviewed below**

Six Month Oral Gavage Reversibility Study in Beagle Dogs (94-783-23)

An Acute Phototoxicity Study in Balb/c Mice Dosed Orally (95-783-27)

**8-Week Oral (Gavage) Subchronic Study of CP-99,219-27 in Hairless Mice, With or Without Added Simulated Sunlight (C-516-001)
reviewed below**

**12-Month Oral (Gavage) Study to Determine the Influence of CP-99,219-27 on Photocarcinogenesis in Hairless Mice (C-516-002)
Protocol Only- Study has been completed and will be reviewed when Final Report is submitted**

Neonatal Study in Sprague-Dawley Rats (94-783-22)

Exploratory Neonatal Study in Sprague-Dawley Rats (95-783-28)

Exploratory Neonatal Study in Sprague-Dawley Rats (95-783-29)

APPROVED FOR RELEASE
BY [illegible]

Exploratory Neonatal Study in Sprague-Dawley Rats (95-783-30)
reviewed below

**A Two-Week Range Finding Study of CP-99,219-27 in Neonatal Beagle Dogs
94461)**
reviewed below

A Four-Week Oral Toxicity Study of CP-99,219 in Neonatal Beagle Dogs 94485)

**CP-395,013, CP-455,276, and CP-425,111-27 [Trovafloracin Mesylate (CP-99,219-27)
Impurities] Single Dose Oral Toxicity Study in Rats (96-1418-01)**

Alatrofloxacin:

Antigenicity Study in Guinea Pigs (94-27-81)

**A Single Dose Oral Toxicity Study in Rats and a Single Dose Dermal Toxicity Study in
Rabbits and a Single Dose Ocular Irritation Study in Rabbits (95-851-14)**
reviewed below

Reproductive Toxicity Studies:

Trovafloracin:

**Oral Fertility and Early Embryonic Development Study (Study I) in Sprague-Dawley
Rats (93-01-41)**

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Oral Maternal Toxicity Study in Sprague-Dawley Rats (93-01-51)

CP-99,219 Oral Teratology Study (Study III) in Sprague-Dawley Rats (93-01-52)
reviewed below

CP-99,219 Oral Maternal Toxicity Study in Japanese White Rabbits (93-01-71)

**CP-99,219 Oral Teratology Study (Study III) in Japanese White Rabbits (93-01-72/93-01-
91)**

Reproductive Study II: Prenatal and Postnatal Development in Sprague-Dawley Rats (94-783-18)

reviewed below

Alatrofloxacin:

Reproductive Study I: Fertility and Early Embryonic Development Intravenous Study in Sprague-Dawley Rats (95-851-16)

Maternal Range Finding Study in Sprague-Dawley Rats (95-27-52)

Teratology Study (Reproductive Study III) in Sprague-Dawley Rats (96-27-53)

Prenatal and Postnatal Development Study (Reproductive Study II) in Sprague-Dawley Rats (95-27-61)

Maternal Range Finding Study in Japanese White Rabbits (95-27-71)

Teratology Study (Reproductive Study III) in Japanese White Rabbits (96-27-72)

Mutagenicity Studies:

Genetic Toxicology Report CP-99,219-27 (90-783-02/90-783-03)

Genetic Toxicology Report CP-116,517-27 (91-851-02)

Pharmacokinetic Studies:

all reviewed below

Absorption:

Pharmacokinetics of Trovafloxacin in Sprague-Dawley Rats Following Single Intravenous Administration of Alatrofloxacin or Trovafloxacin and Single Oral Administration of Trovafloxacin (93-099219-4)

Pharmacokinetics of Trovafloxacin in Beagle Dogs Following Single Intravenous Administration of Alatrofloxacin or Trovafloxacin and Single Oral Administration of Trovafloxacin (93-099219-1)

Pharmacokinetics of Trovafloxacin in Cynomolgus Monkeys Following Single Intravenous Administration of Alatrofloxacin or Trovafloxacin and Single Oral Administration of Trovafloxacin (93-099219-2)

Pharmacokinetics of Trovafloxacin in New Zealand White Rabbits Following Single Intravenous or Oral Administration of Trovafloxacin (96-099219-4)

Protein Binding of Trovafloxacin:

Serum Protein Binding of Trovafloxacin in Rats, Rabbits, Dogs, Monkeys and Humans (92-099219-5)

Tissue Distribution:

Trovafloxacin:

Blood/Plasma Ratios of Trovafloxacin in Rats, Dogs, Monkeys and Humans (93-099219-3)

Distribution of [¹⁴C] Trovafloxacin into Gastric Tissue of Swiss-Webster Mice Following Intravenous Administration (94-099219-3)

Tissue Distribution of Trovafloxacin in Beagle Dogs Following Oral Administration of Multiple Doses (93-099219-5)

Whole-Body Autoradioluminography of Female and Male Long-Evans Rats After Single Intravenous Administration of [¹⁴C] Trovafloxacin (94-099219-1)

Whole-Body Autoradioluminography of Female and Male Long-Evans Rats After Single Oral Administration of [¹⁴C] Trovafloxacin (95-099219-1)

Alatrofloxacin:

Whole-Body Autoradioluminography of Female and Male Long-Evans Rats After Single Intravenous Administration of [¹⁴C] Alatrofloxacin (96-116517-2)

Metabolism and Excretion:

Trovafloxacin:

Identification of Trovafloxacin Metabolites in Human Bile Following Oral Administration of Trovafloxacin (96-099219-2)

Excretion and Metabolism of Trovafloxacin in Man (96-099219-1)

In Vitro Hydrolysis of CP-116,517 to CP-99,219 in Neonatal and Adult Rat, Guinea Pig, Dog, Monkey, and Human Serum (93-116517-1)

In Vitro Metabolism of [¹⁴C] Trovafloxacin by Rat and Human Liver Slices (94-099219-4)

Excretion and Metabolism of Trovafloxacin in Sprague-Dawley Rats (94-099219-2)

Excretion and Metabolism of Trovafloxacin in Beagle Dogs (94-099219-2)

Alatrofloxacin:

Metabolism and Excretion of Alatrofloxacin in Sprague-Dawley Rats (96-116517-1)

REVIEWS OF NONCLINICAL STUDIES:**PHARMACOLOGY STUDIES:****General Pharmacology of CP-99,219-27 (report summarizes several studies)**

A.A. Fossa (Department of General Pharmacology, Pfizer Central Research, Groton, CT)

Report dated 2/20/91

Vol.17, pp. 57-97

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Results from *In Vivo* Experiments: There were no differences in behavior or motor skills between vehicle-treated mice and those treated with up to 32 mg/kg of trovafloxacin. Doses of trovafloxacin between 100-1000 mg/kg were slightly sedating in undisturbed mice (ptosis, reduced locomotor activity, postural changes) and respiration appeared slower at 30-60 minutes after dosing. At 320 mg/kg, 2/3 mice were not able to right themselves on an inverted screen. Gait disturbances, reduced muscle tone, blanched skin and suppressed corneal reflex were observed at 1000 mg/kg, but no mortality occurred within a 24 hour observation period. For the comparator, ciprofloxacin, reduced locomotor activity was observed at 1000 mg/kg, but no other changes were seen at this, or lower doses.

Conscious fasted mongrel dogs were given oral 20 or 40 mg/kg doses of trovafloxacin. Electrocardiogram, heart rate and mean arterial blood pressure were measured prior to dosing and at various time points starting at the beginning of infusion until 240 minutes after infusion. Blood samples were drawn so that plasma concentrations of trovafloxacin could be determined. Emesis was observed in both dogs receiving 40 mg/kg of drug, and the investigators believed that this made them unsuitable for cardiac evaluation although they noted that "no remarkable cardiovascular effects were seen during periods when emesis was not occurring". "Licking of jowls" (said to be a sign of "abdominal discomfort") was seen in the dogs from the 20 mg/kg group, but only one female experienced emesis. This dog was not included in the data analysis of the remaining 5 animals (3 males, 2 females). Increases in heart rate (2-6 beats per minute) and cardiac contractility (manifested by decreased Q-A interval of approximately 6-9 msec, or about 8%) were observed up to 210 minutes after dosing without a concomitant increase in mean arterial pressure. These changes from the baseline values, although modest, were significantly ($p \leq 0.05$) different from current, as well as historical controls. The C_{max} for serum trovafloxacin in this study averaged $1.85 \pm 0.7 \mu\text{g/ml}$ and occurred 2 hours after dosing. The investigators believed that the true C_{max} is likely between 1 and 2 hours as the serum concentration of trovafloxacin 1 hour after dosing was 1.63 ± 0.89 . It should be noted that these plasma concentrations are likely to be below the projected human therapeutic concentration of about $3 \mu\text{g/ml}$.

When administered orally to fasted male Sprague-Dawley rats, trovafloxacin (10 or 20 mg/kg) did not have any effect on renal function as measured by volume of urine excreted or urine osmolarity. Additionally, urinary excretion of sodium, chloride, and potassium was not significantly different in control or trovafloxacin-treated rats.

Trovafloxacin (oral dose of 20 mg/kg) did not appear to affect respiratory function in

fed male rats (species not specified). Blood gas measurements (PO_2 , PCO_2) and pH of arterial blood drawn at 15 minute intervals up to 75 minutes after dosing did not change significantly from baseline levels in either trovafloxacin- or vehicle-treated rats.

The rate of gastric emptying was significantly ($p < 0.05$) decreased in fasted male Sprague-Dawley rats by trovafloxacin at doses of 10 mg/kg (37%) and 20 mg/kg (54%) compared to vehicle. The rate of gastric emptying was measured using a solution of sodium chromate (with ^{51}Cr) given to the animals via oral gavage 30 minutes after drug or vehicle administration. The distribution of radioactivity was assessed throughout the various segments of the GI tract. Doses of ciprofloxacin (5, 10, or 20 mg/kg) also reduced gastric emptying, but statistical significance was only reached at the highest dose which caused a 19% reduction.

Trovafloxacin (5, 20, and 40 mg/kg) did not affect gastric acid secretion in fasted male Sprague-Dawley rats. The positive control, 10 mg/kg of cimetidine, inhibited gastric acid secretion by 52%.

Results from *In Vitro* Experiments: The ability of trovafloxacin to compete with radiolabeled ligands for receptors in bovine brain was assessed. Concentrations of trovafloxacin up to 10 μM did not inhibit ligand binding to the following receptors: α_1 , α_2 , β , dopamine D_2 , Adenosine $_1$, 5HT $_{1A}$, 5HT $_2$, Histamine H_1 , Muscarinic, μ -Opiate, or GABA. Additionally, 20 μM trovafloxacin did not inhibit muscimol binding to the GABA receptor. Data obtained using ciprofloxacin were comparable.

Concentrations of trovafloxacin up to 10 μM did not alter norepinephrine-induced contractions of isolated guinea pig aorta.

Preincubation of isolated guinea pig ileum with 10 μM trovafloxacin for 30 minutes inhibited histamine (1 μM) induced contraction by about 52%. Concentrations of trovafloxacin $\leq 1 \mu M$ or ciprofloxacin up to 10 μM did not have this effect.

The rate of spontaneous beating of isolated guinea pig atrium can be increased by addition of histamine. Trovafloxacin at concentrations up to 10 μM did not alter histamine-induced chronotropic activity in isolated guinea pig atrium.

Trovafloxacin at concentrations up to 10 μM did not alter oxytocin-induced contractions in isolated rat uterus.

General Pharmacology of CP-116,517 (report summarizes several studies)

D.R. Knight (Department of General Pharmacology, Pfizer Central Research, Groton, CT)

Report dated 10/31/91

Vol. 17, pp. 98-111

Results: Conscious cynomolgus monkeys (*M. fascicularis*) were given 20 mg/kg of alatrofloxacin intravenously over a 30 minute period at a dose rate of 0.33 ml/min. Electrocardiogram, heart rate and mean arterial blood pressure were measured prior to dosing and at various time points starting at the beginning of infusion until 240 minutes after infusion. Blood samples were drawn so that plasma concentrations of alatrofloxacin and trovafloxacin could be determined. Emesis was not observed in any of the 5 subjects (3 males, 2 females),

although signs of nausea (salivation, excessive licking and mastication) were seen in one female 15-30 minutes after the start of the infusion. This dose caused emesis in 2/2 primates during a previous study when administered as an IV bolus. All of the animals showed reduced activity from the beginning of the infusion up to 90 minutes after the start. Decreases in mean arterial blood pressure (15-120 minutes after start of infusion) and heart rate (45 and 120 minutes after infusion) were observed in the alatrofloxacin-treated monkeys compared to control, but these changes were not significantly different from the baseline values. No changes in the Q-A intervals or electrocardiograms were seen. Alatrofloxacin blood levels were only detectable at the very end of the infusion ($2.97 \pm 0.28 \mu\text{g/ml}$). At the end of infusion, trovafloxacin serum concentrations averaged $17.7 \pm 2.4 \mu\text{g/ml}$.

The ability of alatrofloxacin to compete with radiolabeled ligands for receptors in bovine brain was assessed *in vitro*. Concentrations of up to $10 \mu\text{M}$ alatrofloxacin did not inhibit ligand binding to the following receptors: α_1 , α_2 , β , dopamine D_2 , Adenosine $_1$, 5HT $_{1A}$, 5HT $_2$, Histamine H_1 , Muscarinic, μ -Opiate, or GABA.

Interaction of Trovafloxacin and Alatrofloxacin with a Non-Steroidal Anti-Inflammatory Drug in Mice (summary report of study)

K. Yamanaka and F. Sawamura (Pharmacology Research Laboratory, Pfizer Pharmaceuticals, Inc., Aichi, Japan)

Not dated

Vol. 17, pp. 112-117

Results: Male mice (5 weeks old, , 5-7 animals per treatment group) were fasted for 14 hours, then dosed orally with one of the following quinolones in 0.3% carboxymethyl cellulose:

1. Trovafloxacin (100, 200, 500, 1000, 1500, or 2000 mg/kg)
2. Enoxacin (10, 25, 50, or 100 mg/kg)
3. Norfloxacin (50, 100, or 200 mg/kg)
4. Ciprofloxacin (100, 200, or 500 mg/kg)
5. Ofloxacin (1500 mg/kg)
6. Sparfloxacin (1500 mg/kg)
7. Tosufloxacin (1500 mg/kg)

After quinolone dosing, mice were given 100 mg/kg of biphenylacetic acid (BPAA, an active metabolite of fenbufen). Convulsions were not observed in mice treated with BPAA and vehicle (carboxymethyl cellulose). Convulsions were not observed in animals dosed with up to 500 mg/kg of trovafloxacin and BPAA, although writhing and piloerection were observed in 2/5 mice in the 500 mg/kg group. Doses of trovafloxacin $\geq 1000 \text{ mg/kg}$ and BPAA were associated with convulsions and death in 1/6 or 2/6 animals. Convulsions, usually followed by death, were observed in mice dosed with BPAA and enoxacin $\geq 50 \text{ mg/kg}$ (3/5 at 50 mg/kg and 5/5 at 100 mg/kg), 200 mg/kg norfloxacin (3/5), 500 mg/kg ciprofloxacin

(5/5), and 1500 mg/kg ofloxacin (2/5). Convulsions were not observed in the mice dosed with sparfloxacin or tosufloxacin followed by BPAA. Convulsions were not observed in the absence of BPAA when mice were orally dosed with up to 500 mg/kg of trovafloxacin, 100 mg/kg of enoxacin, or 200 mg/kg of norfloxacin. Sedation, ataxia, and trembling were observed at doses of trovafloxacin $\geq$ 1000 mg/kg, but convulsions were observed in only 1/6 mice at 1500 mg/kg.

Groups of 10 fasted mice (as above) were dosed intravenously with alatrofloxacin (5, 25, 50, or 75 mg/kg) or norfloxacin (10 or 25 mg/kg) in saline 1 hour after oral administration of 100 mg/kg BPAA. Another group was given norfloxacin without BPAA. Convulsions were not observed in any of the alatrofloxacin/BPAA-treated mice, although sedation and ataxia were noted. Convulsions were seen in 2/10 mice treated with BPAA and 10 mg/kg norfloxacin and 7/10 treated with BPAA and 25 mg/kg norfloxacin. In the absence of BPAA, these doses of norfloxacin did not cause convulsions in mice.

The combination of trovafloxacin with 100 mg/kg of BPAA did not enhance the convulsant activity of this quinolone in mice. For oral dosing, the rank order of potency for the quinolones tested in the presence of BPAA was enoxacin > norfloxacin > ciprofloxacin > ofloxacin > trovafloxacin > sparfloxacin, tosufloxacin. When both drugs were administered intravenously after dosing with BPAA, alatrofloxacin at doses up to 75 mg/kg did not cause convulsions in mice, but doses of norfloxacin $\geq$ 10 mg/kg did.

TOXICOLOGY STUDIES:

Special Toxicology:

Antigenicity Study in Guinea Pigs (Study No. 94-01-81)

H. Yamada (New Product Development Center, Pfizer Pharmaceuticals Inc., Japan)

Report dated 11/22/95, Japanese GLP

Vol. 21, pp. 299-322

Animals : Male Hartley guinea pigs, 5-8 weeks old, approximately 350-500 g, 5 per group

Diet: CG-7 Rodent Chow and water were supplied *ad libitum*.

Drug Dose, Route of Administration and Sensitization Procedure: CP-99,219 (trovafloxacin) was suspended in 0.5% methyl cellulose for oral administration or physiological saline for subcutaneous dosing. The trovafloxacin-BSA (bovine serum albumin) and trovafloxacin-OVA (ovalbumin) conjugates were suspended in physiological saline. Animals were sensitized orally or subcutaneously with trovafloxacin (conjugated or not) or BSA as follows:

1. 20 mg/kg trovafloxacin, oral
2. 100 mg/kg trovafloxacin, oral

3. Trovafloxacin plus Freund's Complete Adjuvant (FCA), 10 mg/animal, SC
4. Trovafloxacin-OVA conjugate plus FCA, 1 mg/animal, SC
5. Saline plus FCA, 0.5 ml/animal, SC
6. BSA plus FCA, 1 mg/animal, SC

Guinea pigs were sensitized by oral administration using a dosing schedule of 5 days per week for 3 weeks. Subcutaneous sensitization was accomplished by administering the agents specified above once a week for 4 weeks. Intravenous challenges of 1 mg trovafloxacin or 10 mg trovafloxacin-BSA were given to groups 1-5 19 days after the last oral sensitizing dose or 16 days after the final subcutaneous sensitizing dose. Group 5 (the negative control) was also challenged intravenously with physiological saline and Group 6 (the positive control) was challenged only with 1 mg of BSA. After challenge, the animals were observed for signs of systemic anaphylaxis. Two days prior to the challenge, blood samples were drawn from each of these guinea pigs for use in a passive cutaneous anaphylaxis (PCA) test.

For the latter test, 50 μ l of a series of diluted sera from the sensitized guinea pigs was injected intradermally into the clipped dorsal skin of a recipient untreated guinea pig. Four hours after injection, either trovafloxacin, trovafloxacin-BSA, saline, or BSA was given to the recipient animals intravenously with Evans blue dye. After 30 minutes, animals were exsanguinated and their skins removed so that the degree of dye extravasation could be measured.

Results: It should be noted that IV challenge with trovafloxacin alone caused 2-4 guinea pigs (from groups deemed not to have had anaphylactic reactions) to rub their nose or ears. The investigators called this an "anaphylactic-like sign", but did not consider that animals who demonstrated this behavior in the absence of other clinical signs or symptoms of anaphylaxis as having an anaphylactic reaction. As ear and nose rubbing was also seen in the negative control group, the reviewer suspects that this is a general reaction of guinea pigs to IV trovafloxacin and agrees that it probably not a symptom of even mild systemic anaphylaxis in this case. Systemic anaphylaxis following IV challenge with either trovafloxacin or trovafloxacin-BSA conjugate was not observed in either group of guinea pigs sensitized orally with trovafloxacin, in the animals sensitized with trovafloxacin and FCA subcutaneously, or in the negative control group. Of the guinea pigs sensitized subcutaneously with trovafloxacin-OVA conjugate and FCA, those challenged with IV trovafloxacin did not experience systemic anaphylaxis, but those challenged with IV trovafloxacin-BSA conjugate experienced fatal anaphylaxis. The positive control guinea pigs who were sensitized subcutaneously with BSA plus FCA all exhibited systemic anaphylaxis upon challenge with IV BSA. In that group, 2/5 animals had fatal reactions and the 3/5 had difficulty breathing that lead to cyanosis, but recovered.

Positive cutaneous anaphylaxis did not occur in recipient guinea pigs injected intradermally with serum from negative controls or guinea pigs that had been orally sensitized with trovafloxacin or subcutaneously with trovafloxacin plus FCA. If recipients were injected with serum from animals sensitized with trovafloxacin-OVA, no positive PCA reactions were observed if they were challenged with trovafloxacin alone. Positive PCA reactions were seen in recipients injected intradermally with this serum if trovafloxacin-BSA was used as the challenge agent and PCA titers were . As expected, when recipients were

injected with serum from animals sensitized subcutaneously to BSA with FCA, all exhibited positive PCA reactions with titers of .

Unconjugated trovafloxacin was not antigenic in guinea pigs under the conditions of this assay.

8-Week Oral (Gavage) Subchronic Study of CP-99,219-27 in Hairless Mice, With or Without Added Simulated Sunlight Protocol No. C-516-001)

Report dated 3/6/96, U.S. GLP

Vol. 22, pp. 1-198

Animals: Male and female Crl:SKH1-hr BR hairless mice, approximately 7 weeks old at the initiation of the study. Gold fluorescent lighting (F40GO) was used in the rooms where mice were housed and exposed to UV to prevent the animals from being exposed to light radiation that could interfere with the study. Each treatment group had 10 mice/sex with an additional 27 mice/sex/group for pharmacokinetic studies of groups 3, 6, and 9-12 and an additional 6 mice/sex/group for pharmacokinetic studies of groups 2 and 8.

Diet: Certified Rodent Diet #5002 and tap water purified via reverse osmosis and chlorinated were available *ad libitum* except during UV exposure periods.

Drug Dose and Route of Administration: CP-99,219-27 (trovafloxacin mesylate) was suspended in 0.5% carboxymethyl cellulose and administered to mice orally via gavage at dose levels of 0 (vehicle control), 30, 100, 200, or 300 mg/kg/day, 5 days a week (Monday-Friday) at a dose volume of 10 ml/kg. The order of administration of drug and UV exposure was rotated. On Monday, Wednesday and Friday, UV exposure occurred one hour after dosing and on Tuesday and Thursday, drug was administered one hour after UV exposure. Treatment groups were as follows:

	Drug Treatment (mg/kg/day)	Daily UV Exposure (Robertson-Berger Units)
1.	None	0
2.	Vehicle	0
3.	Trovafloxacin, 30	0
4.	Trovafloxacin, 100	0
5.	Trovafloxacin, 200	0
6.	Trovafloxacin, 300	0
7.	None	120
8.	Vehicle	120
9.	Trovafloxacin, 30	120
10.	Trovafloxacin, 100	120
11.	Trovafloxacin, 200	120

12. Trovafloxacin, 300 120

The UV source was a 6.5 KW xenon long arc water cooled burner with a 1 mm thick filter of _____ to absorb UVC (≤ 290 nm)- both UVB and UVA were emitted. The dose of UV used in this study was equivalent to 0.3 times the human minimal erythemal dose in untanned human skin (400 Robertson-Berger Units). UV exposure was monitored throughout the study using Robertson-Berger meters mounted on animal racks.

Length of Study: Treatment with drug and/or UV occurred 5 days/week (Monday-Friday) for 8 weeks.

Results: Mortality was greater than controls in mice receiving 100-300 mg/kg of trovafloxacin. No drug related deaths were observed at 30 mg/kg. The numbers below include deaths or moribund sacrifices believed to be drug-related and not those confirmed to be due to intubation accidents. Most of the drug-related mortality was seen in the first 2 weeks of the study. Data from both genders were combined because there appeared to be no difference between the two. Mortality at these dose levels was also observed in mice from the satellite groups, but they are not included here as the satellite animals were not part of the phototoxicity study, but a separate pharmacokinetic study.

	-UV	+UV	Total
100 mg/kg	3/20	1/20	4/40
200 mg/kg	5/20	3/20	8/40
300 mg/kg	6/20	2/20	8/40

The following intubation accidents were confirmed:

	-UV	+UV
Vehicle	2	
30 mg/kg	1	
100 mg/kg	2	
200 mg/kg		1

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Necropsy findings from the mice that died on study (death attributed to drug) in the 200 or 300 mg/kg groups included sand-like substance in the cecum, red cecum, dark (brown or black) areas of erosion in fundic mucosa of stomach, hole in the fundic mucosa of stomach, red-brown substance in the stomach, red substance between mucosal layers of cardiac region of stomach, red fundic mucosa of stomach. Another finding observed in the 200 and 300 mg/kg rats, a red or tan to dark brown perianal substance, was also seen in a mouse from the 100 mg/kg group that died on study.

During weeks 1-2 of the study, body weight loss in the 100, 200 and 300 mg/kg male and female mice was significantly ($p \leq 0.05$) greater than controls for the groups without UV exposure. For the groups with UV exposure, body weight loss was significantly less than controls during weeks 1-2 only in the 200 and 300 mg/kg male mice and the 300 mg/kg female mice (2.7 g). The

mean terminal body weight for the male mice in the 300 mg/kg group exposed to UV was significantly less than vehicle control at termination (35.2 ± 2.0 g vs. 31.6 ± 1.7 g). For the 300 mg/kg males not treated with UV, mean terminal body weight was also less than vehicle control (34.7 ± 2.6 g vs. 32.5 ± 3.7 g), but the difference was not statistically significant. Mean terminal body weights of female mice were comparable among all of the treatment groups.

With the exception of Grade 1 flaking ("barely perceptible scales) noted during week 1 in a single 300 mg/kg female mouse not exposed to UV, no skin reactions were observed during the study. Trovafloxacin in the presence of simulated sunlight was not phototoxic to hairless mice at doses up to 300 mg/kg for approximately 8 weeks. Trovafloxacin-related mortality was observed at doses ≥ 100 mg/kg.

Serum Concentrations and Pharmacokinetics of CP-99,219 Following Oral Administration of CP-99,219 to Mice During Toxicology Study C-516-001 (Appendix C)

Results: Trovafloxacin concentrations were measured in the serum and skin of satellite groups of hairless mice from the phototoxicity study above. Groups of 3/sex per time point were sacrificed at each time point on study days 3 and 33. Concentrations of trovafloxacin in the serum and skin were measured using a validated

As there were no apparent gender differences, data from male and female animals were combined.

Concentration of Trovafloxacin ($\mu\text{g/ml}$) in Serum of Hairless Mice After Oral Administration on Day 3 of Dosing (Mean $\pm$ SD)

Drug Dose (mg/kg)	Predose	Time After Dosing			AUC (0-2) $\mu\text{g}\cdot\text{hr/ml}$
		1 hr	2 hrs	4 hrs	
No UV					
30	BLQ*	9.1 ± 2.6	4.7 ± 1.6	2.8 ± 1.2	6.9
300	5.0 ± 1.4	23.8 ± 9.9	21.5 ± 12.2	20.2 ± 5.6	37.1
+UV					
30	BLQ	6.5 ± 2.0	6.0 ± 3.9	3.1 ± 1.4	6.3
100	0.7 ± 0.7	15.0 ± 2.0	10.0 ± 4.7	7.8 ± 2.3	20.4
200	6.0 ± 7.0	22.4 ± 7.3	15.7 ± 4.5	12.3 ± 8.3	33.3
300	8.0 ± 4.4	30.3 ± 9.5	23.0 ± 11.8	15.3 ± 7.1	45.8

*Below limit of quantification

**Concentration of Trovafloxacin ($\mu\text{g/ml}$) in Serum of Hairless Mice
After Oral Administration on Day 33 of Dosing (Mean $\pm$ SD)**

Drug Dose (mg/kg)	Predose	Time After Dosing		AUC (0-2) $\mu\text{g}\cdot\text{hr/ml}$
		1 hr	2 hrs	
No UV				
30	0.1 $\pm$ 0.1	7.3 $\pm$ 1.3	5.2 $\pm$ 1.4	10.0
300	4.0 $\pm$ 1.3	29.5 $\pm$ 6.2	33.4 $\pm$ 5.0	48.2
+UV				
30	BLQ*	7.3 $\pm$ 2.9	3.2 $\pm$ 1.0	5.3
100	0.3 $\pm$ 0.6	14.6 $\pm$ 3.7	9.6 $\pm$ 7.4	19.6
200	2.3 $\pm$ 1.2	19.8 $\pm$ 4.8	22.5 $\pm$ 12.3	32.2
300	7.1 $\pm$ 7.1	28.8 $\pm$ 7.4	19.9 $\pm$ 8.6	42.3

*Below limit of quantification

**Concentration of Trovafloxacin ($\mu\text{g/g}$) in Skin of Hairless Mice After Oral
Administration After 3 or 33 Days of Dosing (Mean $\pm$ SD)**

Drug Dose (mg/kg)	Day 3			Day 33		
	1 hr	2 hrs	AUC (0-2) $\mu\text{g}\cdot\text{hr/g}$	1 hr	2 hrs	AUC (0-2) $\mu\text{g}\cdot\text{hr/g}$
No UV						
30	5.2 $\pm$ 0.7	4.2 $\pm$ 0.9	7.3	5.9 $\pm$ 0.8	5.1 $\pm$ 0.3	8.5
300	17.3 $\pm$ 2.9	14.9 $\pm$ 3.9	24.8	22.3 $\pm$ 2.7	20.7 $\pm$ 4.2	32.7
+ UV						
30	4.3 $\pm$ 0.8	4.1 $\pm$ 2.0	6.4	6.4 $\pm$ 1.5	4.3 $\pm$ 0.8	8.6
100	9.9 $\pm$ 1.1	10.3 $\pm$ 6.9	15.1	10.9 $\pm$ 2.3	8.4 $\pm$ 3.4	15.1
200	15.1 $\pm$ 2.5	13.5 $\pm$ 4.6	21.9	19.9 $\pm$ 5.1	16.1 $\pm$ 8.3	28.0
300	19.4 $\pm$ 2.0	18.3 $\pm$ 9.2	28.6	16.4 $\pm$ 3.1	19.3 $\pm$ 5.5	26.1

Serum and skin levels of trovafloxacin increased with dose in hairless mice. At the sampling times of 1 and 2 hours after administration, there was usually more drug in serum than in skin. The skin/serum C_{max} ratios on day 3 ranged from _____ and those on day 33 ranged from _____. The skin/serum AUC_{0-2 hr} ratios determined on day 3 ranged from _____ and those on day 33 ranged from _____. Exposure to UV radiation did not appear to have an effect on the serum or skin levels of trovafloxacin.

CP-99,219-27 Exploratory Neonatal Study in Sprague-Dawley Rats Dose Levels: 3, 6, 12, or 25 mg/kg (Study No. 95-783-30)

M.S. Tassinari (Reproductive and Developmental Toxicology, Pfizer, Groton, CT)

Report not dated, Not GLP

Vol. 25, pp. 1-17

Animals: Timed pregnant female Sprague-Dawley rats were received on day 16 of gestation. Eight littered on the same day and their offspring were used for the study. Viable pups were weighed and sexed on postnatal day 1 and randomly distributed among the dams to form litters of 5 per sex containing no more than one male and one female pup that had come from the same original litter. Each dose group had 2 litters.

Diet: Dam's diet not specified; neonates consume dam's milk only.

Drug Dose and Route of Administration: Trovafloxacin was administered once daily to neonates via oral gavage (vehicle was 0.5% methylcellulose) at doses of 3, 6, 12, or 25 mg/kg. Dams were not treated with drug.

Length of Study: Pups were treated with drug on postnatal days 4-7. Pups were bled 0.5, 1, or 2 hours after the last dose for determination of serum trovafloxacin. Brains were harvested from the pups at the same time, also for measurement of drug. The method for determining the serum and brain levels of trovafloxacin was not included in this report.

Results: The purpose of the study was to find the NOEL for tremors in neonate rats dosed with trovafloxacin. Intermittent whole body tremors were observed in pups treated with 25 mg/kg trovafloxacin beginning 1-2 hours after dosing. Tremors were no longer observed in most of these pups 6 hours after administration of the drug. Tremors were not observed in any of the pups from the 3, 6, or 12 mg/kg dose groups.

Trovafloxacin was found in the brains of the pups and the mean brain/serum ratios were 0.8 at C_{max} and 0.8 for AUC. Both serum and brain levels of trovafloxacin were relatively constant over the sampling period within each dose level. Concentrations of trovafloxacin in serum and brain increased in a dose-dependent manner that was close to linear.

**Serum Levels of Trovafloxacin ($\mu\text{g/ml}$) in Neonatal Rats
After 4 Daily Doses (Mean $\pm$ SD)**

Dose (mg/kg)	Time After Dosing (hours)			AUC (0-2) $\mu\text{g}\cdot\text{hr/ml}$
	0.5	1.0	2.0	
3	0.7 $\pm$ 0.3	0.6 $\pm$ 0.2	0.9 $\pm$ 0.2	1.3
6	1.6 $\pm$ 0.1	1.6 $\pm$ 0.2	1.5 $\pm$ 0.6	2.8
12	4.0 $\pm$ 1.3	4.0 $\pm$ 1.6	4.0 $\pm$ 0.5	7.0
25	7.9 $\pm$ 1.3	7.4 $\pm$ 1.7	7.3 $\pm$ 1.1	13.2

Brain Levels of Trovafloxacin ($\mu\text{g/g}$) in Neonatal Rats After 4 Daily Doses (Mean $\pm$ SD)

Dose (mg/kg)	Time After Dosing (hours)			AUC (0-2) $\mu\text{g}\cdot\text{hr/g}$
	0.5	1.0	2.0	
3	0.5 $\pm$ 0.3	0.7 $\pm$ 0.2	0.6 $\pm$ 0.3	1.1
6	1.0 $\pm$ 0.2	1.2 $\pm$ 0.3	1.1 $\pm$ 0.4	2.0
12	2.1 $\pm$ 0.5	3.4 $\pm$ 1.2	2.8 $\pm$ 0.5	5.0
25	4.8 $\pm$ 1.1	6.3 $\pm$ 1.5	5.1 $\pm$ 1.2	9.7

Tremors in neonatal rats were observed after dosing with 25 mg/kg of trovafloxacin, but not 12 mg/kg; thus the threshold dose is somewhere between. The investigators mentioned that tremors were observed sporadically in neonatal rats dosed with 15 mg/kg for an earlier study; this is consistent with the results observed in the current study. The earlier study also demonstrated that rat pups more than 22 days old were not as sensitive as younger pups to the induction of tremors and their brain tissue had lower levels of trovafloxacin than younger pups given the same oral dose. The investigators believe that the blood brain barriers were more developed in the older pups; this is a reasonable assumption. In the current study conducted on 3-7 day old rat pups, brain levels of trovafloxacin $\leq 3.4 \mu\text{g/g}$ were not associated with tremors, but brain levels of trovafloxacin $> 4.8 \mu\text{g/g}$ were. These toxicokinetic data were consistent with previous studies in rat pups.

A Two-Week Range Finding Study of CP -99,219-27 in Neonatal Beagle Dogs Dose Levels 7.5, 15.0 (7.5 BID), 50.0 (25 BID) mg/kg/day (Study No. 94461)

Report dated 3/22/95, U.S. GLP

Vol. 25, pp. 18-102

Animals: Neonatal beagle pups were selected for the study within 48 hours of birth and two per sex were assigned to treatment groups in a fashion to ensure that litter mates were not assigned to the same group. It was not clear whether one dam nursed all 4 members of a treatment group.

Diet: Pups nursed their mothers *ad libitum* except for one hour before dosing. A milk replacement was given to pups that were not nursing adequately. One pup in the 15 mg/kg group was fed milk replacer for one day, and all 4 pups in the 50 mg/kg group were fed the replacer for 1, 4 (2 pups) or 7 days between days 4-11 of the study. The dams were given certified and tap water *ad libitum*.

Drug Dose and Route of Administration: Trovafloxacin was suspended in 0.5% methyl cellulose at concentrations of 1.5 and 5 mg/ml and administered orally via gavage at a dose volume of 5 ml/kg. Pups were removed from their mothers one hour prior to dosing, then returned after the dose of drug was administered. Dose groups were as follows:

1. Control (vehicle, 5 ml/kg b.i.d.)
2. 7.5 mg/kg/day
3. 15 mg/kg/day (7.5 mg/kg b.i.d., 4 hours apart)
4. 50 mg/kg/day (25 mg/kg b.i.d., 4 hours apart)

Length of Study: The duration of dosing was 15, 18, or 21 days. Dosing began on the same day for all animals and continued until an animal was sacrificed. Members of one dose group were not all sacrificed on the same day. For toxicokinetic analysis, blood samples were drawn 1, 4, and 12 hours after the first and last doses of drug.

Results: None of the 50 mg/kg pups survived for the entire study. They were sacrificed in moribund condition on days 5-10 of dosing. The 50 mg/kg pups did not nurse and were hand fed a milk replacer, but they had diarrhea and became dehydrated. Emesis was seen in 2 of the high dose pups. All of the high dose pups were less active than those from the other dose groups and one was described as "lethargic" for 2 days prior to sacrifice. One female in the 15 mg/kg group experienced excessive salivation on day 5 of dosing and had some difficulty breathing on days 5 and 6 of dosing. One female in the control group died from a gavage accident on day 14 of dosing. Soft to watery feces were sporadically observed in pups from the 7.5 and 15 mg/kg groups on days 12-18 of dosing. The investigators described the change in fecal consistency as "not unusual for colony dogs at this age", but none of the control animals had soft or watery feces, so it may have been a drug-related effect.

Body weight gain in animals treated with 7.5 mg/kg of trovafloxacin did not appear to be different from control, but it was modestly suppressed in the 15 mg/kg group and severely suppressed in the 50 mg/kg group.

Treatment of beagle neonates with up to 15 mg/kg trovafloxacin did not appear to affect the attainment of developmental landmarks such as eye and ear opening. As the scheduled sacrifices of the surviving animals began around the time that the pups leave the

pack and tooth eruption occurs, some were sacrificed before these landmarks had been attained. However, there appeared to be no sign of developmental delay at doses of trovafloxacin up to 15 mg/kg/day.

Drug-related changes in hematologic and clinical chemistry parameters were not observed at doses of trovafloxacin up to 15 mg/kg/day. A drop in the number of white blood cells was observed in one male and one female dog in the high dose group at the time of sacrifice. A drop in the number of red blood cells was observed in all of the dogs in the high dose group when they were sacrificed, especially the two females. One high dose female dog also had a very low number of platelets. As these dogs were malnourished and in poor condition at the time of sacrifice, it is difficult to determine whether these changes were due to drug or were secondary to the drug-related lack of nourishment.

No drug-related gross or microscopic findings were observed in the dogs dosed with 75 or 15 mg/kg of trovafloxacin. Absolute organ weights tended to be lower than control in both of these groups; but relative organ weights were similar. Microscopic findings in the tissues of the pups from the 50 mg/kg dose group did not appear to be directly related to drug treatment, but were consistent with malnutrition. These findings included reduced glycogen stores in hepatocytes, depletion of hematopoietic stem cells in marrow of rib, sternum and femur, lymphoid depletion of tonsil, thymus, and spleen, and reduced bone growth (including reduction in size or number of osteoblasts in rib, sternum, femur, humerus) It is difficult to determine whether vacuolar changes in the lenticular fibers of the eye observed in 3/4 50 mg/kg pups were related to trovafloxacin dosing or to the milk replacement given from 4-7 days. The pup in this dose group that received only one day of milk replacer was the one who did not exhibit changes in the eye. Some quinolones have been associated with cataracts in dogs, but subcapsular cataracts have also been associated with milk replacers in orphaned puppies, perhaps due to a nutritional deficiency that has not been definitively identified. Finally, fungal infection of the GI mucosa was observed in one high dose female.

Concentrations of trovafloxacin in serum collected on the first and last days of dosing were measured. On study day 1, the $AUC_{0-12\text{ hr}}$ increased in a close to linear fashion in accordance with the total daily dose. There is evidence of drug accumulation at 15 mg/kg/day.

**Serum Concentrations ($\mu\text{g/ml}$) of Trovafloxacin in Beagles
After the First and Last Doses (Mean $\pm$ SD)**

	7.5 mg/kg	15 mg/kg	50 mg/kg
First Dose			
1.0 hours	1.4 + 0.5	1.2 + 0.9	4.2 + 1.2
4.0 hours	1.1 + 0.5	1.4 + 0.4	3.7 + 1.3
12.0 hours	0.7 + 0.4	1.7 + 0.5	5.2 + 1.9
$AUC_{0-12\text{ h}}$ ($\mu\text{g}\cdot\text{hr/ml}$)	11.6 + 4.8	16.7 + 3.5	49.6 + 10.7

Last Dose			
1.0 hours	1.4 + 0.9	3.1 + 1.1	---
4.0 hours	1.2 + 0.7	2.2 + 0.5	---
12.0 hours	0.6 + 0.4	1.9 + 0.4	---
AUC_{0-12 h} (µg·hr/ml)	12.0 + 7.6	25.9 + 3.3	---

Pharmacokinetic data not available for the last day of dosing of the 15 mg/kg animals as all were sacrificed in moribund condition.

Neonatal beagle pups tolerated up to 15 mg/kg (7.5 mg/kg, b.i.d.) of trovafloxacin for 15-21 days with minimal signs of toxicity (slight suppression of body weight gain, 2 episodes of difficult respiration in one animal), but 50 mg/kg (25 mg/kg, b.i.d.) was very toxic. None of the neonatal beagles dosed with 50 mg/kg survived past day 10 and signs of malnourishment secondary to a drug-related failure to nurse were seen in all animals from this dose group. Feeding a milk replacer to the pups failed to prevent the malnourishment.

CP-116,517-27 A Single Dose Oral Toxicity Study in Rats, and A Single Dose Dermal Toxicity Study in Rabbits, and A Single Dose Ocular Irritation Study in Rabbits (Hazard Assessment Testing) (Study No. 95-851-14)

N.J. Johnson (Pfizer Central Research, Groton, CT)

APPROPRIATE WAY
ON ORIGINAL

Report dated 10/9/95, U.S. GLP

Vol. 26, pp. 34-49

Summary and Results: Studies were designed according to U.S. Department of Transportation guidelines so that hazard classification could be designated.

For the oral dosing study, alatrofloxacin was dissolved in deionized water at a concentration of 100 mg/ml and a single dose (2000 mg/kg, 20 ml/kg) was given to 3 male and 3 female Crl:CD BR, VAF/Plus rats. One female rat died on day 3 after dosing. Before death, it was cold to the touch, appeared weak, vocalized when handled, had decreased respiration rate, soft stool, and exhibited slight pilomotor erection. The remaining 5/6 rats survived for the entire 14 day post dose observation period. One showed no clinical symptoms after dosing, the others showed decreased activity. No gross tissue changes were observed upon necropsy.

For the dermal study, 2000 mg of alatrofloxacin powder was applied to intact skin of 4 male and 1 female New Zealand White rabbits and placed under an occluded dressing for 24 hours. Skin was premoistened with normal saline. None of the animals died during the 14 day observation period following the application of the test material and no clinical signs of toxicity were observed with the exception of reduced food consumption and a concomitant reduction in the size and number of fecal pellets. Very slight erythema was observed on the

skin of 2/5 rabbits after the 24 hour drug exposure period, but this resolved completely by the next day and no other skin changes were seen throughout the remainder of the study.

For the eye irritation study, 20.1 mg of alatrofloxacin powder was applied to the conjunctival sacs of the left eyes of 1 male and 2 female New Zealand White rabbits. The eyes were not rinsed after application and the animals were observed for 4 days. Eyes were observed 1, 5, and 24, 48, and 72 hours after dosing. None of the eyes exhibited corneal opacity or iritis at any time up to 4 days after alatrofloxacin powder was applied. Slight redness of the palpebral conjunctiva, slight chemosis, and a moderate amount of a clear, colorless discharge were observed in all eyes 1 and 5 hours after application of alatrofloxacin powder. Twenty-four hours after dosing, only a slight redness of the palpebral conjunctiva was observed in the treated eyes. All eyes were normal by 72 hours after dosing.

Alatrofloxacin is not poisonous, corrosive, or an eye irritant according to DOT guidelines.

Reproduction Studies:

CP-99,219-27 Oral Teratology Study (Study III) in Sprague-Dawley Rats Dose Levels 5, 15 and 75 mg/kg/day (Study No. 93-01-52)

M. Horimoto (New Product Development Center, Pfizer Pharmaceuticals, Inc., Aichi, Japan)

Report dated 1/28/94, Japanese GLP

Vol. 26, pp. 158-202

Animals: Female Sprague-Dawley Rats (177-218 g on the first day of mating) were mated with males of the same strain (319-359 g on the first day of mating); group assignments made after females were sperm-positive so that each treatment group would have a similar mean body weight. Rats were approximately 10 weeks old at the initiation of the mating period. Each treatment group had 20 females. Males were mated with more than one female, as there were a total of 40 males available for the study. The report does not specify which male was mated to a particular female.

Diet: Pelleted commercial laboratory animal chow and tap water were provided *ad libitum*.

Drug Dose and Route of Administration: CP-99,219-27 (trovafloxacin mesylate) was suspended in 0.5% aqueous methyl cellulose and administered via oral gavage once daily for 12 days (days 6-17 of gestation) to sperm-positive, presumed pregnant female rats at a dose volume of 20 ml/kg. Treatment groups were as follows:

1. Vehicle control
2. 5 mg/kg
3. 15 mg/kg
4. 75 mg/kg

Length of Study: Presumed pregnant females were treated from days 6-17 of gestation and the rats assigned to the reproductive toxicity study groups were sacrificed on day 21. Half of the fetuses were fixed in Bouin's solution and examined for visceral malformations after sections were cut with a razor blade. The other half were stained with alizarin red S and examined for skeletal development and malformations.

Results: None of the dams died during the course of the study and no overt clinical signs of toxicity were observed. One of the rats in the 5 mg/kg group was not pregnant. Mean food consumption and body weights were similar for control and treated groups of dams. Necropsy did not reveal any gross drug-related changes in the dams.

The number of corpora lutea per dam did not differ among the treatment groups, nor would one expect it to since drug treatment did not commence until day 6 of gestation. Dosing pregnant female rats with up to 75 mg/kg of trovafloxacin did not appear to have a biologically significant effect on preimplantation or postimplantation loss.

The mean number of live fetuses per litter did not differ significantly among the treatment groups and mean fetal and placental weights were similar. Trovafloxacin-related external or visceral abnormalities were not observed at dose levels up to 75 mg/kg. An increased incidence of fetuses with skeletal variations (presence of cervical rib and/or shortened 13th rib) was observed in the 75 mg/kg dose group. Additionally, the percentage of fetuses in the 75 mg/kg group with rudimentary 5th sternebra was significantly greater than control ($p < 0.001$, 54.8% vs. 9.2%). An increase in the percentage of fetuses with rudimentary 5th sternebra was also observed at 15 mg/kg (15.6%), and this was suggestive of a dose-response relationship although the increase was not statistically significant. The number of ossified caudal vertebrae and right and left phalanges was significantly ($p < 0.001$) reduced in the 75 mg/kg group compared to control and the number of ossified caudal vertebrae was slightly, but significantly ($p < 0.05$) reduced in the 15 mg/kg fetuses (control: 8.7 ± 0.7 , 15 mg/kg: 8.2 ± 0.7 , 75 mg/kg: 7.0 ± 0.9). The skeletal effects seen at 75 mg/kg are consistent with the increase in variations observed in other rat teratology studies with trovafloxacin or alatrofloxacin.

The NOEL for dams in this study was 75 mg/kg and the NOEL for fetuses was 7.5 mg/kg. It is difficult to dismiss the findings of delayed ossification at 15 mg/kg, although they are slight, due to the apparent dose-response relationship for the number of fetuses with rudimentary 5th sternebra and the reduction in the number of ossified caudal vertebrae. The reviewer believes that the skeletal variations seen in the fetuses at 75 mg/kg demonstrate evidence of teratogenicity.

CP-99,219-27 Reproductive Study II Prenatal and Postnatal Development in Sprague-Dawley Rats Dose Levels 5, 15 and 75 mg/kg/day (Study No. 94-783-18)

W.P. Weisenburger (Pfizer Central Research, Groton, CT)

Report dated 11/27/95, U.S. GLP

Vol. 27, pp. 1-308

Animals: Timed pregnant Sprague-Dawley rats were obtained on gestation day 3 and randomly assigned to treatment groups so that similar mean body weights were achieved at the start of the study. The first 20 females per dose group to litter were used for the study.

Diet: certified rodent diet and tap water purified via reverse osmosis were provided *ad libitum*.

Drug Dose and Route of Administration: CP-99,219-27 (trovafloxacin mesylate) was suspended in 0.5% aqueous methyl cellulose and administered via oral gavage once daily from day 6 of gestation to lactation day 21 at a dose volume of 10 ml/kg. Treatment groups were as follows:

1. Vehicle control
2. 5 mg/kg
3. 15 mg/kg
4. 75 mg/kg

Length of Study: Presumed pregnant females were treated from gestation day 6 to lactation day 21 (as applicable). In order for a litter to continue in the study, on lactation day 4 it had to contain at least 7 pups, with at least 2 pups of each sex. Those not meeting these criteria were sacrificed. Litters containing more than 8 live pups were culled to 8 on lactation day 4 by randomly selecting 4 males and 4 females. Dams completing the study were sacrificed on lactation day 21. At this time, 2 pups per sex per litter was randomly chosen for more behavioral and developmental testing. Of these pups, one male and one female from each litter also underwent reproductive testing.

Results: One dam in the 75 mg/kg group died on gestational day 24 as a result of dystocia. No other dams died during the study, although dystocia was observed in 4 other dams in the 75 mg/kg group. Postpartal pup mortality (deaths during lactation days 1-4) was high in these litters and none met the minimum criteria for numbers of pups, so they did not continue on study after day 4 of lactation. Salivation was observed sporadically in one dam from the 75 mg/kg group during the treatment period.

No treatment-related effects on body weight gain were observed in the dams during gestation or lactation. Additionally, no effects on food consumption were observed. Necropsy did not reveal any gross changes in the F0 dams attributable to trovafloxacin.

The number of implantation sites was similar among treatment groups, as was the number of pups born per litter. Compared to control, the number pups born alive was reduced in the 75 mg/kg dose group (12.8 ± 2.2 vs. 12.3 ± 2.3) with a concomitant increase in the number born dead (0.1 ± 0.2 vs. 1.5 ± 1.5). The mean length of gestation was significantly ($p \leq 0.05$) increased in the treated dams (5 mg/kg: 21.45 ± 0.60 d, 15 mg/kg: 21.85 ± 0.41 d, 75 mg/kg: 21.94 ± 0.54 d) compared to control (20.95 ± 0.51).

Although an increase in early mortality was apparent in the 75 mg/kg group, the number of pups surviving until lactation day 21 was not different from control in the dams from this group that met the criteria for minimum numbers of pups and continued in the study after culling of the litters to 8 pups on day 4. Mean body weights of the female pups from the

75 mg/kg group were slightly, but significantly ($p < 0.05$) less than control from days 4-14 of lactation; the investigators believed that the effect was likely treatment-related. Trend analysis did not reveal any significant differences in the results of the preweaning developmental indices righting reflex (on a surface or in the air) and visual cliff avoidance. Eye opening occurred earlier than control in the 15 and 75 mg/kg male and female pups and eruption of incisors occurred earlier in female pups from these dose groups. In each case, however, the difference between treated and control animals was less than one day. Trend analysis did not reveal any significant differences between treatment groups for data collected on two pups per sex per litter on postnatal day 21 as part of a "Functional Observation Battery" with the exception of a slightly increased reaction to tail pinch in 75 mg/kg females. The "Functional Observation Battery" for the pups included ease of removal from cage, reaction to handling, rearing (in open field), arousal (level of unprovoked activity in open field), defecation frequency (in open field), urination frequency (in open field), approach response (reaction to placing blunt object approximately 3 cm away from animal's face after open field observation), touch response (approach animal from side and touch rump gently with blunt object), click response (use clicker to make sudden sound approximately 5 cm above the back of the animal), tail pinch response, corneal reflexes, reaction of pupil to light, extensor thrust (animal in supine position pushes with its hind feet in response to pressure from observer's hand), and body temperature. The time to vaginal opening did not differ among the treatment groups, but the time to preputial separation was reduced by about 1.2 days in the 75 mg/kg group. The reductions of time to preputial separation and those observed for eye opening and tooth eruption mentioned above may be related to the delay in parturition, making these animals developmentally older at birth. All pups passed an auditory function test (startle or Preyer response to Galton whistle) administered on postnatal day 30. Examination of pups with an ophthalmoscope during postnatal days 21-28 revealed no evidence of treatment-related anomaly. Motor activity (monitored using a video-based system) on postnatal day 23 did not differ between the treatment groups. Learning and memory were tested using a passive avoidance chamber or the Cincinnati Water Maze (1 pup per sex for each of these tests). Passive avoidance testing (latency period before animals cross into a darkened chamber to avoid an unpleasant stimulus) on postnatal days 63-70 revealed no significantly different trends between the groups. Trials in the Cincinnati Water Maze conducted on postnatal days 55-65 showed no significant differences between the treatment groups for the mean number of errors (either total or per individual trial) when either Path A or Path B was used. There was no significant difference in trial latency for the males, but there was a statistically significant increase in the latency for females of the 75 mg/kg group in the last 2 trials using Path B (more complex than Path A). In the absence of an increased number of errors and because the total latency time for the combined trials for each path did not differ between the control and 75 mg/kg female pups, the increased latency period for the last 2 Path B trials in the high dose female pups does not appear to be toxicologically significant.

The mating index was similar among treatment groups, but the percentage of females that were pregnant was less in the 75 mg/kg group than control. It appears unlikely that the reduced pregnancy rate was really drug-related as a similar study with intravenously administered alatrofloxacin showed no evidence of impairment of fertility in F1 offspring at 50 mg/kg. There appeared to be no differences between control and drug treated F1 rats for parameters such as length of gestation, number of implantation sites, and numbers of live and

dead pups born. Mean pup weights did not differ between litters of control or drug-treated F1 dams. The litter size was similar between groups as were the percentages of viable offspring on postnatal day 4 and at weaning time. No drug-related external or visceral malformations were observed in the F2 pups during a gross necropsy (includes stillborn pups, those culled on day 4, any that died during the study, and those who survived until lactation day 21). Mean body weight of the F1 dams were similar among all groups during gestation and lactation.

Oral dosing with trovafloxacin from gestation day 6 until lactation day 21 was not overtly toxic to pregnant rats with the exception of an increase in mean gestational length at doses ≥ 5 mg/kg. Dystocia was observed in several dams at 75 mg/kg. Early postnatal viability was reduced in the 75 mg/kg group compared to control, most likely due to dystocia. Signs of development such as obtaining the righting reflex and visual cliff avoidance did not differ between control and drug-treated litters, but reductions of time to preputial separation, eye opening and tooth eruption observed in some treated animals in the 15 and/or 75 mg/kg groups may be related to the delay in parturition, making these animals developmentally older at birth. Functional neurological development and learning ability of the F1 pups did not appear to be greatly affected by treatment with trovafloxacin. Sexual development and reproductive capacity of the F1 offspring did not appear to have been affected by trovafloxacin treatment of the F0 dams. The F2 offspring were grossly unaffected by F0 drug treatment. In this study, the NOAEL of trovafloxacin for the dams was less than 5 mg/kg (based upon the increased length of gestation observed in all drug-treated groups), the NOAEL for the F1 offspring was 15 mg/kg (based upon the increased early postnatal mortality observed at 75 mg/kg) and the NOAEL for the F2 offspring was 75 mg/kg.

PHARMACOKINETIC STUDIES: (Contained in Volumes 31-32 of NDA; doses were based upon free trovafloxacin equivalents. Concentrations of trovafloxacin and alatrofloxacin in biological fluids were measured. Concentrations of alatrofloxacin were not always determined in the studies due to its rapid hydrolysis to trovafloxacin.)

Absorption/Pharmacokinetics:

Pharmacokinetics of Trovafloxacin in Sprague-Dawley Rats Following Single Intravenous Administration of Alatrofloxacin or Trovafloxacin and Single Oral Administration of Trovafloxacin (93-099219-4)

Four Sprague-Dawley rats per sex received an IV (intrafemoral vein) dose of 10 mg/kg trovafloxacin mesylate in 1:1 glycerol formal/water and another 4/sex received an oral dose of 50 mg/kg trovafloxacin in 0.5% methylcellulose. Sequential blood samples were obtained 0.08 - 8.0 hours after intravenous dosing and 0.16 - 8.0 hours after oral dosing. For the 10 mg/kg IV dose, the mean clearance of trovafloxacin was 13.7 ± 2.7 ml/min/kg, the volume of distribution was 0.9 ± 0.2 l/kg, the AUC was 12.6 ± 2.8 $\mu\text{g}\cdot\text{hr}/\text{ml}$ and the half life was calculated to be 0.7 h. For the 50 mg/kg oral dose, C_{max} was 11.5 ± 3.3 $\mu\text{g}/\text{ml}$, T_{max} was 0.6 ± 0.3 h, AUC was 42.5 ± 11.2 $\mu\text{g}\cdot\text{hr}/\text{ml}$, and the calculated half life and absolute bioavailability 1.9 h and 67%, respectively. The longer half life after oral dosing is believed to be due to prolonged absorption of trovafloxacin because it has a low aqueous solubility.

Adult vs. neonatal rat pharmacokinetics of trovafloxacin were determined after intravenous doses of 10 or 20 mg/kg alatrofloxacin mesylate in mannitol to 4 adults/sex sampled sequentially (0.08 - 4.0 hours after dosing) or 20 mg/kg to 2 neonatal rats/sex per time point. Comparisons between the pharmacokinetic parameters for the 2 adult dose groups and between adults and neonates were as follows:

	Adult 10	Adult 20	Neonate 20
Clearance (ml/min/kg)	21.0 ± 0.8	17.9 ± 0.5	10.5
Volume of Distribution (l/kg)	1.0 ± 0.1	0.9 ± 0.1	1.0
AUC (µg·hr/ml)	8.0 ± 0.3	18.6 ± 0.5	31.8
Half life (h)	0.6	0.6	1.1

Neonate parameters were provided as means only because different animals were used for each time point- the same animals could not be studied sequentially due to their small blood volumes. In the adults, pharmacokinetic parameters were similar between the two dose groups with the obvious exception of AUC. The neonates did not clear drug as rapidly, leading to longer half life and greater AUC for the same 20 mg/kg dose that the adults received. The investigators attributed this to the lower capacity of neonates to metabolize trovafloxacin via phase II conjugation enzymes not yet fully developed in these young rats.

Pharmacokinetics of Trovafloxacin in Beagle Dogs Following Single Intravenous Administration of Alatrofloxacin or Trovafloxacin and Single Oral Administration of Trovafloxacin 73-099219-1)

Alatrofloxacin mesylate was administered intravenously to 3 male beagle dogs via the cephalic vein as a bolus dose of 5 mg/kg. Blood samples were collected 3 minutes to 2 hours after dosing and were immediately acidified with KH_2PO_4 to prevent hydrolysis of alatrofloxacin to trovafloxacin. Alatrofloxacin was detected in plasma only at the 3 minute time point (mean concentration $2.80 \pm 1.27 \mu\text{g/ml}$). It was not detected in subsequent samples, the next of which was drawn 10 minutes after dosing. Alatrofloxacin appears to be rapidly hydrolyzed (loss of 2 L-alanine groups) to trovafloxacin in the dog. A third compound, a mono-L-alanine analog of trovafloxacin, was also detected in plasma 3 minutes after the IV bolus dose of alatrofloxacin and demonstrates a sort of midway point between the conversion of alatrofloxacin (which has 2 L-alanine groups) to trovafloxacin.

A 8-9 minute IV infusion of 10 mg/kg alatrofloxacin mesylate was given to 1 male and 3 female beagles and blood samples were drawn 0 - 8 hours after the beginning of dosing. For the 10 mg/kg IV alatrofloxacin dose, the mean clearance of trovafloxacin was $7.7 \pm 1.1 \text{ ml/min/kg}$, the volume of distribution was $1.5 \pm 0.6 \text{ l/kg}$, the AUC was $22.0 \pm 3.3 \mu\text{g}\cdot\text{hr/ml}$ and the half life was calculated to be 2.0 h.

A 5 minute IV infusion of 5 mg/kg trovafloxacin mesylate was given to 3 male and 3 female beagle dogs. Blood samples were drawn 0 - 8 hours after the end of infusion. One week later, the same dogs were given an oral dose of 20 mg/kg trovafloxacin mesylate in 0.5% methylcellulose and blood was obtained 0 - 12 hours after dosing.

	IV 5 mg/kg	Oral 20 mg/kg
Clearance (ml/min/kg)	11.1 ± 3.0	—
Volume of Distribution (l/kg)	1.7 ± 0.5	—
AUC (µg·hr/ml)	8.0 ± 1.8	17.7 ± 9.0
Half life (h)	1.7	2.4

The mean absolute bioavailability of the oral 20 mg/kg dose of trovafloxacin was 58 ± 41%. The variability among the dogs (range of 17-115%) may have been due to emesis. The C_{max} of trovafloxacin after the oral 20 mg/kg dose was 3.5 ± 1.5 µg/ml and the T_{max} was 2.3 ± 1.2 hours. The half lives of 10 mg/kg IV alatrofloxacin, 5 mg/kg IV trovafloxacin, and 20 mg/kg oral trovafloxacin were similar (1.7 - 2.4 hours) and the volume of distribution (1.5 - 1.7 l/kg) for trovafloxacin was similar whether it was given IV as alatrofloxacin or trovafloxacin.

Pharmacokinetics of Trovafloxacin in Cynomolgus Monkeys Following Single Intravenous Administration of Alatrofloxacin or Trovafloxacin and Single Oral Administration of Trovafloxacin (93-099219-2)

Alatrofloxacin hydrochloride was administered as an IV bolus at a dose of 20 mg/kg to 2 male cynomolgus monkeys. Blood samples were collected 0 - 24 hours after dosing and immediately acidified with KH₂PO₄ to prevent hydrolysis of alatrofloxacin to trovafloxacin. Although alatrofloxacin could not be detected at any time point, the mono L-alanine form of trovafloxacin was detected at the 0.17 and 0.33 hour time points. The mono L-alanine form of trovafloxacin appears to be an intermediate between alatrofloxacin (which contains 2 L-alanine groups) and trovafloxacin. The investigators believe that the L-alanine groups are sequentially hydrolyzed in the plasma; this seems to be a reasonable assumption. For the 20 mg/kg IV alatrofloxacin hydrochloride dose, the mean clearance of trovafloxacin was 7.6 ml/min/kg, the volume of distribution was 4.0 l/kg, the AUC was 43.8 µg·hr/ml and the half life was calculated to be 5.9 h.

A 5 minute IV infusion of 20 mg/kg trovafloxacin mesylate was given to 3 male cynomolgus monkeys. Blood samples were drawn 0 - 24 hours after the end of infusion. Pharmacokinetic parameters were similar to those observed following the alatrofloxacin hydrochloride infusion. For the 20 mg/kg IV trovafloxacin mesylate dose, the mean clearance of trovafloxacin was 7.2 ± 1.1 ml/min/kg, the volume of distribution was 4.3 ± 2.3 l/kg, the AUC was 47.1 ± 7.2 µg·hr/ml and the half life was calculated to be 5.8 h.

Another group of 3 male cynomolgus monkeys was given an oral dose of 20 mg/kg trovafloxacin mesylate in deionized water and blood was drawn 0 - 48 hours after dosing. For the 20 mg/kg oral dose, C_{max} was 4.1 ± 1.9 µg/ml, T_{max} was 4.1 ± 2.3 h, AUC was 54.3 ± 23.1 µg·hr/ml, and the calculated half life was 9.1 hours. Absolute bioavailability (comparison made to the previous set of monkeys) was 115%, indicating complete absorption of 20 mg/kg oral dose by this species.

Pharmacokinetics of Trovafloxacin in New Zealand White Rabbits Following Single Intravenous or Oral Administration of Trovafloxacin (96-099219-4)

A 3-5 minute infusion of 40 mg/kg trovafloxacin mesylate was administered to 6 male New Zealand White rabbits and blood samples were collected 0.25 - 8 hours after dosing. For this dose of trovafloxacin, the mean clearance was 29.5 ± 11.6 ml/min/kg, the volume of distribution was 2.8 ± 0.8 l/kg, the AUC was 29.5 ± 15.4 $\mu\text{g}\cdot\text{hr}/\text{ml}$ and the half life was calculated to be 1.7 h.

An oral dose of 200 mg/kg trovafloxacin mesylate in 0.5% methylcellulose was given to 3 female New Zealand White rabbits and blood samples were collected 0.5 - 24 hours after dosing. For this dose of trovafloxacin, C_{max} was 4.6 ± 0.3 $\mu\text{g}/\text{ml}$, T_{max} was 1.2 ± 0.8 h, AUC was 24.1 ± 8.4 $\mu\text{g}\cdot\text{hr}/\text{ml}$, and the calculated half life was 2.6 hours. Absolute bioavailability (comparison made to the previous set of rabbits) was 16% (range of 13 -23%). The longer-half-life of the drug-after oral administration, compared to IV, was believed to be due to prolonged absorption of trovafloxacin because of its low aqueous solubility.

Protein Binding of Trovafloxacin:

Serum Protein Binding of Trovafloxacin in Rats, Rabbits, Dogs, Monkeys and Humans (92-099219-5)

Fresh serum obtained from rats, rabbits, dogs, monkeys, and humans was used to determine the protein binding capacity of radiolabeled trovafloxacin via 30 minute equilibrium dialysis across Spectra/Por membranes into 0.067 M sodium phosphate buffer (pH 7.44). The mean percentages (duplicates) of unbound trovafloxacin were:

Species	1 $\mu\text{g}/\text{ml}$ Trova	5 $\mu\text{g}/\text{ml}$ Trova
Rat	< 11%	3%
Rabbit	27%	27%
Dog	25%	24%
Monkey	35%	33%
Human	30%	28%

Protein binding was similar within species no matter which concentration of trovafloxacin was used. The percentage of unbound trovafloxacin was similar in serum from rabbit, dog, monkey, and human. The percentage of unbound trovafloxacin in rat serum was lower than for the other species.

Tissue Distribution:

Blood/Plasma Ratios of Trovafloxacin in Rats, Dogs, Monkeys and Humans (93-099219-3)

Fresh blood from Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and humans was incubated for 20 minutes at 37°C with 0.01 μCi of ^{14}C -trovafloxacin mesylate

(99% radiochemical purity, 47.7 $\mu\text{Ci}/\text{mg}$) plus enough "cold" drug to give final trovafloxacin concentrations of 0.5, 5.0 and 20.0 $\mu\text{g}/\text{ml}$. After incubation, blood was centrifuged to separate plasma and erythrocytes and the amounts of radiolabel determined in each. Trovafloxacin did not appear to be preferentially distributed into the red blood cells of any of the species tested (the fraction distributed to rat and human red blood cells was even lower than that distributed to red cells of the monkey and dog). Results of the test did not differ when trovafloxacin concentrations in the blood were varied, so results of the experiments were averaged. The blood/plasma ratios of trovafloxacin in the rat, dog, monkey, and human were 0.84, 0.94, 1.04, and 0.74, respectively. The fractions of trovafloxacin distributed to the red blood cells of these species were 0.29, 0.45, 0.41, and 0.19, respectively.

Distribution of [^{14}C] Trovafloxacin into Gastric Tissue of Swiss-Webster Mice Following Intravenous Administration (94-099219-3)

Swiss-Webster mice (5 per time point) were given an intravenous bolus dose of 10 mg/kg trovafloxacin (mix of $^{14}\text{-C}$ and "cold" drug) through the tail vein. Animals were sacrificed 1, 2, 4, 6, and 24 hours after dosing and the concentrations of trovafloxacin in the serum and gastric tissues were measured. Trovafloxacin did not detect metabolites of trovafloxacin in the samples, so liquid scintillation counting was predominantly relied upon. Trovafloxacin distributed to gastric tissues in the mice, with a higher level in the gastric mucosa than the gastric submucosa. At the time points used for this study, the concentrations of trovafloxacin in the gastric tissues tended to be higher than the serum concentration.

Tissue Distribution of Trovafloxacin in Beagle Dogs Following Oral Administration of Multiple Doses (93-099219-5)

Two male beagle dogs received 10 mg/kg daily oral doses of trovafloxacin for 5 days. Two hours after the final dose of drug, animals were sacrificed and tissues harvested. UV detection was used to determine mean trovafloxacin concentrations in the following:

	$\mu\text{g}/\text{g}$ or $\mu\text{g}/\text{ml}$	Ratio with Serum
Serum	3.9	---
Urine	25	6.4
Cerebrospinal Fluid	0.7	0.2
Bile	254	65
Lung	3.5	0.9
Liver	18.4	4.7
Heart	7.5	1.9
Kidney	7.8	2.0
Brain	1.7	0.4
Skeletal Muscle	6.2	1.6
Fat (White)	0.6	0.1

Results are consistent with biliary and urinary excretion of trovafloxacin and good

tissue penetration of the drug. Distribution of trovafloxacin to the brain and CSF was less than that for most of the other tissues measured except for fat.

Whole-Body Autoradioluminography of Female and Male Long-Evans Rats After Single Intravenous Administration of [¹⁴C] Trovafloxacin 94-099219-1)

Fasted male and female Long Evans rats received intravenous infusions of 10 mg/kg unradiolabeled and ¹⁴C-trovafloxacin. Rats were sacrificed 1, 4, 8, and 168 hours after dosing and frozen immediately in a hexane-dry ice bath. Carcasses were embedded in 3% CMC and 25 mm sections were cut from various levels. Sections were placed in phosphor cassettes for 8 days before the imaging screens in the cassettes were scanned using

One hour after infusion, radioactivity could be observed in most tissues with the highest levels in the GI tract. In the eye, the uvea contained about 30 times more radioactivity than the vitreous humor. The brain and spinal cord contained less radioactivity than the blood. The amount of radioactivity in all tissues except for the cecum and uvea were lower at the 4 hour time point than they had been 1 hour after infusion. Levels of radioactivity in all tissues fell further 8 and 168 hours after infusion. At the 8 hour time point, the GI tract, uvea, and skin contained the greatest amounts of radioactivity. At the 168 hour time point, radioactivity was still detectable in these tissues and also in the arterial wall, pineal gland, and liver. As has been demonstrated with other quinolones, trovafloxacin appears to be associated with melanin.

Whole-Body Autoradioluminography of Female and Male Long-Evans Rats After Single Oral Administration of [¹⁴C] Trovafloxacin 95-099219-1)

The study immediately above was repeated using an oral dose of 10 mg/kg trovafloxacin dissolved in 0.5% methylcellulose. Rats were sacrificed 1, 4, 8, 100, 300, and 600 hours after dosing. The investigators were particularly interested in estimating the half life of trovafloxacin-associated radioactivity in melanin-rich tissues. The GI tract had the highest levels of radioactivity 1 hour after dosing, but levels in the stomach and small intestine fell to undetectable levels 8 hours after dosing. In the cecum, peak radioactivity occurred 4 hours after dosing, had declined by 8 hours after dosing, and was not detected beyond the 100 hour time point. Radioactivity was detected in the pineal gland, but not other cerebral tissue, 1, 4, and 8 (males only) hours after dosing, but not later. Most tissues in the body (kidney cortex, kidney medulla, heart, liver, lung, muscle, spleen) peaked 1 hour after dosing and declined over the next 7 hours. Radioactivity was detected in the uvea (highest in the ciliary body, then choroid, then iris) 1 hour after dosing with a peak observed at the 8 hour time point. Levels of radioactivity in the components of the uvea slowly declined throughout the rest of the study, but could still be detected 600 hours after dosing. The half life of trovafloxacin-associated radioactivity in the uvea was estimated to be 23 days in the female pigmented rat and 15 days in the males. The levels of radioactivity in pigmented skin were greater than those in non-pigmented skin. Radioactivity could be detected in pigmented skin up to 100 hours after dosing, but was not detected in nonpigmented skin after the 1 hour time point in females or the 4 hour time point in males. The presence of radioactivity in blood vessel walls and in intravertebral discs may indicate an affinity for elastin as well as melanin.

Whole-Body Autoradioluminography of Female and Male Long-Evans Rats After Single Intravenous Administration of [¹⁴C] Alatrofloxacin 96-116517-2)

The studies immediately above were repeated with ¹⁴C-Alatrofloxacin mesylate. Alatrofloxacin was infused into the jugular veins of Long Evans rats at a dose of 15.7 mg/kg and the animals sacrificed 0.25, 1, 4, 8, 100, 300, and 600 hours after dosing. Amounts of radioactivity in frozen sections of the rats were consistent with those observed in the studies with intravenously and orally administered radiolabelled trovafloxacin.

Metabolism and Excretion:**Identification of Trovafloxacin Metabolites in Human Bile Following Oral Administration of Trovafloxacin 96-099219-2)**

Bile samples were collected from a human subject 12-16 hours after a single oral trovafloxacin dose of 200 mg. was used to identify free trovafloxacin, trovafloxacin glucuronide (the primary metabolite found in bile), and trovafloxacin sulfate. A peak corresponding with N-acetyltrovafloxacin was barely detectable.

Excretion and Metabolism of Trovafloxacin in Man 96-099219-1)

A single oral dose of ¹⁴C-trovafloxacin (200 mg) was given to healthy human male volunteers. Urine and feces were collected for the next 240 hours (24 hour sampling intervals) and blood was drawn 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours after dosing. Total radioactivity was measured in blood, urine, and homogenized feces (b)(4) was used to separate trovafloxacin and its metabolites in these biological samples and was used for identification. The major route of excretion of trovafloxacin-associated radioactivity over 240 hours was the feces (63.27 ± 2.21% of the dose) and most of it was parent drug (43.25% of the dose). Approximately 23.05 ± 3.69% of the radioactive dose was excreted in urine, with trovafloxacin glucuronide as the major portion (12.75% of the dose). Other metabolites detected in urine were N-acetyl trovafloxacin (0.42% of dose), unchanged trovafloxacin (5.9% of dose), trovafloxacin N-sulfate conjugate (0.21% of dose), M 12 (0.16% of dose), M8 (0.16% of dose), and M6 (an acetylated trovafloxacin, 1.18% of dose). Other metabolites detected in feces were trovafloxacin N-sulfate conjugate (3.89% of dose), M12 (0.88% of dose), and M6 (9.19% of dose). The mean C_{max} of trovafloxacin was 2.85 µg/ml and it occurred about 1.25 ± 0.5 hours after dosing. The terminal half life of the drug was 13.59 hours and the mean AUC was 32.18 ± 8.63 µg·hr/ml. In the first 4 hours of sampling, the parent drug accounted for 90% of the drug in serum and from over the next 20 hours. Metabolites detected in serum included 2 ester glucuronides and acetylated trovafloxacin.

In Vitro Hydrolysis of CP-116,517 to CP-99-219 in Neonatal and Adult Rat, Guinea Pig, Dog, Monkey and Human Serum 93-116517-1)

Fresh serum obtained from neonatal rats, adult rats, guinea pigs, dogs, monkeys, and

humans was used to determine the rate of alatrofloxacin hydrolysis to trovafloxacin *in vitro*. Alatrofloxacin was added to give final concentrations of 75-100 $\mu\text{g/ml}$ (based on free trovafloxacin equivalents) and serum was incubated for 1-5 hours at 37°C. Aliquots of serum were taken at various times after the start of incubation and acidified with KH_2PO_4 to prevent further hydrolysis of alatrofloxacin. detection was used to measure the concentrations of alatrofloxacin, trovafloxacin, and a mono L-alanine intermediate. Hydrolysis of alatrofloxacin occurred rapidly in all species with half lives less than 3 minutes in neonatal and adult rats, guinea pigs, and humans. Alatrofloxacin half lives in dog and monkey were still relatively short, at about 21 and 9 minutes, respectively. It should be noted that dog data generated with alatrofloxacin *in vivo* (above) suggested an even shorter half life for alatrofloxacin hydrolysis. Rapid formation and disappearance of the mono-L-alanyl intermediate suggested sequential hydrolysis of the L-alanyl groups.

In Vitro Metabolism of [^{14}C] Trovafloxacin by Rat and Human Liver Slices 94-099219-4)

Rat or human liver slices were incubated at 37°C in Henseliet buffer (pH 7.5) with ^{14}C -trovafloxacin at a concentration of 15 $\mu\text{g/ml}$ for 15-240 minutes (rat) or 60-240 minutes (human). Over time, the amount of radioactivity in the buffer decreased while the amount in the liver slices increased. HPLC analysis of the buffer and slice homogenates showed that the majority of the radioactivity in both rat and human preparations was unchanged trovafloxacin (95%). Measurable amounts of N-acetyl-trovafloxacin were detected in both preparations after 120 minutes. A smaller amount of N-acetyl, acyl glucuronide conjugate of trovafloxacin was detected in the rat preparations after 60 minutes, but not in the human slices or incubation buffer.

Excretion and Metabolism of Trovafloxacin in Sprague-Dawley Rats 94-099219-2)

^{14}C -trovafloxacin mesylate was given to 6 male and 6 female fasted Sprague-Dawley rats as a single oral dose of 10 mg/kg as a suspension in 0.1% methylcellulose. Half of the rats underwent bile duct cannulation; all were housed in metabolism cages for collection of urine and feces. Animals were fed 4 hours after dosing and given access to 5% sucrose solution during the whole study.

Another 12 fasted male rats were given an oral dose of 50 mg/kg ^{14}C -trovafloxacin mesylate. These rats were fed 6 hours after dosing and had free access to water. Blood was collected from 2 rats per time point 0, 1, 2, 4, 6, 8, and 24 hours after dosing. These samples were used to quantify the amounts of trovafloxacin and its metabolites in serum.

trovafloxacin from its metabolites in the biological samples collected above.

The major route of excretion of trovafloxacin in the noncannulated rats after a 10 mg/kg oral dose was fecal, with a mean of $97.9 \pm 5.9\%$ of the dose recovered in males and $96.3 \pm 1.0\%$ of the dose recovered in females in 96 hours (with the majority recovered within the first 24 hours). The mean percentages of the dose excreted in urine were $4.4 \pm 2.6\%$ and $4.1 \pm 0.6\%$, respectively. In the bile duct cannulated rats, about 60% of the dose was

recovered in the bile of male and female over 96 hours. In the males, $9.3 \pm 9.4\%$ was recovered in urine and $28.2 \pm 15.2\%$ was recovered in feces. In the females, recovery was not as complete with $7.0 \pm 4.7\%$ of the dose in urine and $5.4 \pm 3.9\%$ in feces.

Several glucuronide conjugates were detected in bile from the male and female rats. They were believed to be ester glucuronides as they were resistant to the action of β -glucuronidase. Together, they accounted for the majority of the bile radioactivity.

Another major peak in the bile was identified as a N-acetyl derivative of trovafloxacin. Unchanged trovafloxacin was also found in bile as was a sulfamate derivative of trovafloxacin, and a glycine conjugate of N-acetyl trovafloxacin. Several of these metabolites were also found in urine of cannulated and noncannulated rats: glucuronides- associated with 90% of radioactivity in the urine, unchanged trovafloxacin, N-acetyl trovafloxacin, and a trace of trovafloxacin sulfate conjugate. The feces of noncannulated rats contained predominantly N-acetyl trovafloxacin (about 62%) and unchanged trovafloxacin (about 15%), with a trace of the sulfate conjugate. N-acetyl trovafloxacin was not detected in feces from bile-duct cannulated rats.

The metabolites of trovafloxacin found in serum pooled from samples drawn 1-24 hours after dosing were an ester glucuronide of N-acetyl trovafloxacin (16% of radioactivity), a trace of ester glucuronide of trovafloxacin, N-acetyl trovafloxacin (18% of radioactivity). About 55% of the radioactivity of the pooled serum was associated with unchanged trovafloxacin.

The data indicate that the major route of elimination of trovafloxacin in Sprague-Dawley rats is fecal, with major biliary excretion.

Excretion and Metabolism of Trovafloxacin in Beagle Dogs (14-099219-2)

^{14}C -trovafloxacin mesylate was given to 4 male and 4 female fasted beagle dogs as a single oral dose of 10 mg/kg as a suspension in 0.1% methylcellulose. Half of the dogs underwent bile duct cannulation; all were housed in metabolism cages for collection of urine and feces. The dogs were fed 4 hours after dosing and had free access to water. Blood samples were collected from cannulated dogs 0, 1, 2, 4, 6, 24, 48, 72, and 96 hours after dosing and from noncannulated dogs 1 and 4 hours after dosing.

trovafloxacin from its metabolites in the biological samples collected above.

In noncannulated dogs, the main route of trovafloxacin excretion after a 10 mg/kg oral dose was fecal, with a mean of 97.0% of the dose recovered in males and 98.5% of the dose recovered in females in 96 hours. Mean urinary excretion in these dogs was 4.3% for males and 1.1% for females over 96 hours. In the cannulated dogs, 40.0% and 51.8% of the dose was excreted in the urine of males and females, respectively, over the same time period. The bile contained 41.0% (males) and 15.7% (females) of the dose and the feces contained 15.9% (males) and 30.3% (females).

Metabolites were recovered in bile, urine, feces, and blood as follows:

**Trovafloxacin Metabolites in Bile Duct Cannulated and Non-Cannulated Beagles
After a Single Oral Dose of 10 mg/kg (Mean % Total Dose for Males and Females)**

Metabolite	Bile	Urine		Feces	
		Can	Non	Can	Non
Ester Glucuronide	11.5	10.6	ND*	ND	ND
Unchanged Trovafloxacin	6.4	19.8	1.31	13.6	59.0
Pyrroline Ester Glucuronide + Diacid + Hydroxy Carboxylic Acid (Co-Eluted)	1.9	1.4	0.5	ND	Trace
N-Acetyl Trova + Amide (Co-Eluted)	0.15	1.1	Trace	ND	23.7 [#]
Cyclopropanone	0.4	ND	ND	ND	ND
Pyrroline	1.2	Trace	ND	ND	Trace

*Not Detected

[#]All radioactivity accounted for by N-Acetyl-trovafloxacin in feces of noncannulated dogs

The metabolites listed in the table above (except for the cyclopropanone which was not detected in the serum of noncannulated dogs) were also detected in serum of cannulated and noncannulated dogs. The majority of radioactivity circulating in the serum was associated with unchanged trovafloxacin (55% of serum radioactivity). The metabolites each accounted for of serum radioactivity; the trovafloxacin ester glucuronide was highest at about 10.5%.

The data indicate that in noncannulated dogs, most of a 10 mg/kg trovafloxacin dose was eliminated in the feces. Biliary excretion of trovafloxacin occurred in the dog, particularly of the unchanged drug and its ester glucuronide. *In vitro* studies using freshly harvested dog cecae suggested that the intestinal microflora in these animals were primarily responsible for the production of N-acetyl-trovafloxacin. A significant amount of this metabolite was found in the feces of noncannulated dogs. Oxidative metabolic pathways did not appear to play a major role in trovafloxacin metabolism in the dog as relatively small amounts of oxidized trovafloxacin metabolites were found in the blood and excreta.

Metabolism and Excretion of Alatrofloxacin in Sprague-Dawley Rats (96-116517-1)

¹⁴C-alatrofloxacin mesylate was infused into the jugular vein of 6 male and 6 female Sprague-Dawley rats at a dose level of 10 mg/kg. Two rats per gender underwent bile duct cannulation; all were housed in metabolism cages for collection of urine and feces. Bile was

collected in an ammonium formate buffer (pH 3) to prevent alatrofloxacin hydrolysis. The rats were fed 4 hours after dosing and had free access to water. Blood samples were collected from noncannulated rats 0, 0.03, 0.08, 0.17, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 24 hours after dosing.

trovafloxacin from its metabolites in the biological samples collected above.

Over 96 hours, 96.1% of the radioactivity was excreted in the feces and 4.9% in the urine of noncannulated rats. In the bile duct cannulated rats, of the radioactive dose was recovered in the bile during the first 8 hours of collection. The bile contained 2 metabolites that were not detected in blood, feces, or urine: a glucuronide conjugate of trovafloxacin (16% of bile radioactivity) and a glucuronide conjugate of N-acetyl-trovafloxacin (51% of bile radioactivity). N-acetyl-trovafloxacin was identified in bile (12.6% or bile radioactivity) of cannulated rats, and in the serum (8% of serum radioactivity), urine (3.1% of dose) and feces (60% of dose) in noncannulated rats. Trovafloxacin was found in bile (1% of bile radioactivity) of cannulated rats, and in the serum (81% of serum radioactivity), urine (0.9% of dose), and feces (21.5% of dose) of noncannulated rats. The mono L-alanine trovafloxacin (an intermediate of alatrofloxacin conversion to trovafloxacin) was identified in bile (12.5% of bile radioactivity) and serum (5.7% of serum radioactivity). A trace of unchanged alatrofloxacin was also detected in bile and serum. Bile contained two other radioactive peaks that could not be elucidated, but they accounted for a relatively small portion of bile radioactivity.

Alatrofloxacin is rapidly converted to trovafloxacin in the blood of Sprague-Dawley rats. Its metabolic and excretion profile are consequently similar to that of trovafloxacin. The primary route of elimination was in the feces and extensive biliary excretion occurred. Glucuronidation was a major metabolic pathway in the rats.

APPROVED FOR RELEASE
ON 10/10/01

SUMMARY AND EVALUATION:

Trovafloxacin is well absorbed from the GI tract in animals and man. Absolute bioavailability in humans, cynomolgus monkeys, dogs, and rats is about 88%, 115%, 58% (estimate may be low due to vomiting in some dogs), and 67%, respectively. Bioavailability in the rabbit is much lower, about 16%. Protein binding is moderate (about 70%) in most species, including humans, but is greater in the rat ($\geq 90\%$). Alatrofloxacin is rapidly converted to trovafloxacin in the blood upon intravenous infusion. Metabolism and elimination of both trovafloxacin and alatrofloxacin are similar, with the feces as the main route of elimination in humans, rats, and dogs. Biliary excretion of trovafloxacin is extensive in rats and is also significant in dogs and humans. Glucuronidation appears to be a major metabolic pathway for trovafloxacin in rats, dogs, and humans, with much less oxidative metabolism in these species. Unchanged trovafloxacin was the most abundant form of the drug found in the serum of rats, dogs, and humans. The plasma half life of the drug in most animal species studied was much shorter than for humans. Trovafloxacin half life in dogs, rats, and rabbits was 2-2.5 hours after a 5-40 mg/kg oral dose, 9.1 hours in monkeys after a 20 mg/kg oral dose and 13.6 hours in humans after a 200 mg total oral dose. Like most fluoroquinolones, trovafloxacin is widely distributed to vascular tissues after oral or IV administration (although distribution into the brain and spinal cord was less than most other tissues) and appears to have an affinity for melanin.

Single oral doses of trovafloxacin were relatively nontoxic. The minimum lethal oral dose was between 1000-2000 mg/kg in both mice and rats and the clinical signs observed included decreased activity and respiration, ptosis, ataxia and piloerection. The rat that died at

this dose level experienced clonic convulsions with death occurring 4 hours after administration of trovafloxacin. Mortality was delayed in the mice, occurring 7-8 days after dosing. The minimum lethal intraperitoneal dose of trovafloxacin was 100-250 mg/kg for mice and 250-500 mg/kg for rats. Clinical signs similar to those observed following oral dosing were reported with the additional observation of writhing, perhaps indicative of discomfort at the site of injection.

The minimum lethal single intravenous dose of alatrofloxacin was between 50-125 mg/kg for mice and greater than 75 mg/kg (the highest dose tested) for rats. Clinical signs observed in the mice included exophthalmia, "jittery appearance", ataxia, vocalization, decreased activity and respiration, darkening eyeballs, flushed feet, ptosis, tremors, straub tail, and clonic convulsions. Mortality occurred within 10 minutes after dosing. Clinical signs in the rats included "jittery appearance", ataxia, decreased activity and respiration, flushing of ears and feet, exophthalmia, and ptosis.

No mortality was observed in rats given 50-200 mg/kg of trovafloxacin via oral gavage for 2 weeks. No treatment-related gross or histopathologic changes were seen at necropsy, but there were slight reductions in hemoglobin in high dose females and in total serum protein in mid (100 mg/kg) and high dose males. There was also a slight suppression of body weight gain in the high dose males; the mean body weight of these rats was about 7% less than control at the end of the study. Slight reductions in serum magnesium observed in most of the animals were believed to have been due to chelation of Mg^{++} ion by trovafloxacin. Rats given trovafloxacin via oral gavage for one month at doses of 25-200 mg/kg experienced no mortality. Again, no treatment-related gross or histopathologic changes were seen at necropsy. The only clinical sign noted was salivation in most high dose rats. Reduction in body weight gain was observed in the high dose males, but no reduction in food consumption was seen. Small reductions in serum albumin and globulin were seen in high dose males and mid (75 mg/kg) and high dose females, but the values remained in the normal range for rats. Slight reductions in hematocrit and hemoglobin were observed in rats from the high dose group, but also remained in the normal range. The NOAEL in this 4 week study was 75 mg/kg for males (based upon the reduction in body weight gain at the highest dose) and 200 mg/kg for females. No drug-related mortality was observed in rats given trovafloxacin via oral gavage daily for 6 months at 25-200 mg/kg. Salivation was observed in rats from each dose group; the incidence increased with dose. Inhibition of body weight gain was observed in the high dose males. Hematocrit and hemoglobin were slightly lower in trovafloxacin-treated male rats compared to controls. Mean serum protein and globulin concentrations were less in high dose rats than controls. A dose-related increase in the incidence of minimal to mild "fatty change" was seen in the livers of male rats from all trovafloxacin groups. Tubular degeneration of the testes was observed in 1-2 rats from each trovafloxacin group and is considered drug-related despite the relatively low incidence. The NOAEL in the 6 month study was 200 mg/kg for the female rats, but was not determined in males due to the histopathologic observations in the liver and testes.

Two (one male, one female) out of 4 rats receiving intravenous alatrofloxacin at 100 mg/kg during a 2 week study died within 5 minutes after the first dose. All 4 rats experienced tonic/clonic convulsions. The survivors, and the remaining 4 mice in this dose group received 75 mg/kg of alatrofloxacin for the remainder of the study. Rats that received 50 or 75 mg/kg of alatrofloxacin demonstrated clinical signs such as salivation, hypoactivity, prostration. Rats

in the 75 mg/kg group also experienced dyspnea and generalized erythema. No clinical signs were observed at 20 mg/kg, the NOAEL for this study. Drug-related gross or histopathologic changes were not observed upon necropsy. In a one month intravenous alatrofloxacin study, no trovafloxacin-related mortality was observed at 6.5, 20, or 50 mg/kg. Hypoactivity, labored breathing, sternal recumbency, erythema and salivation were observed in the high dose group. Slight reductions in hematocrit and hemoglobin were seen in the high dose rats and a slight reduction in serum magnesium was detected in the high dose females. Drug-related gross or histopathologic changes were not observed in the high dose rats; tissues from the 2 lower dose groups were not examined microscopically.

Neonatal rats were more sensitive to trovafloxacin-induced tremors than adults or older pups. This may be due to the younger animals having less developed blood brain barriers; therefore, higher trovafloxacin concentrations are achieved in the brain.

Studies in mice indicated that biphenyl acetic acid, an active metabolite of the nonsteroidal anti-inflammatory drug fenbufen, did not enhance the capacity of either oral trovafloxacin or intravenous alatrofloxacin to cause convulsions in these animals. The pro-convulsant properties of several other quinolones, particularly enoxacin and norfloxacin, are enhanced by fenbufen or its metabolite.

No mortality was observed in beagles dosed orally with 12.5-50 mg/kg of trovafloxacin for 14 days. Due to emesis, the high dose was administered as 25 mg/kg BID. This lowered the frequency of emesis. Erythema, salivation, and hypoactivity were also observed in the high dose group. Glomerular hypoplasia was observed in the kidneys of both high dose dogs; however, the effect was not observed at this dose in a subsequent study with a longer period of administration. When trovafloxacin was given orally to beagles for one month at 5, 15 (7.5 BID), or 50 (25 BID) mg/kg, no dogs died. Emesis occurred occasionally in the mid and high dose groups, erythema of the ears and salivation were seen in the high dose dogs, and decreased activity was seen in all dose groups. Slight reductions in serum globulins were observed in high dose males and all females. Erosion of articular cartilage at the knee joint was observed in one high dose male. The NOAEL in this study was 5 mg/kg based upon the observation of emesis, but was 15 mg/kg if emesis is not considered. In a 6-month study, mortality was not observed at doses of 7.5, 15 (7.5 BID), or 50 (25 BID) mg/kg. General or localized erythema was observed in all dose groups and salivation and emesis were observed in dogs from the highest dose group. Microscopic examination of the liver revealed hepatocellular vacuolar degeneration and necrosis in 2/8 (1 male and 1 female) dogs from the high dose group and both animals had elevated serum liver enzymes. Testicular degeneration (slight or mild vacuolation of germinal epithelium, multinucleated giant cells in seminiferous tubules) was seen in 4/4 high dose male dogs and has been observed in animals treated with other quinolones. The NOAEL in this 6-month beagle study was 15 mg/kg. In a subsequent study, beagles were given 50 mg/kg/day of trovafloxacin via the oral route until their serum liver enzymes (measured every 2 weeks) were 3X greater than baseline or for up to 6 months if no liver enzyme elevations were detected. Liver biopsies were taken prior to the study, when 3-fold increases in serum liver enzymes were observed, and randomly during the study in dogs showing no increase. Dosing with trovafloxacin was discontinued in 3/16 dogs demonstrating 3-fold increased in liver enzymes whose biopsies revealed hepatocellular changes. An additional dog demonstrated elevated liver enzymes with no evidence of necrotizing hepatocellular inflammation. This animal continued trovafloxacin treatment and

the serum liver enzyme levels fell over time. All animals were biopsied again at the end of 6 months and liver tissue was collected at necropsy from some controls and all drug-treated dogs for microscopic evaluation. No dogs without elevated hepatic enzyme elevations demonstrated necrotizing hepatocellular inflammation. Data from this study indicated that elevation in liver enzymes, especially ALT, accurately predicted the presence of necrotizing inflammation of periportal hepatocytes. The necrotic changes were no longer evident approximately 2 months after discontinuation of the drug.

Intravenous doses of alatrofloxacin at 2, 10, or 20 mg/kg administered daily for 10 days did not cause mortality in beagle dogs. Animals receiving the mid and high doses demonstrated dose-related salivation and emesis. Erythema was observed in animals from all dose groups. Only sporadic salivation and erythema were observed in the 2 mg/kg group. In a one month study of intravenous alatrofloxacin at the same dose levels, convulsions were observed in the 20 mg/kg group and the dose level was dropped in steps to 15, then 12 mg/kg. One female in the high dose group received 10 mg/kg for most of the study due to convulsions at 12 mg/kg. The incidence of convulsions fell as the high dose was lowered, but tremors were still observed in this group. No mortality occurred during the study. Dose-related clinical signs observed in the high and mid dose dogs included small muscle contractions, salivation, emesis (incidence decreased after first week of dosing), cutaneous erythema, and hypoactivity. Erythema, salivation, and emesis were sporadically observed in the low dose group as well. Microscopic examination of the tissues revealed no apparent alatrofloxacin-related lesions. On the basis of the CNS effects observed in the 2 higher dose groups, the NOAEL for alatrofloxacin in this one month study was 2 mg/kg/day.

Orally or subcutaneously administered trovafloxacin was not antigenic in guinea pigs; however, subcutaneous alatrofloxacin was antigenic in this animal model.

The phototoxic potential of single oral doses of trovafloxacin was less than that of lomefloxacin in female BALB/c mice exposed to ultraviolet A radiation, even at trovafloxacin doses as high as 250 mg/kg where signs of systemic toxicity were observed (reduced activity, tremors). Phototoxic reactions after 250 mg/kg of trovafloxacin were described as well-defined erythema of the ears. At 90 mg/kg, phototoxicity was still evident, but less than that observed at 250 mg/kg. The reviewer's NOEL for trovafloxacin-induced phototoxicity in this study was 10 mg/kg as slight evidence of phototoxicity was observed at 30 mg/kg. Oral doses of trovafloxacin up to 300 mg/kg administered for approximately 8 weeks in conjunction with exposure to simulated sunlight were not phototoxic to hairless mice. Trovafloxacin-related mortality was observed at doses ≥ 100 mg/kg.

Like other members of the quinolone class of antimicrobials, trovafloxacin will induce cartilage lesions in the joints of juvenile animals. Erosion of articular cartilage was observed in the knee joint of a dog (4-6 months old) that received 50 mg/kg (25 mg BID) for 4 weeks.

Trovafloxacin did not induce reverse mutation at the *his* locus of *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 in the presence or absence of metabolic activation. A similar test in the *E. coli* strain WP2 pKM101 in the absence of metabolic activation was also negative, but an increase in mutation frequency was observed in WP2 pKM101 in the presence of metabolic activation and in WP2 *uvrA* pKM101 regardless of metabolic activation. Alatrofloxacin did not induce an increase in mutation frequency in any of the *Salmonella* strains in the presence or absence of metabolic activation; however, a small increase in mutation frequency was observed in the *E. coli* strains in the presence (but not the absence) of

metabolic activation. In Chinese hamster ovary cells, neither trovafloxacin nor alatrofloxacin induced forward mutation at the HGPRT locus in the presence or absence of metabolic activation. Chromosomal aberrations were not induced in cultured human lymphocytes in the presence or absence of metabolic activation by trovafloxacin. Data from a similar assay with alatrofloxacin showed a small increase in abnormal cells, but lack of a clear dose-response relationship made interpretation of these data difficult. *In vivo*, chromosomal aberrations were not induced in bone marrow cells harvested from mice dosed orally with up to 1000 mg/kg of trovafloxacin or intravenously with up to 100 mg/kg of alatrofloxacin.

Trovafloxacin (given orally) and alatrofloxacin (given intravenously) did not affect the fertility of male or female rats at oral and IV doses of 75 mg/kg/day and 50 mg/kg/day, respectively. However, oral doses of trovafloxacin at 200 mg/kg/day were associated with increased preimplantation loss in rats. Alatrofloxacin induced skeletal variations and malformations in the offspring of rats and rabbits when intravenous doses ≥ 20 mg/kg/day were administered during the period of organogenesis. An increase in skeletal variations was observed in rat fetuses after daily oral 75 mg/kg maternal doses of trovafloxacin were administered during organogenesis. Maternal doses of intravenous alatrofloxacin at 50 mg/kg/day and oral trovafloxacin at 75 mg/kg/day were fetotoxic in rats (increased perinatal mortality and decreased body weights of offspring). Fetotoxicity and fetal skeletal malformations have been associated with other quinolones. Oral doses of trovafloxacin ≥ 5 mg/kg were associated with an increased gestation time in rats and several dams at 75 mg/kg experienced uterine dystocia.

The toxicities observed with trovafloxacin and alatrofloxacin in animal models are generally similar to those that have been observed with other fluoroquinolones. These include phototoxicity, induction of arthropathy in juvenile dogs, convulsions and other CNS disturbances, and teratogenicity (fetal skeletal malformations). None of these toxicities appears to be worse for trovafloxacin than for other approved fluoroquinolones. The liver toxicity observed in dogs (necrotizing inflammation of perivenular hepatocytes) was successfully monitored using an increase in serum liver enzymes as a marker and appeared reversible upon discontinuation of the drug.

RECOMMENDATION: The pharmacologist does not object to the approval of this NDA. The nonclinical data for trovafloxacin and alatrofloxacin are comparable to other quinolones marketed for clinical use. The label contains appropriate cautions regarding potential quinolone-related toxicities such as CNS effects, juvenile arthropathy, tendon rupture, and phototoxicity. The sponsor will submit
a Phase IV commitment.

/S/

APPROVED THIS WAY
ORIGINAL

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Orig. NDA

cc:

HFD-520

HFD-590

HFD-520/Pharm Team Ldr/Osterberg

HFD-590/Pharm Team Ldr/Hastings

~~HFD-520/Pharm Team Ldr/Osterberg~~

HFD-590/MO Team Ldr/Leissa

HFD-590/MO/Coyne

HFD-520/Chem/Shetty

HFD-590/CSO/Fogarty

HFD-520/Micro/Altaie

Concurrence Only:

HFD-520/RE Osterberg

HFD-520/LGavrilovich

at:
/S/ 4/15/97
/S/ 12/16/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20759/20760

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEC 9 1997

NDA, Drug Name, and Its Formulation: 20-759: Trovan® Tablets (Trovafloracin Mesylate)
20-760: Trovan® Injection (Alatrofloracin Mesylate Injection)
Drug Class: 1-S
Applicant: Pfizer Inc.

Indications: Of 17 indications totally, 9 by this reviewer
1. Complicated intra-abdominal infections
2. Gynecologic and pelvic infections
3. Surgical prophylaxis - elective colorectal surgery
4. Surgical prophylaxis - elective abdominal and vaginal hysterectomy
5. Non-gonococcal urethritis and cervicitis
6. Pelvic inflammatory disease
7. Uncomplicated urinary tract infection
9. Bacterial prostatitis
For other 8 indications, see statistical review reports by Nancy Silliman, Ph.D. and Daphne Lin, Ph.D.

Documents Reviewed: NDA volumes 1.1-1.8 dated December 19, 1996 and electronic submission
Type of Review Clinical

Medical Officer: Regina Alivisatos, M.D., Daniel Davis, M.D., Brad Leissa, M.D., HFD-590,
Mamodikoe Makhene, M.D., HFD-520
Statistical Reviewer: Joel Jiang, Ph.D., HFD-725
Project Manager: Pauline Fogarty, HFD-590

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APPROVED FOR RELEASE

Review's Note: Throughout the review, the following terms are abbreviated and referred to as: CRF = Case Report Form, EOS = End of study Visit, EOT = End of Treatment Visit. Reviewer comments are given in italics throughout the review.

APPROVED FOR RELEASE

I. COMPLICATED INTRA-ABDOMINAL INFECTIONS

I.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-124, as evidence to support intravenous alatrofloxacin followed by oral trovafoxacin regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general design of the study is as follows:

Study 154-124 was a randomized, double-blind, multicenter trial which compared the safety and efficacy of intravenous alatrofloxacin followed by oral trovafoxacin for a maximum treatment duration of 14 days versus intravenous imipenem/cilastatin followed by oral amoxicillin/clavulanic acid for a maximum treatment duration of 14 days for the treatment of subjects with complicated intra-abdominal infections requiring hospitalization, surgery, or percutaneous drainage, and initial intravenous therapy.

I.B. STUDY 154-124

I.B.1. METHODS

In study 154-124, a total of approximately 300 subjects with a clinical diagnosis consistent with an intra-abdominal infection were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At baseline (Day 1), subjects who met the criteria for clinical diagnosis of intra-abdominal infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of male and female inpatients, who were 18 years of age or older with clinically documented intra-abdominal infection.

At the baseline assessment (Day 1), baseline assessments were performed. At Day 4, efficacy observations were performed to assess response to study therapy. At Day 14 (EOT), efficacy observations were repeated to assess response to study therapy. Safety was also assessed. The investigator provided an evaluation of time of recovery and an evaluation of clinical response. At Day 30 (EOS), efficacy observations were repeated to assess response to study therapy. Safety was also assessed. The investigator provided an evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 124.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug for intravenous administration was prepared by the study site pharmacist using a double-dummy technique to maintain blinding. Subjects received one of the following intravenous treatment regimens: 1. alatrofloxacin 300 mg (3x100 mg vials) in 200 ml of D5W administered once daily as a 60-minute infusion; 200 ml D5W (alatrofloxacin placebo) administered as a 60-minute infusion twice daily, once in the afternoon (1 vial) and once in the evening (1 vial); 2. imipenem/cilastatin 1 g (1x1 gram vial) in 200 ml of D5W administered every 8 hours as a 60-minute infusion. All subjects received intravenous study medication every 8 hours in combinations of active drug and placebos for active drug. Based upon clinical impressions, the subject was switched from intravenous to oral therapy to complete a total maximum treatment duration of 14 days. Study drug for oral administration was in the form of trovafoxacin tablets and amoxicillin/clavulanic acid suspension and was packaged using a double-dummy technique to maintain blinding. Eight hours after the last intravenous treatment with randomized study

medication, subjects received one of the following treatments orally: 1. trovafloxacin 200 mg (2x100 mg tablets) administered as a single daily dose in the morning and 10 ml of suspension administered every 8 hours (amoxicillin/clavulanic acid placebo); 2. amoxicillin/clavulanic acid 500 mg (1x10 ml suspension) administered every 8 hours and two tablets administered once daily in the morning (trovafloxacin placebo). All subjects received oral study medication three times daily (every 8 hours) in combinations of active drug and placebo for active drug. The decision to stop therapy was based on the investigator's assessment of clinical outcome.

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 4	Day 14	Day 30
Allowable Window	-48 hours	Day 3-5	Day 10-14	Day 28-42
Treatment Period	Day 1 to Day 14			
Follow-up Period	Day 15 to Day 42			
Informed Consent	X			
Demographic Information	X			
Physical Examination	X		X	X
Maximum Body Temperature	X		X	X
Vital Signs	X	X	X	X
Concomitant Medication	X	X	X	X
APACHE Scoring	X	X	X	
Dosing Record		X	X	
Clinical Signs & Symptoms	X		X	X
Assessment of Bowel Function	X		X	X
Microbiology				
• blood	X	X	X	X
• peritoneal	X			
Safety Laboratory Tests				
• hematology	X	X	X	abn
• biochemistry	X	X	X	abn
• urinalysis	X	X	X	abn
• pregnancy test	X			
Adverse Events	X		X	X
Investigator's Assessment of clinical response			X	X
Time of Recovery	X		X	X
Health Care Resource Utilization	X		X	X

abn Abnormal at previous visit or clinically significant adverse event.

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically and bacteriologically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoints were clinical response at EOT, and pathogen outcomes at EOT and EOS.

Clinical response was determined by the sponsor and evaluated at EOT (Day 14) and at EOS (Day 30), or at the time of discontinuation from study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. The clinical

response was classified as cure, improvement, or failure. Pathogen bacteriologic outcome was classified as eradication, presumed eradication, persistence, presumed persistent, superinfection, or colonization.

Reviewer's Note: *The Medical Officer agreed with both clinical and bacteriological evaluability criteria chosen by the Applicant, and assessed clinical and bacteriological efficacy outcomes according to the Applicant clinical and bacteriological criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's efficacy outcome definitions and Medical Officer's comments.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of clinical laboratory tests, vital signs, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between alatrofoxacin/trovafoxacin and imipenem/cilastatin/amoxicillin/clavulanac.

Efficacy analyses were based on the clinical and bacteriological responses at EOT and EOS. The treatment groups were compared with respect to the clinical success (cure+improvement) rate and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success rate at EOS in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: *All efficacy analyses were conducted for the Applicant clinically and bacteriologically evaluable subjects. All of the subjects in these groups were assessed for their clinical or bacteriological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.*

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

I.B.2. RESULTS

A total of 420 subjects were enrolled across centers in the USA (80), Canada (9), and Europe (31) between April 12, 1995 and June 20, 1996. Of these enrolled subjects, 7 were withdrawn prior to randomization because they did not meet study entrance criteria. Two hundred four subjects were randomized to receive alatrofoxacin/trovafoxacin and 210 subjects were randomized to receive imipenem/cilastatin/amoxicillin/clavulanac. Two hundred one alatrofoxacin/trovafoxacin and 207 comparator regimen subjects received treatment. Two hundred alatrofoxacin/trovafoxacin and 199 comparator regimen subjects were included in the clinical intent-to-treat analyses; 171 alatrofoxacin/trovafoxacin and 164 comparator regimen subjects were included in the bacteriological intent-to-treat analyses. The most common reason for exclusion from clinically evaluable analyses was insufficient therapy. Reasons for exclusion from the bacteriologically evaluable analyses were no baseline pathogen or baseline culture performed outside of the evaluable window.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 124.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

Treatment Group for Response	Subjects Included	
	Alatrofoxacin Trovafoxacin (N=204)	Imipenem/cilastatin Amoxicillin/clavulanac (N=210)
Clinically ITT	200 (98.0%)	199 (94.8%)
Bacteriologically ITT	171 (83.8%)	164 (78.1%)
Applicant Clinically Evaluable		
Clinically Evaluable at EOT	155 (76.0%)	142 (67.6%)
Clinically Evaluable at EOS	156 (76.5%)	152 (72.4%)
Applicant Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	135 (66.2%)	123 (58.6%)
Bacteriologically Evaluable at EOS	135 (66.2%)	131 (62.4%)

The clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 124.3A and 124.3B, respectively. Confidence interval results from analyses showed that alatrofoxacin/trovafoxacin was therapeutically equivalent to imipenem/cilastatin/amoxicillin/clavulanac with respect to the success rates at both EOT and EOS.

TABLE 124.3A: STUDY 154-124: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Alatrofloxacin Trovafoxacin (N=155)	Imipenem/cilastatin Amoxicillin/clavulanac (N=142)
Success (cure+improvement)	136 (87.8%)	122 (85.9%)
Failure	19 (12.3%)	20 (14.1%)
A./T. vs I./C./A./C. by Success	1.8%, 95% C.I.: -6.6%, 10.2%	

TABLE 124.3B: STUDY 154-124: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin Trovafoxacin (N=156)	Imipenem/cilastatin Amoxicillin/clavulanac (N=152)
Success (cure+improvement)	129 (82.7%)	127 (83.6%)
Failure	27 (17.3%)	25 (16.4%)
A./T. vs I./C./A./C. by Success	-0.9%, 95% C.I.: -9.9%, 8.2%	

Analyses of the pathogen eradication rates of the Applicant bacteriologically evaluable subjects at EOT and EOS are displayed in Tables 124.4A and 124.4B, respectively. Comparisons (95% confidence intervals) of the difference in *E. coli* eradication rates between the two treatment groups supported equivalence of alatrofloxacin/trovafoxacin versus imipenem/cilastatin/amoxicillin/clavulanac at both timepoints.

TABLE 124.4A: STUDY 154-124: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Alatrofloxacin Trovafoxacin	Imipenem/cilastatin Amoxicillin/clavulanac	95% CI
<i>E. coli</i>	73/77 (94.8%)	53/58 (91.4%)	-6.8%, 13.7%
<i>B. fragilis</i>	30/30 (100%)	31/34 (91.2%)	
<i>Streptococcus</i> sp.	28/30 (93.3%)	40/41 (97.6%)	
<i>S. viridans</i>	19/20 (95.0%)	22/23 (95.7%)	
<i>P. aeruginosa</i>	15/16 (93.8%)	16/17 (94.1%)	

TABLE 124.4B: STUDY 154-124: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Alatrofloxacin Trovafoxacin	Imipenem/cilastatin Amoxicillin/clavulanac	95% CI
<i>E. coli</i>	67/77 (87.0%)	52/59 (88.1%)	-13.8%, 11.5%
<i>B. fragilis</i>	27/30 (90.0%)	28/36 (77.8%)	
<i>Streptococcus</i> sp.	26/30 (86.7%)	40/43 (93.0%)	
<i>S. viridans</i>	18/20 (90.0%)	19/23 (82.6%)	
<i>P. aeruginosa</i>	14/16 (87.5%)	15/18 (83.3%)	

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 124.5. The alatrofloracin/trovafloracin group experienced a significantly higher rate of adverse events in the central and peripheral nervous system regardless of relationship to study drug than did the imipenem/cilastatin/amoxicillin/clavulanac group.

TABLE 124.5: STUDY 154-124: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Alatrofloracin/ Trovafloracin (N=201)	Imipenem/Cilastatin /Amoxicillin/ Clavulanac Acid (N=207)	Fisher's P-value
At Least One AE	128/201 (63.7%)	120/207 (58.0%)	0.253
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	32 (15.9%)	13 (6.3%)	0.002
Confusion	8 (4.0%)	5 (2.4%)	0.410
Dizziness	9 (4.5%)	2 (1.0%)	0.034
Headache	11 (5.5%)	5 (2.4%)	0.131
At Least One Treatment Related AE	29/201 (14.4%)	23/207 (11.1%)	0.373
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	8 (4.0%)	2 (1.0%)	0.059
Dizziness	3 (1.5%)	2 (1.0%)	0.681
Headache	1 (0.5%)	0 (1.0%)	0.493
Discontinuations Due to an AE	19/201 (9.5%)	19/207 (9.2%)	1.000
Clinically Significant Lab Abnormalities	142/198 (71.7%)	153/205 (74.6%)	0.574

Eleven subjects in the alatrofloracin/trovafloracin group and 11 subjects in the comparator regimen died during this study. None of these deaths were considered by the investigator to be related to study drug. Thirty-four (17%) subjects in the alatrofloracin/trovafloracin group and 44 (21%) in the imipenem/cilastatin/amoxicillin/clavulanac group had serious adverse events during this study, among which 32 subjects in the alatrofloracin/trovafloracin group and 44 subjects in the comparator regimen were considered by the investigator to be unrelated to study drug.

Reviewer's Summary and Conclusions: See Section X.

II. GYNECOLOGIC AND PELVIC INFECTIONS

II.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-144, as evidence to support intravenous alatrofoxacin followed by oral trovafoxacin regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general design of the study is as follows:

Study 154-144 was a randomized, double-blind, multicenter trial which compared the safety and efficacy of intravenous alatrofoxacin followed by oral trovafoxacin for a maximum total treatment duration of 14 days versus intravenous cefoxitin followed by oral amoxicillin/clavulanic acid for a maximum total treatment duration of 14 days for the treatment of female subjects with acute pelvic infections requiring initial intravenous therapy.

II.B. STUDY 154-144

II.B.1. METHODS

In study 154-144, a total of approximately 300 subjects with a clinical diagnosis consistent with acute pelvic infection were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the baseline assessment (Day 1), subjects who met the criteria for clinical diagnosis of acute pelvic infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of female inpatients or outpatients, who were 18 years of age or older with clinically documented acute pelvic infection.

At Day 1 (baseline), baseline assessments and clinical assessment of signs and symptoms of acute pelvic infection were performed. At Day 3, efficacy observations were performed to assess response to study therapy. Safety was assessed. The investigator provided an evaluation of clinical response. At Day 5, if the subject remained hospitalized, efficacy observations were repeated to assess response to study therapy. Safety was assessed. At Day 14 (EOT) efficacy observations were repeated. Safety was assessed. The investigator provided an evaluation of clinical response. At Day 30 (EOS), efficacy observations were performed to assess response to study therapy. The investigator provided an evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 144.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug for intravenous administration was prepared by a study site pharmacist using a double-dummy technique to maintain blinding. Subjects received one of the following intravenous treatment regimens: 1. alatrofoxacin 300 mg in 200 ml of D5W administered once daily as a 60-minute infusion (3x100 mg vials) and 200 ml D5W with the addition of a multivitamin solution every 6 hours (cefoxitin placebo); 2. cefoxitin 2 g in 200 ml of D5W administered every 6 hours as a 60-minute infusion (2x1 gram vials) and 200 ml D5W once daily (alatrofoxacin placebo). All subjects received intravenous study medication every 6 hours in combinations of active drug and placebos for active drug. Six hours after the last intravenous treatment with randomized study medication subjects received one of the following treatments orally: 1. trovafoxacin 200 mg/day as a single active dose (2x100 mg tablets) and 10 ml of suspension three times

daily (amoxicillin/clavulanic acid placebo); 2. amoxicillin/clavulanic acid 1500 mg/ 30 ml/day in three equally divided doses and two tablets once daily (trovafoxacin placebo). All subjects received oral study medication three times daily (every 8 hours) in combinations of active drug and placebos for active drug. The decision to stop therapy was based on the investigator's assessment of clinical outcome. Typically, study drug therapy continued until the subject was afebrile for a period of 24 to 48 hours.

TABLE 144.1: STUDY 154-144: VISIT TIMING AND PROCEDURES				
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 3	Day 5	Day 3-
Allowable Window	-48 hours	Day 2-4	Day 5-7	Day 28-42
Treatment Period	Day 1 to Day 14			
Follow-up Period	Day 15 to Day 12			
Informed Consent	X			
Demographic Information	X			
Maximum Body Temperature	X		X	
Targeted Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Clinical Signs and Symptoms	X	X	X	X
Concomitant Medication	X		X	X
Dosing Record	X		X	
Microbiology				
• pelvic areas	X	X	X	X
• blood	X	X	X	X
• urine	X	X	X	X
Safety Laboratory Tests				
• hematology	X	X	X	abn
• biochemistry	X	X	X	abn
• urinalysis	X	X	X	abn
Adverse Event	X		X	X
Investigator's Assessment of Clinical Response		X	X	X
Health Care Resource Utilization	X		X	X

abn Abnormal at previous visit or clinically significant adverse event.

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically and bacteriologically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoints were clinical response at EOT, and pathogen outcomes at EOT and EOS.

Clinical response to therapy was determined by the sponsor and evaluated 48 hours after initiation of therapy (Day 3), at EOT (Day 14) and at EOS (Day 30) (primary endpoint), or at the time of discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. The clinical response was classified as cure, improvement, or failure. Pathogen bacteriologic outcome was classified as eradication, presumed eradication, persistence, presumed persistent, superinfection, or colonization.

Reviewer's Note: *The Medical Officer also defined his clinically and bacteriologically evaluable subjects, and assessed clinical and bacteriological efficacy outcomes according to his clinical and bacteriological criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of clinical laboratory tests, vital signs, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between alatrofloracin/trovafloracin and cefoxitin/amoxicillin/clavulanic.

Efficacy analyses were based on the clinical and bacteriological responses at EOT and EOS. The treatment groups were compared with respect to the clinical success (cure+improvement) rate and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success rate at EOS in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: *All efficacy analyses were conducted for the Medical Officer clinically and bacteriologically evaluable subjects, and the Applicant clinically and bacteriologically evaluable subjects. All of the subjects in these groups were assessed for their clinical or bacteriological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.*

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

II.B.2. RESULTS

A total of 317 subjects were enrolled at 55 centers in the USA between June 21, 1995 and May 3, 1996. Of the 160 alatrofloxacin/trovafoxacin and 157 cefoxitin/amoxicillin/clavulanic subjects, 47 and 29 subjects, respectively, were prematurely discontinued from treatment. One hundred fifty nine alatrofloxacin/trovafoxacin and 157 cefoxitin/amoxicillin/clavulanic subjects were included in the clinical intent-to-treat analyses; 132 alatrofloxacin/trovafoxacin and 122 cefoxitin/amoxicillin/clavulanic subjects were included in the bacteriological intent-to-treat analyses. The Applicant clinically evaluable group at EOS comprised 226 subjects, and there were 203 subjects in the Medical Officer clinically evaluable group at EOS. The most common reason for exclusion from clinical evaluable analyses was concomitant antibiotic therapy for intercurrent illness. The only reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 144.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

TABLE 144.2: STUDY 154-144: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP

Treatment Group for Response	Subjects Included	
	Alatrofloxacin Trovafoxacin (N=161)	Cefoxitin Amoxicillin/clavulanic (N=159)
Clinically ITT	159 (98.8%)	157 (98.7%)
Bacteriologically ITT	132 (82.0%)	122 (76.7%)
Applicant Clinically Evaluable		
Clinically Evaluable at EOT	93 (57.8%)	104 (65.4%)
Clinically Evaluable at EOS	107 (66.5%)	119 (74.8%)
MO Clinically Evaluable		
Clinically Evaluable at EOT	84 (52.2%)	91 (57.2%)
Clinically Evaluable at EOS	96 (59.6%)	107 (67.3%)
Applicant Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	77 (47.8%)	83 (52.2%)
Bacteriologically Evaluable at EOS	88 (54.7%)	93 (58.5%)
MO Bacteriologically Evaluable		
Bacteriologically Evaluable at EOS	78 (48.4%)	87 (54.7%)

Clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 144.3A and 144.3B, respectively. Confidence interval results from analyses showed that alatrofloxacin/trovafoxacin was therapeutically equivalent to cefoxitin/amoxicillin/clavulanic with respect to the success rates at both EOT and EOS.

Reviewer's Note: The clinical cure rates of the Medical Officer clinically evaluable subjects at EOT and EOS are presented in Tables 144.4A and 144.4B, respectively. Therapeutic equivalence of alatrofloxacin/trovafoxacin to cefoxitin/amoxicillin/clavulanic with respect to clinical cure rates was demonstrated at both time points.

TABLE 144.3A: STUDY 154-144: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Alatrofloxacin Trovafoxacin (N=93)	Cefoxitin Amoxicillin/clavulanic (N=104)
Success (cure+improvement)	83 (89.2%)	87 (83.7%)
Failure	10 (10.8%)	17 (16.3%)
A./T. vs C./A./C. by Success	5.6%, 95% C.I.: -4.9%, 16.1%	

TABLE 144.3B: STUDY 154-144: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin Trovafoxacin (N=107)	Cefoxitin Amoxicillin/clavulanic (N=119)
Success (cure+improvement)	96 (89.7%)	102 (85.7%)
Failure	11 (10.3%)	17 (14.3%)
A./T. vs C./A./C. by Success	4.0%, 95% C.I.: -5.4%, 13.4%	

TABLE 144.4A: STUDY 154-144: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Alatrofloxacin Trovafoxacin (N=84)	Cefoxitin Amoxicillin/clavulanic (N=91)
Success (cure+improvement)	74 (88.1%)	75 (82.4%)
Failure	10 (11.9%)	16 (17.6%)
A./T. vs C./A./C. by Success	5.7%, 95% C.I.: -5.9%, 17.3%	

TABLE 144.4B: STUDY 154-144: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin Trovafoxacin (N=96)	Cefoxitin Amoxicillin/clavulanic (N=107)
Success (cure+improvement)	85 (88.5%)	89 (83.2%)
Failure	11 (11.5%)	18 (16.8%)
A./T. vs C./A./C. by Success	5.4%, 95% C.I.: -5.2%, 15.9%	

Analyses of the pathogen eradication rates of the Applicant bacteriologically evaluable subjects at EOT and EOS are displayed in Tables 144.5A and 144.5B, respectively. Comparisons (95% confidence intervals) of the difference in *E. faecalis* eradication rates between the two treatment groups supported equivalence of alatrofloxacin/trovafoxacin versus cefoxitin/amoxicillin/clavulanic at both timepoints.

Reviewer's Note: Table 144.6 shows the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at EOS. Alatrofloxacin/trovafoxacin showed therapeutic equivalence to cefoxitin/amoxicillin/clavulanic at EOS with respect to the eradication rate of *E. faecalis*.

TABLE 144.5A: STUDY 154-144: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Alatrofoxacin Trovafoxacin	Cefoxitin Amoxicillin/clavulanic	95% C.I.
<i>E. faecalis</i>	24/24 (100%)	25/28 (89.3%)	-4.6%, 26.0%
<i>Peptostreptococcus sp.</i>	11/13 (84.6%)	15/16 (93.8%)	
<i>Prevotella sp.</i>	14/15 (93.3%)	11/12 (91.7%)	
<i>Corynebacterium sp.</i>	17/20 (85.0%)	12/15 (80.0%)	
<i>Enterococcus sp.</i>	20/20 (100%)	20/25 (80.0%)	

TABLE 144.5A: STUDY 154-144: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Alatrofoxacin Trovafoxacin	Cefoxitin Amoxicillin/clavulanic	95% C.I.
<i>E. faecalis</i>	28/29 (96.6%)	29/32 (90.6%)	-9.4%, 21.3%
<i>Peptostreptococcus sp.</i>	14/16 (87.5%)	18/19 (94.7%)	
<i>Prevotella sp.</i>	17/18 (94.4%)	14/15 (93.3%)	
<i>Corynebacterium sp.</i>	20/23 (87.0%)	12/16 (75.0%)	
<i>Enterococcus sp.</i>	26/26 (100%)	22/27 (81.5%)	

TABLE 144.6: STUDY 154-144: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Alatrofoxacin Trovafoxacin	Cefoxitin Amoxicillin/clavulanic	95% C.I.
<i>E. faecalis</i>	25/26 (96.2%)	26/30 (86.7%)	-8.3%, 27.3%
<i>Peptostreptococcus sp.</i>	12/14 (85.7%)	16/17 (94.1%)	
<i>Prevotella sp.</i>	16/17 (94.1%)	15/16 (93.8%)	
<i>S. agalactiae</i>	13/14 (92.9%)	9/13 (69.2%)	
<i>S. epidermidis</i>	12/14 (85.7%)	6/8 (75.0%)	

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 144.7. With respect to all these adverse event rates except the rates of clinically significant laboratory abnormalities, alatrofoxacin/trovafoxacin had significantly higher rates than cefoxitin/amoxicillin/clavulanic. The alatrofoxacin/trovafoxacin group also had a significantly higher incidence rate of dizziness than its comparator group.

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TABLE 144.7: STUDY 154-144: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Alatrofoxacin/ Trovafoxacin (N=160)	Cefoxitin Amoxicillin/clavula. (N=157)	Fisher's P-value
At Least One AE	83/160 (51.9%)	56/157 (35.7%)	0.005
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	25 (15.6%)	11 (7.0%)	0.021
Dizziness	11 (6.9%)	1 (0.6%)	0.005
Headache	15 (9.4%)	10 (6.4%)	0.406
At Least One Treatment Related AE	38/160 (23.8%)	10/157 (6.4%)	<0.001
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	14 (8.8%)	1 (0.6%)	0.001
Dizziness	9 (5.6%)	1 (0.6%)	0.020
Headache	4 (2.5%)	0 (0%)	0.123
Discontinuations Due to an AE	30/160 (18.8%)	9/157 (5.7%)	0.001
Clinically Significant Lab Abnormalities	103/146 (70.6%)	99/152 (65.1%)	0.325

No subject in either treatment group died during this study. Fifteen (9%) subjects in the alatrofoxacin/trovafoxacin group and 10 (6%) in the cefoxitin/amoxicillin/clavulanic group had serious adverse events during this study. Two subjects in the alatrofoxacin/trovafoxacin group had serious adverse events that were considered to be related to study drug.

Reviewer's Summary and Conclusions: See Section X.

APPENDIX 1
UNCLASSIFIED

III. SURGICAL PROPHYLAXIS - ELECTIVE COLORECTAL SURGERY

III.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-128, as evidence to support a single intravenous dose of alatrofloxacin regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general design of the study is as follows:

Study 154-128 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of intravenous therapy with alatrofloxacin (200 mg single infusion) versus cefotetan (2 g single infusion) for the prophylaxis of primary site infection following elective colo-rectal surgery.

III.B. STUDY 154-128

III.B.1. METHODS

In study 154-128, a total of approximately 400 subjects (at least 15 subjects per center) who underwent elective colo-rectal surgery were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. During the Pre-dose (Pre-surgery) period, subjects who met the criteria for elective colo-rectal surgery, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of inpatient men or women, who were 18 years of age or older undergoing elective operations of the colon or rectum.

During the Pre-dose (Pre-surgery) period, baseline assessments and hematology, serum chemistry, and urinalysis determinations were performed. On Day 1 (Surgery Day), skin preparation and the operative technique were performed. Forty-eight hours after surgery, safety was assessed by repeating laboratory evaluations. Adverse events were recorded throughout the study. On the day of discharge from the hospital, the investigator recorded all symptoms and physical findings of any infections found during the hospitalization period. The severity of any primary wound infection was noted by the investigator. At Day 30 (Day 28-35, EOS, the final assessment), subjects had a targeted physical examination. The investigator assessed and recorded whether any infection occurred during the post-hospitalization period.

The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 128.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of intravenous solution and was supplied in vials using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. alatrofloxacin 200 ml single infusion; 2. cefotetan 20 ml single infusion. Alatrofloxacin was administered within 2 hours of surgical incision and cefotetan was administered within 30 to 60 minutes of surgical incision.

TABLE 128.1: STUDY 154-128: VISIT TIMING AND PROCEDURES			
Visit Number	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-48 hours		28-35
Informed Consent	X		
Demographic Information	X		
Physical Exam of the Abdomen	X	X	X
Maximum Body Temperature	X	X	X
Vital Signs	X	X	X
Concomitant Medication	X	X	X
Bowel Preparation	X		
Dosing Record		X	
Safety Laboratory Tests			
• hematology	X	X	abn
• biochemistry	X	X	abn
• urinalysis	X	X	abn
• pregnancy test	X		
Adverse Events	X	X	X
Investigator's Report of Infection History/Presence		X	X
Health Care Resource Utilization			X
<i>abn</i> Abnormal at previous visit or clinically significant adverse event.			

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoint was clinical response at hospital discharge.

Clinical response was determined by the sponsor and evaluated at hospital discharge and at EOS (Day 30). Clinical response was based primarily on the investigator's assessment of symptoms and physical findings of any wound infections found during the 30 day study period. Clinical response was classified as success or failure.

Reviewer's Note: *The Medical Officer agreed with clinical evaluability criteria chosen by the Applicant, and assessed clinical efficacy outcomes according to the Applicant clinical criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's efficacy outcome definitions and Medical Officer's comments.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of clinical laboratory tests, vital signs, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between alatrofloxacin and cefotetan.

Efficacy analyses were based on clinical responses at hospital discharge and EOS. The treatment groups were compared with respect to the clinical success rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success rate at EOS in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: *All efficacy analyses were conducted for the Applicant clinically evaluable subjects and the Applicant clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection. All of the subjects in these groups were assessed for their clinical responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.*

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

III.B.2. RESULTS

A total of 518 subjects were enrolled across centers in the USA (76) and Canada (6) between April 10, 1995 and March 12, 1996. Of the 256 alatrofloxacin and 236 cefotetan subjects, seven alatrofloxacin subjects were prematurely discontinued from treatment during the 1-hour infusion period and one cefotetan subject was prematurely discontinued from treatment during the 5-minute infusion period. Of the 269 alatrofloxacin and 249 cefotetan randomized subjects, 23 alatrofloxacin and 13 cefotetan subjects were excluded from clinical intent-to-treat and evaluable analyses because of not having elective, uncomplicated surgery on the colon or rectum, and not having surgery or having frank stool found during surgery. Of the 246 alatrofloxacin and 236 cefotetan clinically intent-to-treat subjects, 85 in the alatrofloxacin group and 80 in the cefotetan group were not clinically evaluable; therefore, 161 subjects in the alatrofloxacin group and 156 subjects in the cefotetan group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was concomitant antibiotic therapy for intercurrent illness.

Reviewer's Note: *The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 128.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 128.2: STUDY 154-128: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Treatment Group for Response	Subjects Included	
	Alatrofloxacin (N=269)	Cefotetan (N=249)
Clinically ITT	246 (91.4%)	236 (94.8%)
Applicant Clinically Evaluable		
Clinically Evaluable at HOS	161 (59.9%)	156 (62.7%)
Clinically Evaluable at EOS	161 (59.9%)	156 (62.7%)
Applicant Clinically Evaluable +		
Clinically Evaluable + at HOS	210 (78.1%)	204 (81.9%)
Clinically Evaluable + at EOS	210 (78.1%)	204 (81.9%)

HOS Hospital Discharge
+ Plus subjects Receiving Concomitant Antibiotics for Distant Site Infection

Clinical responses at hospital discharge and EOS are shown for the Applicant clinically evaluable subjects in Tables 128.3A and 128.3B, respectively. Confidence interval results from analyses show that alatrofloxacin was therapeutically equivalent to ciprofloxacin with respect to the success rates at both timepoints.

TABLE 128.3A: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT HOSPITAL DISCHARGE		
Clinical Response	Alatrofloxacin (N=161)	Cefotetan (N=156)
Success	127 (78.9%)	128 (82.1%)
Failure	34 (21.1%)	28 (17.9%)
Alatro. vs Cefot. by Success	-3.2%, 95% C.I.: -12.5%, 6.2%	

TABLE 128.3B: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin (N=161)	Cefotetan (N=156)
Success	116 (72.0%)	113 (72.4%)
Failure	45 (28.0%)	43 (27.6%)
Alatro. vs Cefot. by Success	-0.4%, 95% C.I.: -10.9%, 10.1%	

Tables 128.4A and 128.4B show clinical responses of the clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection at hospital discharge and EOS, respectively. Confidence interval results show that the two treatment groups were therapeutically equivalent with respect to the cure rates at both timepoints.

TABLE 128.4A: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION AT HOSPITAL DISCHARGE		
Clinical Response	Alatrofloxacin (N=210)	Cefotetan (N=204)
Success	165 (78.6%)	158 (77.5%)
Failure	45 (21.4%)	46 (22.5%)
Alatro. vs Cefot. by Success	1.1%, 95% C.I.: -7.3%, 9.6%	

TABLE 128.4B: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION AT EOS		
Clinical Response	Alatrofloxacin (N=210)	Cefotetan (N=204)
Success	152 (72.4%)	139 (68.1%)
Failure	58 (27.6%)	65 (31.9%)
Alatro. vs Cefot. by Success	4.2%, 95% C.I.: -5.0%, 13.5%	

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 128.5. With respect to the rate of treatment related adverse events, alatrofloxacin subjects had significantly higher rates than cefotetan subjects.

TABLE 128.5: STUDY 154-128: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Alatrofloxacin (N=256)	Cefotetan (N=236)	Fisher's P-value
At Least One AE	156/256 (60.9%)	135/236 (57.2%)	0.410
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	19 (7.4%)	15 (6.4%)	0.723
Confusion	7 (2.7%)	5 (2.1%)	0.774
Dizziness	3 (1.2%)	2 (0.9%)	1.000
Headache	8 (3.1%)	5 (2.1%)	0.580
At Least One Treatment Related AE	26/256 (10.2%)	6/236 (2.5%)	0.001
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	2 (0.8%)	1 (0.4%)	1.000
Dizziness	2 (0.8%)	0 (0%)	0.500
Headache	0 (0%)	1 (0.4%)	0.480
Discontinuations Due to an AE	5/256 (2.0%)	0/236 (0%)	0.062
Clinically Significant Lab Abnormalities	191/246 (77.6%)	184/231 (79.7%)	0.655

Four subjects in the alatrofloxacin group and seven subjects in the cefotetan group died during or following completion of this study. Sixty-nine (27%) subjects in the alatrofloxacin group and 70 (30%) subjects in

the cefotetan group had serious adverse events during this study. One subject in each treatment group had serious adverse events that were considered to be related to study drug.

Reviewer's Summary and Conclusions: See Section X.

IV. SURGICAL PROPHYLAXIS - ELECTIVE ABDOMINAL AND VAGINAL HYSTERECTOMY

IV.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-146, as evidence to support a single oral dose of trovafoxacin regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general design of the study is as follows:

Study 154-146 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of a single oral dose of trovafoxacin versus a single intravenous infusion of cefoxitin for the prophylaxis of infection following elective abdominal or vaginal hysterectomy.

APPEARS THIS WAY
ON ORIGINAL

IV.B. STUDY 154-146

IV.B.1. METHODS

In study 154-146, a total of approximately 350 subjects (at least 16 subjects per center) who underwent elective abdominal or vaginal hysterectomy were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. During the Pre-dose (Pre-surgery) period, subjects who met the criteria for elective hysterectomy, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of inpatient women, who were 18 years of age or older undergoing elective abdominal or vaginal hysterectomy.

During the Pre-dose (Pre-surgery) period, baseline assessments were performed. On Day 1 (Surgery Day), skin preparation and the operative technique were performed. Forty-eight hours after surgery, safety was assessed by repeating laboratory evaluations. Adverse events were recorded throughout the study. On the day of discharge from the hospital, the investigator reviewed all relevant information and recorded all symptoms and physical findings of any infections found during the hospitalization period. At Day 30 (EOS, the final assessment), subjects had a targeted physical examination. The investigator assessed and recorded whether any infection occurred during the post-hospitalization period. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 146.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was prepared using a double dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafoxacin 200 mg (2x100 mg tablets) administered once, 45 (±15) minutes prior to the estimated time of surgical incision and 50 ml D5W with 0.1 ml MVI administered no earlier than 30 minutes prior to, and no later than the time of, surgical incision as a 10 (±5) minute infusion (cefoxitin placebo); 2. cefoxitin 2 g in 50 ml of D5W administered no earlier than 30 minutes prior to, and no later than the time of, surgical incision as a 10 (±5) minute infusion and two tablets administered once, 45 (±15) minutes prior to the estimated time of surgical incision (trovafoxacin placebo).

TABLE 146.1: STUDY 154-146: VISIT TIMING AND PROCEDURES			
Visit Number	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-72 hours		24-36
Informed Consent	X		
Demographic Information	X		
History & Physical Examination for Signs and Symptoms of Infection with Abdominal/Perineal Exam	X	X	X
Oral Body Temperature	X	X	X
Vital Signs	X	X	X
Concomitant Medication	X	X	X
Dosing Record	X		
Safety Laboratory Tests			
• hematology	X	X	abn
• biochemistry	X	X	abn
• urinalysis	X	X	abn
Adverse Events	X	X	X
Investigator's Assessment of Infection		X	X
Health Care Resource Utilization			X
<i>abn</i> Abnormal at previous visit or clinically significant adverse event.			

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoint was clinical response at hospital discharge.

Clinical response was determined by the sponsor and evaluated at hospital discharge and at EOS (Day 30). Clinical response was based primarily on the investigator's assessment of symptoms and physical findings of any wound infections found during the 30 day study period. Clinical response was classified as success or failure.

Reviewer's Note: The Medical Officer agreed with clinical evaluability criteria chosen by the Applicant, and assessed clinical efficacy outcomes according to the Applicant clinical criteria.

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's efficacy outcome definitions and Medical Officer's comments.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of clinical laboratory tests, vital signs, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between trovafloxacin and cefoxitin.

Efficacy analyses were based on clinical responses at hospital discharge and EOS. The treatment groups were compared with respect to the clinical success rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success rate at EOS in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: All efficacy analyses were conducted for the Applicant clinically evaluable subjects, the Applicant clinically evaluable subjects except those receiving bicitra, and the Applicant clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection except those receiving bicitra. All of the subjects in these groups were assessed for their clinical responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

IV.B.2. RESULTS

One hundred and ninety six trovafloxacin and 191 cefoxitin randomized subjects were enrolled at 18 centers in the USA between January 18, 1996 and June 11, 1996. Of the 188 trovafloxacin and 175 cefoxitin treated subjects, five trovafloxacin and no cefoxitin subject were prematurely discontinued from treatment. The reasons for discontinuation were due to an unrelated adverse event, or surgery postponed, or penicillin allergy. Of the 183 trovafloxacin and 185 cefoxitin clinically intent-to-treat subjects, 50 in the trovafloxacin group and 58 in the cefoxitin group were not clinically evaluable; therefore, 133 subjects in the trovafloxacin group and 127 subjects in the cefoxitin group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was concomitant antibiotic therapy for intercurrent illness.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 146.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

TABLE 146.2: STUDY 154-146: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Treatment Group for Response	Subjects Included	
	Trovafoxacin (N=196)	Cefoxitin (N=191)
Clinically ITT	183 (93.4%)	185 (96.9%)
Applicant Clinically Evaluable		
Clinically Evaluable at HOS	133 (67.9%)	127 (66.5%)
Clinically Evaluable at EOS	133 (67.9%)	127 (66.5%)
Applicant Clinically Evaluable -		
Clinically Evaluable - at HOS	103 (52.6%)	97 (50.8%)
Clinically Evaluable - at EOS	103 (52.6%)	97 (50.8%)
Applicant Clinically Evaluable + -		
Clinically Evaluable + - at HOS	131 (66.8%)	130 (68.1%)
Clinically Evaluable + - at EOS	131 (66.8%)	130 (68.1%)
HOS Hospital Discharge - Excluding Subjects who Received Bicitra + Plus subjects Receiving Concomitant Antibiotics for Distant Site Infection		

Clinical responses at hospital discharge and EOS are shown for the Applicant clinically evaluable subjects in Tables 146.3A and 146.3B, respectively. Confidence interval results from analyses show that trovafoxacin was therapeutically equivalent to cefoxitin with respect to the clinical success rates at hospital discharge, but not at EOS. In fact, the clinical success rate for trovafoxacin at EOS was significantly lower than that for cefoxitin.

TABLE 146.3A: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT HOSPITAL DISCHARGE		
Clinical Response	Trovafoxacin (N=133)	Cefoxitin (N=127)
Success	128 (96.2%)	122 (96.1%)
Failure	5 (3.8%)	5 (3.9%)
Trova. vs Cefot. by Success	0.2%, 95% C.I.: -5.3%, 5.6%	

TABLE 146.3B: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Trovafoxacin (N=133)	Cefoxitin (N=127)
Success	111 (83.5%)	117 (92.1%)
Failure	22 (16.5%)	10 (7.9%)
Trova. vs Cefot. by Success	-8.7%, 95% C.I.: -17.3%, 0%	

Tables 146.4A and 146.4B show clinical responses of the clinically evaluable subjects except those

receiving bicitra at hospital discharge and EOS, respectively. Confidence interval results show that the two treatment groups were therapeutically equivalent with respect to the success rates at hospital discharge, but not at EOS. Similar results were obtained for the clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection except those receiving bicitra, which are presented in Tables 146.5A and 146.5B.

APPROVED FOR
C. J. [unclear]

TABLE 146.4A: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT HOSPITAL DISCHARGE		
Clinical Response	Trovafoxacin (N=103)	Cefoxitin (N=97)
Success	99 (96.1%)	93 (95.9%)
Failure	4 (3.9%)	4 (4.1%)
Trova. vs Cefot. by Success	0.2%, 95% C.I.: -6.2%, 6.7%	

TABLE 146.4B: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT EOS		
Clinical Response	Trovafoxacin (N=103)	Cefoxitin (N=97)
Success	91 (88.3%)	88 (90.7%)
Failure	12 (11.7%)	9 (9.3%)
Trova. vs Cefot. by Success	-2.4%, 95% C.I.: -11.8%, 7.1%	

TABLE 146.5A: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT HOSPITAL DISCHARGE		
Clinical Response	Trovafoxacin (N=131)	Cefoxitin (N=130)
Success	123 (93.9%)	126 (96.9%)
Failure	8 (6.1%)	4 (3.1%)
Trova. vs Cefot. by Success	-3.0%, 95% C.I.: -8.9%, 2.8%	

TABLE 146.5B: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT EOS		
Clinical Response	Trovafoxacin (N=131)	Cefoxitin (N=130)
Success	112 (85.5%)	118 (90.8%)
Failure	19 (14.5%)	12 (9.2%)
Trova. vs Cefot. by Success	-5.3%, 95% C.I.: -13.9%, 3.3%	

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 146.6. Trovafoxacin was not significantly different from cefoxitin with respect these safety variables.

TABLE 146.6: STUDY 154-146: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trovafoxacin (N=188)	Cefoxitin (N=175)	Fisher's P-value
At Least One AE	114/188 (60.6%)	97/175 (55.4%)	0.339
CENTRAL AND PERIPHERAL NERVOUS	15 (8.0%)	13 (7.4%)	1.000
Dizziness	6 (3.2%)	4 (2.3%)	0.752
Headache	8 (4.3%)	8 (4.6%)	1.000
At Least One Treatment Related AE	0/188 (0%)	2/175 (1.1%)	0.232
Discontinuations Due to an AE	1/188 (0.5%)	0/175 (0%)	1.000
Clinically Significant Lab Abnormalities	110/179 (61.5%)	95/172 (55.2%)	0.279

No subject in either treatment group died during this study. Twenty-six (14%) subjects in the trovafoxacin group and 10 (6%) in the cefoxitin group had serious adverse events during this study. All were considered by the investigator to be unrelated to study drug.

Reviewer's Summary and Conclusions: See Section X.

V. NON-GONOCOCCAL URETHRITIS AND CERVICITIS

V.A. INTRODUCTION

The Applicant submitted two pivotal studies as evidence to support oral trovafoxacin regarding this indication, in which Study 154-123 was a controlled study and Study 154-105 was an open label study. Statistical review focuses on 154-123 which forms the basis of this application. The general designs of these two studies are as follows:

Study 154-105 was an open, randomized, non-comparative, two-center, dose-ranging trial which evaluated the safety and efficacy of four different multiple dose regimens of trovafoxacin in the treatment of uncomplicated chlamydial urethritis/cervicitis.

Study 154-123 was a randomized, double-blind, double-dummy, comparative, multicenter trial which compared the safety and efficacy of trovafoxacin administered orally for 5 days versus doxycycline administered orally for 7 days for the treatment of uncomplicated chlamydial urethritis/cervicitis.

V.B. STUDY 154-105

V.B.1. METHODS

In study 154-105, up to 80 evaluable subjects with uncomplicated chlamydial urethritis/cervicitis were to be enrolled and assigned to one of four treatment groups in a 1:1:1:1 ratio. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for a presumptive diagnosis of genital chlamydial infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of male and female subjects, who were 18 years of age or older with presumptive chlamydial urethritis/cervicitis infection.

At Visit 1 (Day 1, baseline), baseline assessments were performed. At the follow-up visits (Visits 2 and 3, follow-up visits; Visit 4, EOS visit), all subjects with culture-confirmed chlamydial infection of any site returned for follow-up urethral/cervical cultures for *C. trachomatis*. Clinical signs and symptoms of urethritis/cervicitis were evaluated to assess subject responses to therapy. Safety was assessed. The investigator provided an evaluation of clinical response to therapy at Visits 2, 3, and 4. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 105.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of tablets or oral suspension that were supplied to each investigator in amounts sufficient to complete 10 evaluable subjects at each dose regimen. Subjects received one of the following regimens: 1. trovafoxacin 200 mg once daily for 7 days; 2. trovafoxacin 200 mg once daily for 5 days; 3. trovafoxacin 100 mg once daily for 7 days; 4. trovafoxacin 50 mg once daily for 7 days.

TABLE 105.1: STUDY 154-105: VISIT TIMING AND PROCEDURES				
Visit Number	Baseline	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 8	Day 15	Day 29
Allowable Window	Day 1	Day 5-9	Day 12-18	Day 25-35
Treatment Period	Day 1 to Day 7			
Follow-up Period	Day 7 to Day 29			
Historical and Physical Assessment	X			
Clinical Laboratory	X	X	X	X
• FTA or RPR	X			
• hematology	X	X	X	abn
• serum Chemistry	X	X	X	abn
• urinalysis	X	X	X	abn
• gram stain	X			
• cultures for <i>C. trachomatis</i>	X	X	X	X
• cultures for <i>N. gonorrhoeae</i>	X	X	X	X
• pregnancy tested	X			
Adverse Event		X	X	X

abn Abnormal at previous visit or clinically significant adverse event.

EFFICACY EVALUATION

Efficacy analyses were performed on the bacteriologically and clinically evaluable subjects. The primary efficacy endpoint was subject bacteriological response at EOS. The secondary endpoints were clinical response at EOS, and pathogen outcome at EOS.

Bacteriological response was evaluated separately for each site of infection with *C. trachomatis*, determined by the sponsor, and evaluated at the final evaluation which was classified as eradication or persistence. Clinical response was based primarily on the global evaluations at EOS and was classified as cure, improvement, or failure. Pathogen outcome was classified as eradication, persistence, or presumed persistent.

Reviewer's Note: *The Medical Officer agreed with both bacteriological and clinical evaluability criteria chosen by the Applicant, and assessed bacteriological and clinical efficacy outcomes according to the Applicant bacteriological and clinical criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's efficacy outcome definitions and Medical Officer's comments.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of physical examinations, clinical laboratory tests, vital sign measurements, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial, regardless of treatment group or suspected causal relationship to study drug, were recorded on the CRF.

STATISTICAL METHODS

In this study, interest focused on summarizing data collected on the efficacy variables and obtaining descriptive information about trovafoxacin drawn from defined bacteriological and clinical subject populations.

Efficacy description by gender and overall subjects were based on the bacteriological and clinical responses at EOS. The treatment groups were summarized with respect to the subject bacteriological eradication rate, the clinical success (cure+improvement) rate, and the pathogen bacteriological eradication rate.

Description of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: *Since the sample sizes of the four trovafoxacin treatment groups were considerably small, no formal statistical analyses were conducted. All efficacy variables were summarized for the Applicant bacteriologically and clinically evaluable subjects. All of the subjects in these groups, were assessed for their bacteriological or clinical responses. Results were displayed both by gender and overall. This reviewer summarized safety information with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities.*

V.B.2. RESULTS

A total of 130 subjects were enrolled at 2 centers in the USA between August 10, 1994 and February 6, 1996. Of these enrolled subjects, 44 subjects were withdrawn from the study (11 subjects were withdrawn during treatment and 33 subjects were withdrawn during follow-up). In all cases, the reason for discontinuation was lost to follow-up. No subject in any of the four treatment groups was discontinued from treatment due to inadequate response. Thus, 119 subjects (28, trovafoxacin 200 mg x 7 days; 32, trovafoxacin 200 mg x 5 days; 26, trovafoxacin 100 mg x 7 days; and 33, trovafoxacin 50 mg x 7 days) completed treatment and 86 subjects (21, trovafoxacin 200 mg x 7 days; 22, trovafoxacin 200 mg x 5 days; 19, trovafoxacin 100 mg x 7 days; and 24, trovafoxacin 50 mg x 7 days) completed the study. One hundred-three randomized subjects (50, males; 53, females) were included in the bacteriologically intent-to-treat analyses; 92 randomized subjects (42, males; 50, females) were included in the clinically intent-to-treat analyses. The Applicant bacteriologically evaluable group comprised 73 subjects (35, male; 38, female). The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline culture in the evaluable analysis window.

Reviewer's Note: *The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Tables 105.2A and 105.2B. There was no statistically significant treatment difference with respect to the percentage of subjects, as well as gender characteristics, included in each of four analysis groups.*

TABLE 105.2A: STUDY 154-105: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Treatment Group for Response	Subjects Included			
	Trovafoxacin 200mg x 7days (31)	Trovafoxacin 200mg x 5days (34)	Trovafoxacin 100mg x 7days (28)	Trovafoxacin 50mg x 7days (37)
Clinically ITT	25 (80.6%)	22 (64.7%)	20 (71.4%)	25 (67.6%)
Bacteriologically ITT	26 (83.9%)	23 (67.6%)	24 (85.7%)	30 (81.1%)
Applicant Clinically Evaluable	19 (61.3%)	17 (50.0%)	12 (42.9%)	19 (51.4%)
Applicant Bacteriologically Evaluable	20 (64.5%)	18 (52.9%)	14 (50.0%)	21 (56.8%)

TABLE 105.2B: STUDY 154-105: NUMBER OF MALE AND FEMALE SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Treatment Group for Response	Male Subjects Included			
	Trovafoxacin 200mg x 7days (16)	Trovafoxacin 200mg x 5days (19)	Trovafoxacin 100mg x 7days (13)	Trovafoxacin 50mg x 7days (16)
Clinically ITT	12 (75.0%)	11 (57.9%)	7 (53.8%)	12 (75.0%)
Bacteriologically ITT	13 (81.3%)	12 (63.2%)	11 (68.8%)	14 (73.7%)
Applicant Clinically Evaluable	8 (50.0%)	8 (42.1%)	4 (30.8%)	10 (62.5%)
Applicant Bacteriologically Evaluable	9 (56.3%)	9 (47.4%)	6 (37.5%)	11 (57.9%)
Treatment Group for Response	Female Subjects Included			
	Trovafoxacin 200mg x 7days (15)	Trovafoxacin 200mg x 5days (15)	Trovafoxacin 100mg x 7days (15)	Trovafoxacin 50mg x 7days (21)
Clinically ITT	13 (86.7%)	11 (73.3%)	13 (86.7%)	13 (61.9%)
Bacteriologically ITT	13 (86.7%)	11 (73.3%)	13 (86.7%)	16 (76.2%)
Applicant Clinically Evaluable	11 (73.3%)	9 (60.0%)	8 (53.3%)	9 (42.9%)
Applicant Bacteriologically Evaluable	11 (73.3%)	9 (60.0%)	8 (53.3%)	10 (47.6%)

Subject bacteriological response at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 105.3. Subject eradication rates were similar for male and female subjects in all four treatment groups at EOS; however, the counts upon which these rates were based were considerably small.

The pathogen eradication rates at EOS are presented by gender and overall for bacteriologically evaluable subjects in Table 105.4. Table 105.5 shows clinical response of the Applicant clinically evaluable subjects at EOS. Those results appeared similar among male and female subjects in all four treatment groups, however, these rates were based upon small counts.

TABLE 105.3: STUDY 154-105: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trovafoxacin 200mg x 7days	Trovafoxacin 200mg x 5days	Trovafoxacin 100mg x 7days	Trovafoxacin 50mg x 7days
Male				
Eradication	9 (100%)	9 (100%)	5 (83.3%)	10 (90.9%)
Persistent	0 (0%)	0 (0%)	1 (16.7%)	1 (9.1%)
Female				
Eradication	10 (90.9%)	9 (100%)	7 (87.5%)	10 (100%)
Persistent	1 (9.1%)	0 (0%)	1 (12.5%)	0 (0%)
Overall				
Eradication	19 (95.0%)	18 (100%)	12 (85.7%)	21 (100%)
Persistent	1 (5.0%)	0 (0%)	2 (14.3%)	0 (0%)

TABLE 105.4: STUDY 154-105: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Pathogen Bacteriological Outcome	Trovafoxacin 200mg x 7days	Trovafoxacin 200mg x 5days	Trovafoxacin 100mg x 7days	Trovafoxacin 50mg x 7days
Male				
<i>C. trachomatis</i>	8/8 (100%)	9/9 (100.0%)	5/6 (83.3%)	10/11 (90.9%)
<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	1/1 (100%)	0	0	0
Female				
<i>C. trachomatis</i>	9/10 (90.0%)	7/7 (100%)	4/5 (80.0%)	10/10 (100%)
<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	1/1 (100%)	2/2 (100%)	3/3 (100%)	0
Overall				
<i>C. trachomatis</i>	17/18 (94.4%)	16/16 (100%)	9/11 (81.8%)	20/21 (95.2%)
<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	2/2 (100%)	2/2 (100%)	3/3 (100%)	0

TABLE 105.5: STUDY 154-105: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trovafoxacin 200mg x 7days	Trovafoxacin 200mg x 5days	Trovafoxacin 100mg x 7days	Trovafoxacin 50mg x 7days
Male				
Success	8 (100.0%)	8 (100.0%)	4 (100.0%)	10 (100.0%)
Failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Female				
Success	11 (100%)	9 (100.0%)	7 (100.0%)	8 (88.9%)
Failure	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)
Overall				
Success	19 (100%)	17 (100.0%)	11 (100.0%)	18 (94.7%)
Failure	0 (0%)	0 (0%)	0 (0%)	1 (5.3%)

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 105.6. No subject in any of the four treatment regimens was discontinued from treatment due to an adverse event. The percentage of subjects reporting at least one treatment related adverse event was 3.2% in the trovafoxacin 200 mg x 7 days group, and numerically it was considerably lower than the other treatment groups.

Safety Outcome	Trovafoxacin 200mg x 7days (N=31)	Trovafoxacin 200mg x 5days (N=34)	Trovafoxacin 100mg x 7days (N=28)	Trovafoxacin 50mg x 7days (N=37)
At Least One AE	5/31 (16.1%)	6/34 (17.6%)	6/28 (21.4%)	5/37 (13.5%)
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	1 (3.2%)	5 (14.7%)	2 (7.1%)	0 (0%)
Dizziness	1 (3.2%)	5 (14.7%)	1 (3.6%)	0 (0%)
At Least One Treatment Related AE	1/31 (3.2%)	5/34 (14.7%)	3/28 (10.7%)	3/37 (8.1%)
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	1 (3.2%)	5 (14.7%)	1 (3.6%)	0 (0%)
Dizziness	1 (3.2%)	5 (14.7%)	1 (3.6%)	0 (0%)
Discontinuations Due to an AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Clinically Significant Lab Abnormalities	4/20 (20.0%)	2/17 (11.8%)	2/9 (22.2%)	1/17 (5.9%)

No serious adverse events or deaths were reported in any of the four treatment groups. Overall, the most common treatment related adverse event was dizziness.

Reviewer's Summary and Conclusions: See Section X.

V.C. STUDY 154-123

V.C.1. METHODS

In study 154-123, a total of approximately 500 subjects with uncomplicated chlamydial urethritis/cervicitis were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio in order to obtain 400 evaluable subjects, with 100 males and 100 females per treatment group. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for a presumptive diagnosis of genital chlamydial infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of male and female outpatients, who were 16 years of age or older with clinically and laboratory documented uncomplicated chlamydial urethritis/cervicitis.

At Visit 1 (Day 1, baseline), baseline assessments were performed. Clinical assessments of signs and symptoms of uncomplicated chlamydial urethritis/cervicitis were recorded as present or absent. At Visit 2 (Day 10, EOT), efficacy observations were performed to assess response to study therapy. At Visit 3 (Day 21), efficacy observations were performed to assess response to study therapy. At Visit 4 (Day 35, EOS), efficacy observations were performed, and a final evaluation of clinical response was provided by the investigator. The reasons for discontinuation of any subject were recorded on the CRF, as well as all

concomitant medications. Table 123.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of trovafloxacin tablets and doxycycline capsules. Drugs were packaged in blister cards using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafloxacin 200 mg/day as a single dose (2x100 mg tablets) and doxycycline placebo twice daily (one capsule); 2. doxycycline 100 mg twice daily (1x100 mg capsule) and trovafloxacin placebo once daily (two tablets). All subjects received study medication in the morning and evening in combinations of active drug and placebos for active drug, and trovafloxacin was administered orally for 5 days while doxycycline was administered orally for 7 days.

Visit Number	Baseline	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 10	Day 21	Day 35
Allowable Window	Day 1	Day 9-11	Day 19-23	Day 31-39
Treatment Period	Day 1 to Day 7			
Follow-up Period	Day 7 to Day 39			
Compliance Checks Historical and Physical	X	X		
Assessment				
Clinical	X	X	X	X
Laboratory				
• FTA or RPR	X			
• hematology	X	X	abn	abn
• serum Chemistry	X	X	abn	abn
• urinalysis	X	X	abn	abn
• gram stainc	X			
• cultures for <i>C. trachomatis</i>	X	X	X	X
• cultures for <i>N. gonorrhoeae</i>	X	X	X	X
• pregnancy tested	X			
Adverse Event	X	X	X	

abn Abnormal at previous visit or clinically significant adverse event.

EFFICACY EVALUATION

Efficacy analyses were performed on the bacteriologically and clinically evaluable subjects. The primary efficacy endpoint was subject bacteriological response at EOS. The secondary endpoints were clinical response at EOS, and pathogen outcome at EOS.

Subject bacteriological response, clinical response, and pathogen outcome were determined by the sponsor and evaluated for each subject at EOS (Visit 4; Day 35), or at the time of discontinuation from the study. Subject bacteriological response was classified as eradication or persistence; clinical response was classified as cure, improvement, or failure; pathogen outcome was classified as eradication, persistence, or presumed persistent.

Reviewer's Note: *The Medical Officer also defined her bacteriologically and clinically evaluable subjects, and assessed bacteriological and clinical efficacy outcomes according to her bacteriological and clinical criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of physical examinations, clinical laboratory tests, vital sign measurements, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between trovafloxacin and doxycycline.

Efficacy analyses, stratified by gender, were based on the bacteriological and clinical responses at EOS. The treatment groups were compared with respect to the subject bacteriological eradication rate, the clinical success (cure+improvement) rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the subject bacteriological eradication rate at EOS in the bacteriologically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: All efficacy analyses were conducted for the Medical Officer bacteriologically and clinically evaluable subjects, and the Applicant bacteriologically and clinically evaluable subjects. All of the subjects in these groups were assessed for their bacteriological or clinical responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

V.B.2. RESULTS

A total of 988 subjects were enrolled across centers in the USA (27) and UK (4) between March 27, 1995 and May 22, 1996. Of these enrolled subjects, 11 were withdrawn prior to randomization, 495 subjects were randomized to receive trovafloxacin, and 482 were randomized to receive doxycycline. Two hundred thirty seven trovafloxacin and 220 doxycycline subjects were included in the clinical intent-to-treat analyses; 332 trovafloxacin and 301 doxycycline subjects were included in the bacteriological intent-to-treat analyses. Most of those subjects were discontinued at Visit 2 because they had no baseline pathogens. The Applicant bacteriologically evaluable group comprised 511 subjects, and there were 452 subjects in the Medical Officer bacteriologically evaluable group. The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline cultures in the EOS visit windows. The most common reason for exclusion from the clinically evaluable analyses was no baseline clinical signs and symptoms.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Tables 123.2A and 123.2B. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

TABLE 123.2A: STUDY 154-123: NUMBER OF SUBJECTS INCLUDED IN ANALYSIS GROUPS		
Treatment Group for Response	Subjects Included	
	Trovafoxacin (N=495)	Doxycycline (N=482)
Clinically ITT	237 (47.9%)	220 (45.6%)
Bacteriologically ITT	332 (67.1%)	301 (62.4%)
Applicant Clinically Evaluable	181 (36.6%)	179 (37.1%)
MO Clinically Evaluable	182 (36.8%)	179 (37.1%)
Applicant Bacteriologically Evaluable	265 (53.5%)	246 (51.0%)
MO Bacteriologically Evaluable	235 (47.5%)	217 (45.0%)

TABLE 123.2B: STUDY 154-123: NUMBER OF MALE AND FEMALE SUBJECTS INCLUDED IN ANALYSIS GROUPS

Treatment Group for Response	Male Subjects Included	
	Trovafoxacin (N=203)	Doxycycline (N=203)
Clinically ITT	95 (46.5%)	93 (45.8%)
Bacteriologically ITT	126 (62.1%)	123 (60.6%)
Applicant Clinically Evaluable	72 (35.5%)	79 (38.9%)
MO Clinically Evaluable	73 (36.0%)	79 (38.9%)
Applicant Bacteriologically Evaluable	100 (49.3%)	102 (50.2%)
MO Bacteriologically Evaluable	85 (41.9%)	94 (46.3%)
Treatment Group for Response	Female Subjects Included	
	Trovafoxacin (N=292)	Doxycycline (N=279)
Clinically ITT	142 (48.6%)	127 (45.5%)
Bacteriologically ITT	206 (70.5%)	178 (63.8%)
Applicant Clinically Evaluable	109 (37.3%)	100 (35.8%)
MO Clinically Evaluable	109 (37.3%)	100 (35.8%)
Applicant Bacteriologically Evaluable	165 (56.5%)	144 (51.6%)
MO Bacteriologically Evaluable	150 (51.4%)	123 (44.1%)

Subject bacteriological response at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 123.3. Confidence interval results from analyses show that trovafoxacin was therapeutically equivalent to doxycycline with respect to the eradication rates at EOS in female subjects and overall subjects. The two treatments were not considered equally effective at EOS for male subjects; lower eradication rates were observed in the trovafoxacin group compared to the doxycycline group. Indeed, the results indicated the inferiority of trovafoxacin to doxycycline in male subjects.

Reviewer's Note: The subject eradication rates of the Medical Officer bacteriologically evaluable subjects at EOS are presented in Table 123.4. Comparisons (95% confidence intervals) of the difference in subject bacteriological eradication rates at EOS between the two treatment groups supported the equivalence of trovafoxacin to doxycycline in female subjects and all subjects combined, but did not support the equivalence of the two treatments in male subjects.

TABLE 123.3: STUDY 154-123: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Eradication	89 (89.0%)	101 (99.0%)	-17.4%, -2.6%
Persistent	11 (11.0%)	1 (0.0%)	
Female			
Eradication	157 (95.2%)	138 (96.5%)	-6.5%, 3.8%
Persistent	8 (4.8%)	5 (3.5%)	
Overall			
Eradication	246 (92.8%)	239 (97.6%)	-8.8%, -0.7%
Persistent	19 (7.2%)	6 (2.4%)	

TABLE 123.4: STUDY 154-123: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Eradication	79 (92.9%)	93 (98.9%)	-12.9%, 1.0%
Persistent	6 (7.1%)	1 (1.1%)	
Female			
Eradication	144 (96.0%)	118 (95.9%)	-5.4%, 5.5%
Persistent	6 (4.0%)	5 (4.1%)	
Overall			
Eradication	223 (94.9%)	211 (97.2%)	-6.3%, 1.7%
Persistent	12 (5.1%)	6 (2.8%)	

The pathogen eradication rates at EOS are presented by gender and overall for bacteriologically evaluable subjects in Table 123.5. Pathogen eradication rates for baseline isolates of *C. trachomatis* were comparable between the trovafoxacin and doxycycline groups at EOS in female subjects and overall subjects. Eradication rates for *C. trachomatis* at EOS were not considered comparable in male subjects.

Reviewer's Note: Table 123.6 shows the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at EOS, and similar trends were observed for males, females, and all subjects combined.

Table 123.7 shows clinical response of the Applicant clinically evaluable subjects at EOS. Comparisons (95% confidence intervals) of the difference in clinical success rates at EOS supported equivalence of the two treatments in female subjects and overall subjects, but failed to show equivalence in male subjects.

Reviewer's Note: Analyses of the cure rates of the Medical Officer clinically evaluable subjects at EOS are displayed in Table 123.8. The results showed that two treatments were therapeutically equivalent to doxycycline in female subjects and overall subjects, however, trovafoxacin was found to be inferior to doxycycline in males.

TABLE 123.5: STUDY 154-123: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS				
Pathogen Bacteriological Outcome	Source	Trovafoxacin	Doxycycline	95% C.I.
Male				
<i>C. trachomatis</i>	Urethra	86/96 (89.6%)	96/97 (99.0%)	-16.9%, 1.9%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Urethra	3/4 (75.0%)	5/5 (100%)	
Female				
<i>C. trachomatis</i>	Urethra/Cervix	153/160 (95.6%)	129/133 (97.0%)	-6.4%, 3.6%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Cervix	4/5 (80.0%)	9/10 (90.0%)	
Overall				
<i>C. trachomatis</i>	Urethra/Cervix	239/256 (93.4%)	225/230 (97.8%)	-8.5%, -0.5%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Urethra/Cervix	7/9 (77.8%)	14/15 (93.3%)	

TABLE 123.6: STUDY 154-123: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Pathogen Bacteriological Outcome	Source	Trovafoxacin	Doxycycline	95% C.I.
Male				
<i>C. trachomatis</i>	Urethra	76/81 (93.8%)	88/89 (98.9%)	-11.9%, 1.8%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Urethra	3/4 (75.0%)	5/5 (100%)	
Female				
<i>C. trachomatis</i>	Urethra/Cervix	140/145 (96.6%)	111/115 (96.5%)	-5.2%, 5.3%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Cervix	4/5 (80.0%)	7/8 (87.5%)	
Overall				
<i>C. trachomatis</i>	Urethra/Cervix	216/226 (95.6%)	199/204 (97.5%)	-5.9%, 1.9%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Urethra/Cervix	7/9 (77.8%)	12/13 (92.3%)	

TABLE 123.7: STUDY 154-123: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Success	68 (94.4%)	79 (100%)	-12.2%, 1.1%
Failure	4 (5.6%)	0 (0%)	
Female			
Success	105 (96.3%)	94 (94.0%)	-4.5%, 9.1%
Failure	4 (3.7%)	6 (6.0%)	
Overall			
Success	173 (95.6%)	173 (96.6%)	-5.6%, 3.5%
Failure	8 (4.4%)	6 (3.4%)	

TABLE 123.8: STUDY 154-123: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Success	67 (91.8%)	79 (100%)	-15.8%, -0.6%
Failure	6 (8.2%)	0 (0%)	
Female			
Success	104 (95.4%)	94 (94.0%)	-5.6%, 8.5%
Failure	5 (4.6%)	6 (6.0%)	
Overall			
Success	171 (94.0%)	173 (96.6%)	-7.6%, 2.2%
Failure	11 (6.0%)	6 (3.4%)	

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 123.9. With respect to the subjects reporting adverse events and the subjects experiencing adverse events related to study medication, the rates were significantly higher in the trovafloxacin group than in the doxycycline group. Significantly more subjects had dizziness and headache in the trovafloxacin group.

TABLE 123.9: STUDY 154-123: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trovafoxacin (N=489)	Doxycycline (N=481)	Fisher's P-value
At Least One AE	222/489 (45.4%)	185/481 (38.5%)	0.032
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	141 (28.8%)	47 (9.8%)	<0.001
Dizziness	105 (21.5%)	17 (3.5%)	<0.001
Headache	55 (11.3%)	29 (6.0%)	0.004
At Least One Treatment Related AE	195/489 (39.9%)	146/481 (30.4%)	0.002
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	131 (26.8%)	38 (7.9%)	<0.001
Dizziness	102 (20.9%)	16 (3.3%)	<0.001
Headache	46 (9.4%)	22 (4.6%)	0.004
Discontinuations Due to an AE	11/489 (2.3%)	13/481 (2.7%)	0.684
Clinically Significant Lab Abnormalities	51/366 (13.9%)	58/381 (15.2%)	0.679

There were no deaths reported during or following completion of the study. Only one subject in the doxycycline group was hospitalized for acute appendicitis that was considered to be unrelated to study drug.

Reviewer's Summary and Conclusions: See Section X.

VI. PELVIC INFLAMMATORY DISEASE

VI.A. INTRODUCTION

The Applicant submitted two pivotal controlled studies, Study 154-122 and Study 154-125, as evidence to support oral trovafloracin regarding this indication, and statistical review focuses on the two clinical trials which form the basis of this application. The general designs of these two studies are as follows:

Study 154-122 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of alatrofloracin administered intravenously followed by oral trovafloracin versus cefoxitin plus doxycycline administered intravenously followed by oral doxycycline for the treatment of acute pelvic inflammatory disease (PID) in hospitalized subjects. Each subject was administered intravenous study medication for a period of at least 48 hours following an improvement in clinical signs and symptoms of PID, followed by oral study medication to complete 14 days of total therapy.

Study 154-125 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of trovafloracin versus ofloxacin and clindamycin for the treatment of acute pelvic inflammatory disease (PID) in ambulatory subjects. Subjects received study medication orally for a duration of 14 days.

VI.B. STUDY 154-122

VI.B.1. METHODS

In study 154-122, a total of approximately 300 subjects with acute pelvic inflammatory disease were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the baseline visit (Visit 1, Day 1), subjects who met the criteria for a presumptive diagnosis of genital chlamydial infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of hospitalized female subjects, who were 16 years of age or older with presumptive diagnosis of acute PID.

At Visit 1 (Day 1, baseline), baseline assessments was performed. The investigator assessed the degree of direct and rebound abdominal tenderness. At Visit 2 (72 hours after initiation of therapy), all clinical signs and symptoms of acute PID were assessed. At Visit 3 (2-4 days following completion of therapy), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. At Visit 4 (2-4 weeks following completion of therapy, EOS), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. The investigator provided an evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 122.1 demonstrates during treatment, and post treatment procedures which were specified by the protocol.

Study drug for intravenous administration was prepared by a designated pharmacist who kept assigned drug information strictly confidential. Subjects received one of the following intravenous treatment regimens: 1. alatrofloracin 200 mg in 200 ml of D5W administered once daily as a 60-minute infusion (2x100 mg vials) and 200 ml D5W with multivitamins (cefexitin placebo) every 6 hours and 200 ml D5W

with multivitamins (doxycycline placebo) every 12 hours; 2. cefoxitin 2 g in 200 ml administered every 6 hours as a 60-minute infusion and doxycycline 100 mg in 200 ml of D5W solution administered every 12 hours as a 60-minute infusion and 200 ml D5W once daily (alatrofoxacin placebo). All subjects received intravenous study medication every 6 hours in combinations of active drug and placebos for active drug until the investigator had determined that there had been a substantial improvement in clinical signs and symptoms of acute PID for at least 48 hours. At this time the subject was switched from intravenous to oral therapy. Study drug for oral administration was in the form of trovafoxacin tablets and doxycycline capsules and was packaged in blister packs, using a double-dummy technique to maintain blinding. Following the completion of intravenous therapy, subjects received one of the following treatments orally: 1. trovafoxacin 200 mg/day as a single active dose (2x100 mg tablets) and one capsule twice daily (doxycycline placebo); 2. doxycycline 200 mg/day in two equally divided doses (1x100 mg capsule per dose) and two tablets once daily (trovafoxacin placebo). All subjects received oral study medication in the morning and evening in combinations of active drug and placebos to complete a total treatment duration of 14 days.

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	72 Hours	Day 16-18	Day 28-42
Treatment Period	Day 1 to Day 14			
Post Therapy Period	Day 16 to Day 42			
Compliance Checks		X	X	X
Informed Consent	X			
Demographic Information	X			
Targeted Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Clinical Assessment*	X	X	X	X
Culdocentesis Endometrial Biopsy, and/or Laparoscope	X		X	
Laboratory				
• hematology	X	X	X	X
• serum chemistry	X	X	X	X
• urinalysis	X	X	X	X
• microbiology				
a. <i>N. gonorrhoeae</i> cultures	X		X	X
b. <i>C. trachomatis</i> cultures	X		X	X
c. Anaerobic/aerobic cultures	X		X	
• FTA or RPR	X			
• pregnancy test	X		X	
Adverse Event	X	X	X	X

* Assessments to be done daily during hospitalization

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically and bacteriologically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoints were bacteriological response at EOS and pathogen outcome at EOS.

Clinical response was determined by the sponsor and evaluated at two interim timepoints: Visit 2 and Visit 3. A final evaluation was given at Visit 4 (EOS). Clinical response was classified as cure or failure. Bacteriological response was determined by the sponsor and evaluated at Visit 3 and at Visit 4 (EOS). Bacteriological response for each subject was classified as satisfactory or unsatisfactory. Pathogen clinical outcome was classified as cure or failure. Pathogen bacteriologic outcome was classified as eradication, presumed eradication, persistence, presumed persistent, superinfection, or colonization.

Reviewer's Note: *The Medical Officer agreed with both clinical and bacteriological evaluability criteria chosen by the Applicant, and assessed clinical and bacteriological efficacy outcomes according to the Applicant clinical and bacteriological criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's efficacy outcome definitions and Medical Officer's comments.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of clinical laboratory tests and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between alatrofloxacin/trovafoxacin and cefoxitin/doxycycline.

Efficacy analyses were based on the clinical and bacteriological responses at EOS. The treatment groups were compared with respect to the clinical cure rate, the subject bacteriological satisfactory rate, the pathogen clinical cure rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical cure rate at EOS in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: *All efficacy analyses were conducted for the Applicant clinically and bacteriologically evaluable subjects. All of the subjects in these groups were assessed for their clinical or bacteriological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.*

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

VI.B.2. RESULTS

A total of 161 subjects were enrolled across centers in the USA (36) and South Africa (5) between June 8, 1995 and May 9, 1996. Three subjects were withdrawn prior to randomization because they did not meet entrance criteria. Seventy nine subjects were randomized to receive alatrofloxacin/trovafoxacin and 79 subjects were randomized to receive cefoxitin/doxycycline. All randomized subjects in both treatment groups received treatment. Fifty-six alatrofloxacin/trovafoxacin and 69 cefoxitin/doxycycline subjects completed treatment, and 60 alatrofloxacin/trovafoxacin and 62 cefoxitin/doxycycline subjects completed the study. Of the 79 alatrofloxacin/trovafoxacin and 79 cefoxitin/doxycycline clinical intent-to-treat subjects, 53 subjects in the alatrofloxacin/trovafoxacin group and 55 subjects in the cefoxitin/doxycycline group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was no post-baseline clinical assessments. Of the clinically evaluable subjects, 31 subjects in the alatrofloxacin/trovafoxacin and 33 subjects in the cefoxitin/doxycycline group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 122.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

Treatment Group for Response	Subjects Included	
	Alatrofloxacin/ Trovafoxacin (N=79)	Cefoxitin/ Doxycycline (N=79)
Clinically ITT	79 (100%)	79 (100%)
Bacteriologically ITT	51 (64.6%)	49 (62.0%)
Applicant Clinically Evaluable	53 (67.1%)	55 (69.6%)
Applicant Bacteriologically Evaluable	31 (39.2%)	33 (41.8%)

Clinical response at EOS is shown for the Applicant clinically evaluable subjects in Table 122.3. Confidence interval results from analyses failed to show that alatrofloxacin/trovafoxacin was therapeutically equivalent to cefoxitin/doxycycline with respect to the cure rates at EOS.

Subject bacteriological response at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 122.4.

Pathogen clinical outcome at EOS is shown for the Applicant clinically evaluable subjects in Table 122.5. The pathogen bacteriological outcome at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 122.6.

TABLE 122.3: STUDY 154-122: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Alatrofloxacin/ Trovafoxacin (N=53)	Cefoxitin/ Doxycycline (N=55)
Cure	43 (81.1%)	50 (90.9%)
Failure	10 (18.9%)	5 (9.1%)
A./T. vs C./D. by Cure	-9.8%, 95% C.I.: -24.6%, 5.1%	

TABLE 122.4: STUDY 154-122: BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Alatrofloxacin/ Trovafoxacin (N=31)	Cefoxitin/ Doxycycline (N=33)
Satisfactory	21 (67.7%)	27 (81.8%)
Unsatisfactory	10 (32.3%)	5 (18.2%)
A./T. vs C./D. by Satisfactory	-14.1%, 95% C.I.: -38.3%, 10.1%	

TABLE 122.5: STUDY 154-122: PATHOGEN CURE RATE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Clinical Outcome	Alatrofloxacin/ Trovafoxacin	Cefoxitin/ Doxycycline
<i>N. gonorrhoeae</i>	11/18 (61.1%)	16/17 (94.1%)
<i>Peptostreptococcus sp.</i>	8/11 (72.7%)	11/13 (84.6%)
<i>C. trachomatis</i>	4/6 (66.7%)	10/10 (100%)
<i>E. coli</i>	5/5 (100%)	4/5 (80.0%)

TABLE 122.6: STUDY 154-122: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Alatrofloxacin/ Trovafoxacin	Cefoxitin/ Doxycycline
<i>N. gonorrhoeae</i>	10/18 (55.6%)	14/16 (87.5%)
<i>C. trachomatis</i>	4/5 (80.0%)	10/10 (100%)
<i>Peptostreptococcus sp</i>	3/5 (60.0%)	5/7 (71.4%)

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 122.7. Alatrofloxacin/trovafoxacin was not significantly different from cefoxitin/doxycycline with respect to these safety variables..

TABLE 122.7: STUDY 154-122: CLINICAL ADVERSE EVENT RATES			
Safety outcome	Alatrofloracin/ Trovafloracin (N=79)	Cefoxitin/ Doxycycline (N=79)	Fisher's P-value
At Least One AE	57/79 (72.2%)	53/79 (67.1%)	0.604
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	11 (13.9%)	8 (10.1%)	0.626
Dizziness	3 (3.8%)	2 (2.5%)	1.000
Headache	10 (12.7%)	6 (7.6%)	0.430
At Least One Treatment Related AE	37/79 (46.8%)	36/79 (45.6%)	1.000
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	5 (6.3%)	3 (3.8%)	0.719
Dizziness	3 (3.8%)	1 (1.3%)	0.620
Headache	4 (5.1%)	2 (2.5%)	0.681
Discontinuations Due to an AE	10/79 (12.7%)	4/79 (5.1%)	0.160
Clinically Significant Lab Abnormalities	42/75 (58.3%)	44/77 (57.1%)	1.000

No subject from either treatment group died during the study. The alatrofloracin/trovafloracin group (11, 14%) had a significantly higher rate of serious adverse events than the cefoxitin/doxycycline group (2, 3%) (p=0.017 using Fisher's exact test). Only one subject in the cefoxitin/doxycycline group experienced an adverse event that was considered by the investigator to be related to study drug.

Reviewer's Summary and Conclusions: See Section X.

VI.C. STUDY 154-125

VI.C.1 METHODS

In study 154-125, a total of approximately 300 subjects with acute pelvic inflammatory disease were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for clinical diagnosis of acute PID, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of ambulatory female subjects, who were 16 years of age or older with presumptive diagnosis of acute PID.

At Visit 1 (Day 1, baseline), baseline assessments were performed. The investigator assessed the degree of direct and rebound abdominal tenderness. At Visit 2 (72 hours after initiation of therapy), all clinical signs and symptoms of acute PID were assessed. At Visit 3 (2 weeks following initiation of therapy), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. Visit 4 (EOS; 4-6 weeks following initiation of therapy), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. The investigator provided an evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 125.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of trovafoxacin tablets and ofloxacin and clindamycin capsules, packaged in blister packs using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafoxacin 200 mg/day as a single dose (2x100 mg tablets) and two capsules (ofloxacin placebo) twice daily and three capsules (clindamycin placebo) four times daily; 2. ofloxacin 800 mg/day in two equally divided doses (2x200 mg capsules) plus clindamycin 1800 mg/day in four equally divided doses (3x150 mg capsules) and two tablets (trovafoxacin placebo) once daily. All subjects received oral study medication four times daily in combinations of active drug and placebo for active drug for 14 days.

TABLE 125.1: STUDY 154-125: VISIT TIMING AND PROCEDURES				
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	72 Hours	Day 14-20	Day 28-42
Treatment Period	Day 1 to Day 14			
Post Therapy Period	Day 14 to Day 42			
Compliance Checks		X	X	X
Informed Consent	X			
Demographic Information	X			
Targeted Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Clinical Assessment*	X	X	X	X
Culdocentesis Endometrial Biopsy	X		X	X
Laboratory				
• hematology	X	X	X	X
• serum chemistry	X	X	X	X
• urinalysis	X	X	X	X
• microbiology				
a. <i>N. gonorrhoeae</i> cultures	X		X	X
b. <i>C. trachomatis</i> cultures	X		X	X
c. Anaerobic/aerobic cultures	X		X	X
• FTA or RPR	X			
• pregnancy test	X		X	
Adverse Event	X	X	X	X

* Assessments to be done daily during hospitalization

Efficacy evaluation, safety evaluation, and statistical methods were similar to those described for Study 154-122 in Section VI.B.1.

VI.C.2. RESULTS

A total of 327 subjects were enrolled across centers in the USA (55) and South Africa (1) between June 5, 1995 and May 8, 1996. Twelve subjects were withdrawn prior to randomization because they did not meet entrance criteria. One hundred fifty-five subjects were randomized to receive trovafoxacin and 161 subjects were randomized to receive ofloxacin/clindamycin. One hundred forty-nine trovafoxacin and 156 ofloxacin/clindamycin subjects received treatment. One hundred twenty-one trovafoxacin and 109 ofloxacin/clindamycin subjects completed treatment; 124 trovafoxacin and 126 ofloxacin/clindamycin

subjects completed the study. Of the 152 trovafloxacin and 159 ofloxacin/clindamycin clinical intent-to-treat subjects, 101 subjects in the trovafloxacin group and 97 subjects in the ofloxacin/clindamycin group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was no post-baseline clinical assessments. Of the clinical intent-to-treat subjects, 40 subjects in the trovafloxacin group and 43 subjects in the ofloxacin/clindamycin group were included in the bacteriological intent-to-treat analysis; 21 subjects in the trovafloxacin and 27 subjects in the ofloxacin/clindamycin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 125.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

Treatment Group for Response	Subjects Included	
	Trovafoxacin (N=155)	Ofloxacin/ Clindamycin (N=161)
Clinically ITT	152 (98.1%)	159 (98.8%)
Bacteriologically ITT	40 (25.8%)	43 (26.7%)
Applicant Clinically Evaluable	101 (65.2%)	97 (60.2%)
Applicant Bacteriologically Evaluable	21 (13.5%)	27 (16.9%)

Clinical response at EOS is shown for the Applicant clinically evaluable subjects in Table 125.3. Confidence interval results from analyses showed that trovafloxacin was therapeutically equivalent to ofloxacin/clindamycin with respect to the cure rates at EOS.

Clinical Response	Trovafoxacin (N=101)	Ofloxacin/ Clindamycin (N=97)
Cure	92 (91.1%)	89 (91.8%)
Failure	9 (8.9%)	8 (8.2%)
Trova. vs. O./C. by Cure	-0.7%, 95% C.I.: -9.5%, 8.1%	

Table 125.4 shows subject bacteriological response of the Applicant bacteriologically evaluable subjects at EOS. Trovafoxacin showed therapeutic equivalence to ofloxacin/clindamycin.

Pathogen clinical outcome at EOS is shown for the Applicant clinically evaluable subjects in Table 125.5. Pathogen bacteriological outcome at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 125.6.

TABLE 125.4: STUDY 154-125: BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trovafoxacin (N=21)	Ofloxacin/ Clindamycin (N=27)
Satisfactory	21 (100%)	25 (92.6%)
Unsatisfactory	0 (0%)	2 (7.4%)
Trova. vs. O./C by Satisfactory	7.4%, 95% C.I.: -6.7%, 21.5%	

TABLE 125.5: STUDY 154-125: PATHOGEN CURE RATE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Clinical Outcome	Trovafoxacin	Ofloxacin/ Clindamycin
<i>N. gonorrhoeae</i>	12/12 (100%)	8/8 (100%)
<i>C. trachomatis</i>	11/12 (91.7%)	14/14 (100%)

TABLE 125.6: STUDY 154-125: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trovafoxacin	Ofloxacin/ Clindamycin
<i>N. gonorrhoeae</i>	10/10 (100%)	8/8 (100%)
<i>C. trachomatis</i>	10/10 (100%)	13/13 (100%)

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Table 125.7. There were significantly more trovafoxacin subjects who experienced dizziness and headache.

TABLE 125.7: STUDY 154-125: CLINICAL ADVERSE EVENT RATES

Safety outcome	Trovafoxacin (N=149)	Ofloxacin /Clindamycin (N=156)	Fisher's P-value
At Least One AE	114/149 (76.5%)	110/156 (70.5%)	0.246
CENTRAL AND PERIPHERAL NERVOUS	65 (43.6%)	24 (15.4%)	<0.001
Dizziness	55 (36.9%)	10 (6.4%)	<0.001
Headache	31 (20.8%)	12 (7.7%)	0.002
At Least One Treatment Related AE	91/149 (61.1%)	94/156 (60.3%)	0.907
CENTRAL AND PERIPHERAL NERVOUS	58 (38.9%)	17 (10.9%)	<0.001
Dizziness	47 (31.5%)	8 (5.1%)	<0.001
Headache	22 (14.8%)	7 (4.5%)	0.003
Discontinuations Due to an AE	19/149 (12.8%)	24/156 (15.4%)	0.622
Clinically Significant Lab Abnormalities	44/141 (31.2%)	41/140 (29.3%)	0.795

No subject from either treatment group died during the study. Four (3%) subjects in the trovafoxacin group and seven (4%) subjects in the ofloxacin/clindamycin group had serious adverse events during this study. Only one subject in the ofloxacin/clindamycin group experienced an adverse event that was considered by the investigator to be related to study drug.

Reviewer's Summary and Conclusions: See Section X.

VII. UNCOMPLICATED URINARY TRACT INFECTIONS

VII.A. INTRODUCTION

The Applicant submitted two pivotal controlled studies, Study 154-103 and Study 154-116, as evidence to support oral trovafoxacin regarding this indication, and statistical review focuses on the two clinical trials which form the basis of this application. The general designs of these two studies are as follows:

Study 154-103 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of two doses of trovafoxacin (100 mg q.d. or 100 mg b.i.d.) versus ciprofloxacin hydrochloride (250 mg b.i.d.) administered orally for 7 days for the treatment of subjects with uncomplicated urinary tract infections. The study was initiated on December 10, 1993 and completed on June 16, 1994.

Study 154-116 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of 3 and 7 days of oral therapy with trovafoxacin (100 mg q.d.) versus 3 days of oral therapy with norfloxacin (400 mg b.i.d.), for the treatment of uncomplicated acute urinary tract infections. The study was initiated on March 15, 1995 and completed on November 13, 1995.

VII.B. STUDY 154-103

VII.B.1. METHODS

In study 154-103, a total of approximately 200 subjects with uncomplicated urinary tract infections were to be enrolled and to be randomized to one of the three treatment groups in a 1:1:1 ratio. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for clinical diagnosis of uncomplicated urinary tract infection, gave informed consent, and met all inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of male and female outpatients (about 95% of subjects were female), who were 18 years of age or older and 65 years of age or younger with clinically documented uncomplicated urinary tract infection.

At Visit 1 (Day 1, baseline), baseline assessments and clinical assessments of signs and symptoms of urinary tract infection were performed. At Visit 2 (Day 5), subjects with no clinical improvement were requested to return to the clinic to have a formal evaluation. At Visit 3 (Day 15, 1 week following study drug completion, EOT), microbiological tests and clinical assessments of signs and symptoms of urinary tract infection were performed. Vital signs were recorded and hematology, chemistry, and urinalysis determinations were repeated. The investigator provided an evaluation of clinical response. At Visit 4 (Day 36, 4 weeks following study drug completion, EOS), microbiological tests and clinical assessments were the same as those performed at Visit 3. Repeat laboratory tests were only performed if a clinically significant abnormality was present at Visit 3 (Day 15). Additionally, the investigator provided a final evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF. All concomitant medications were recorded. Table 103.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of tablets and capsules and was packaged in blister cards using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafloxacin 100 mg/day as a single dose (1x100 mg tablet); 2. trovafloxacin 200 mg/day in two equally divided doses (1x100 mg tablet); 3. ciprofloxacin 500 mg/day in two equally divided doses (1x250 mg tablet). All subjects received study medication in the morning and evening in combinations of active drug and placebos for active drug, administered orally for 7 days.

TABLE 103.1: STUDY 154-103: VISIT TIMING AND PROCEDURES				
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 12	Day 15	Day 36
Allowable Window	Day 1	Day 4-6	Day 11-19	Day 29-43
Treatment Period	Day 1 to Day 8			
Follow-up Period	Day 9 to Day 36			
Informed Consent	X			
Demographic Information	X			
Medical History	X			
Physical Examination	X			
Concomitant Medication	X		X	X
Vital Signs	X		X	X
Dosing Record		X	X	
Adverse Experiences			X	X
Clinical Signs & Symptoms	X	X		X
Urine Assessments				
• pyuria	X		X	X
• quantitative urine				
• culture & sensitivity	X		X	X
Safety Laboratory Tests				abn
• ESR, PT, APTT	X		X	abn
• CBC+chemistry	X		X	abn
• urinalysis	X		X	
Pregnancy test	X			
Investigator's Clinical Evaluation		X	X	

abn Abnormal at previous visit or clinically significant adverse event.

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EFFICACY EVALUATION

Efficacy analyses were performed on the bacteriologically and clinically evaluable subjects. The primary efficacy endpoint was subject bacteriological response at EOT. The secondary endpoints were: subject bacteriological response at EOS, clinical responses at EOT and EOS, and pathogen outcomes at EOT and EOS.

Subject bacteriological response, clinical response, and pathogen outcome were determined by the sponsor and evaluated at Visit 3 (EOT) and Visit 4 (EOS). Subject bacteriologic response was classified as eradication or persistence; clinical response was classified as cure, improvement, failure, or relapse; pathogen outcome was classified as eradication, persistence, or presumed persistent.

Reviewer's Note: The Medical Officer also defined her bacteriologically and clinically evaluable subjects, and assessed bacteriological and clinical efficacy outcomes according to her bacteriological and clinical criteria.

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of physical examinations, clinical laboratory tests, concomitant medication use, vital sign measurements, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

There are three pairwise comparisons of interest in the study: trovafoxacin q.d. versus ciprofloxacin, trovafoxacin b.i.d. versus ciprofloxacin, and trovafoxacin q.d. versus trovafoxacin b.i.d.

Efficacy analyses were based on the bacteriological and clinical responses at EOT (Day 15) and EOS (Day 36). The three treatment groups were compared with respect to the subject bacteriological eradication rate, the clinical success (cure+improvement) rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the subject bacteriological eradication rate at EOT in the bacteriologically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: All efficacy analyses were conducted for the Medical Officer bacteriologically and clinically evaluable subjects, and the Applicant bacteriologically and clinically evaluable subjects. All of the subjects in these groups were assessed for their bacteriological or clinical responses. Bonferroni's adjustment in the Type I error probability was applied for this multiple comparison. Equivalence between pairs of the three treatments with respect to efficacy variables was assessed by computing the two-tailed 98.3% confidence interval (95% family confidence interval) of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The pairwise comparisons among the three treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% family level of significance.

VII.B.2. RESULTS

A total of 221 subjects were enrolled at 16 centers in the USA between March 15, 1995 and November 13, 1995. Of these enrolled subjects, 18 subjects were prematurely discontinued from treatment. Seventy two trovafloxacin q.d., 74 trovafloxacin b.i.d., and 75 ciprofloxacin subjects were included in the clinical intent-to-treat analyses; 56 trovafloxacin q.d.; 57 trovafloxacin b.i.d., and 51 ciprofloxacin subjects were included in the bacteriological intent-to-treat analyses. The Applicant bacteriologically evaluable group at EOT comprised 124 subjects, and there were 73 subjects in the Medical Officer bacteriologically evaluable group at EOT. The most common reason for exclusion from the bacteriologically evaluable subset analysis was no post-baseline cultures. The most common reason for exclusion of subjects from the clinically evaluable subset was insufficient.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 103.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

Treatment Group for Response	Subjects Included		
	Trovafoxacin q.d. (N=72)	Trovafoxacin b.i.d. (N=74)	Ciprofloxacin (N=75)
Clinically ITT	71 (98.6%)	74 (100%)	75 (100%)
Bacteriologically ITT	56 (77.8%)	57 (77.0%)	51 (68.0%)
Applicant Clinically Evaluable			
Clinically Evaluable at EOT	44 (61.1%)	42 (56.8%)	45 (60.0%)
Clinically Evaluable at EOS	46 (63.9%)	44 (59.5%)	44 (58.7%)
MO Clinically Evaluable			
Clinically Evaluable at EOT	22 (30.6%)	22 (29.7%)	28 (37.3%)
Clinically Evaluable at EOS	18 (25.0%)	19 (25.7%)	22 (29.3%)
Applicant Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	43 (59.7%)	40 (54.1%)	41 (54.7%)
Bacteriologically Evaluable at EOS	39 (54.2%)	39 (52.7%)	39 (52.0%)
MO Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	22 (30.6%)	22 (29.7%)	29 (38.7%)
Bacteriologically Evaluable at EOS	21 (29.2%)	21 (28.4%)	27 (36.0%)

Subject bacteriological responses at EOT and EOS are shown for the Applicant bacteriologically evaluable subjects in Tables 103.3A and 103.3B, respectively. The subject eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT and EOS are presented in Tables 103.4A and 103.4B, respectively.

Pathogen bacteriological outcomes at EOT and EOS are shown for the Applicant bacteriologically evaluable subjects in Tables 103.5A and 103.5B, respectively. The pathogen eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT is presented in Tables 103.6.

Clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 103.7A and 103.7B, respectively. The success rates of the Medical Officer clinically evaluable subjects at EOT and EOS are presented in Tables 103.8A and 103.8B, respectively.

REVIEWER COMMENT: With respect to all the efficacy variables, comparisons of the difference between treatment groups were performed. Numerically, the results showed that the three treatment groups were similar at EOT and at EOS. Because this study did not have sufficient power to show equivalence due to small sample size, no definitive conclusions regarding equivalency of the three treatments could be drawn.

TABLE 103.3A: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT			
Subject Bacteriological Response	Trova q.d. (N=43)	Trova b.i.d. (N=40)	Ciprofloxacin (N=41)
Eradication	41 (95.3%)	37 (92.5%)	38 (92.7%)
Persistent	2 (4.7%)	3 (7.5%)	3 (7.3%)
Trova q.d. vs Cipro	2.7%, 98.3% C.I.: -12.1%, 17.5%		
Trova b.i.d. vs Cipro	-0.2%, 98.3% C.I.: -16.6%, 16.2%		
Trova q.d. vs Trova b.i.d.	2.8%, 98.3% C.I.: -12.2%, 17.9%		

TABLE 103.3B: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trova q.d. (N=39)	Trova b.i.d. (N=39)	Ciprofloxacin (N=39)
Eradication	31 (79.5%)	34 (87.2%)	31 (79.5%)
Persistent	8 (20.5%)	5 (12.8%)	8 (20.5%)
Trova q.d. vs Cipro	0%, 98.3% C.I.: -24.5%, 24.5%		
Trova b.i.d. vs Cipro	7.7%, 98.3% C.I.: -15.0%, 30.4%		
Trova q.d. vs Trova b.i.d.	-7.7%, 98.3% C.I.: -30.4%, 15.0%		

TABLE 103.4A: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT			
Subject Bacteriological Response	Trova q.d. (N=22)	Trova b.i.d. (N=22)	Ciprofloxacin (N=29)
Eradication	21 (95.5%)	19 (86.4%)	27 (93.1%)
Persistent	1 (4.5%)	3 (13.6%)	2 (6.9%)
Trova q.d. vs Cipro	2.4%, 98.3% C.I.: -17.1%, 21.8%		
Trova b.i.d. vs Cipro	-6.7%, 98.3% C.I.: -31.6%, 18.1%		
Trova q.d. vs Trova b.i.d.	9.1%, 98.3% C.I.: -15.9%, 34.1%		

TABLE 103.4B: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trova q.d. (N=21)	Trova b.i.d. (N=21)	Ciprofloxacin (N=27)
Eradication	15 (71.4%)	18 (85.7%)	22 (81.5%)
Persistent	6 (28.6%)	3 (14.3%)	5 (18.5%)
Trova q.d. vs Cipro	-10.1%, 98.3% C.I.: -43.9%, 23.8%		
Trova b.i.d. vs Cipro	4.2%, 98.3% C.I.: -25.6%, 34.0%		
Trova q.d. vs Trova b.i.d.	-14.3%, 98.3% C.I.: -48.9%, 20.3%		

TABLE 103.5A: STUDY 154-103: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trova q.d.	Trova b.i.d.	Ciprofloxacin
<i>E. coli</i>	37/38 (97.4%)	32/33 (97.0%)	30/31 (96.8%)
Trova q.d. vs Cipro	0.6%, 98.3% C.I.: -12.2%, 13.3%		
Trova b.i.d. vs Cipro	0.2%, 98.3% C.I.: -13.4%, 13.8%		
Trova q.d. vs Trova b.i.d.	0.4%, 98.3% C.I.: -11.9%, 12.7%		

TABLE 103.5B: STUDY 154-103: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trova q.d.	Trova b.i.d.	Ciprofloxacin
<i>E. coli</i>	27/34 (79.4%)	29/32 (90.6%)	25/30 (83.3%)
Trova q.d. vs Cipro	-3.9%, 98.3% C.I.: -30.3%, 22.5%		
Trova b.i.d. vs Cipro	7.3%, 98.3% C.I.: -16.4%, 31.0%		
Trova q.d. vs Trova b.i.d.	-11.2%, 98.3% C.I.: -34.9%, 12.5%		

TABLE 103.6: STUDY 154-103: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trova q.d.	Trova b.i.d.	Ciprofloxacin
<i>E. coli</i>	19/19 (100%)	17/18 (94.4%)	21/21 (100%)
Trova q.d. vs Cipro	0%, 98.3% C.I.: -5.0%, 5.0%		
Trova b.i.d. vs Cipro	-5.6%, 98.3% C.I.: -23.6%, 12.5%		
Trova q.d. vs Trova b.i.d.	5.6%, 98.3% C.I.: -12.8%, 23.9%		

TABLE 103.7A: STUDY 154-103: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT

Clinical Response	Trova q.d. (N=44)	Trova b.i.d. (N=42)	Ciprofloxacin (N=45)
Success (cure+improvement)	42 (95.5%)	41 (97.6%)	41 (91.1%)
Failure (failure+relapse)	2 (4.5%)	1 (2.4%)	4 (8.9%)
Trova q.d. vs Cipro	4.3%, 98.3% C.I.: -10.5%, 19.2%		
Trova b.i.d. vs Cipro	6.5%, 98.3% C.I.: -7.4%, 20.4%		
Trova q.d. vs Trova b.i.d.	-2.2%, 98.3% C.I.: -13.9%, 9.6%		

TABLE 103.7B: STUDY 154-103: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS			
Clinical Response	Trova q.d. (N=46)	Trova b.i.d. (N=44)	Ciprofloxacin (N=44)
Success (cure+improvement)	42 (91.3%)	41 (93.2%)	37 (84.1%)
Failure (failure+relapse)	4 (8.7%)	3 (6.8%)	7 (15.9%)
Trova q.d. vs Cipro	7.2%, 98.3% C.I.: -11.5%, 26.0%		
Trova b.i.d. vs Cipro	9.1%, 98.3% C.I.: -9.2%, 27.4%		
Trova q.d. vs Trova b.i.d.	-1.9%, 98.3% C.I.: -17.6%, 13.8%		

TABLE 103.8A: STUDY 154-103: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT			
Clinical Response	Trova q.d. (N=22)	Trova b.i.d. (N=22)	Ciprofloxacin (N=29)
Success (cure+improvement)	21 (95.5%)	21 (95.5%)	28 (96.6%)
Failure (failure+relapse)	1 (4.5%)	1 (4.5%)	1 (3.4%)
Trova q.d. vs Cipro	-1.1%, 98.3% C.I.: -18.5%, 16.3%		
Trova b.i.d. vs Cipro	-1.1%, 98.3% C.I.: -18.5%, 16.3%		
Trova q.d. vs Trova b.i.d.	0%, 98.3% C.I.: -19.6%, 19.6%		

TABLE 103.8B: STUDY 154-103: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS			
Clinical Response	Trova q.d. (N=18)	Trova b.i.d. (N=19)	Ciprofloxacin (N=26)
Success (cure+improvement)	16 (89.9%)	17 (89.5%)	22 (84.6%)
Failure (failure+relapse)	2 (11.1%)	2 (10.5%)	4 (15.4%)
Trova q.d. vs Cipro	4.3%, 98.3% C.I.: -25.0%, 33.5%		
Trova b.i.d. vs Cipro	4.9%, 98.3% C.I.: -23.6%, 33.3%		
Trova q.d. vs Trova b.i.d.	-0.6%, 98.3% C.I.: -30.5%, 29.3%		

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Tables 103.9A, 103.9B, and 103.9C. With respect to all these adverse event rates, significant differences were only detected in the number of subjects who reported at least one treatment related adverse events between the treatment groups of trovafloxacin 100 mg b.i.d. and ciprofloxacin, and there was a significantly higher rate in the trovafloxacin 100 mg b.i.d. group than in the ciprofloxacin group. Significantly more subjects had dizziness in both trovafloxacin groups when compared with ciprofloxacin.

TABLE 103.9A: STUDY 154-103: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova q.d. (N=72)	Ciprofloracin (N=75)	Fisher's P-value
At Least One AE	40/72 (55.6%)	42/75 (56.0%)	1.000
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	26 (36.1%)	18 (24.0%)	0.149
Dizziness	18 (25.0%)	5 (6.7%)	0.003
Headache	12 (16.7%)	5 (6.7%)	0.073
At Least One Treatment Related AE	26/72 (36.1%)	21/75 (28.0%)	0.377
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	16 (22.2%)	9 (12.0%)	0.125
Dizziness	10 (13.9%)	6 (8.0%)	0.297
Headache	11 (15.3%)	5 (6.7%)	0.116
Discontinuations Due to an AE	3/72 (4.2%)	2/75 (2.7%)	0.677
Clinically Significant Lab Abnormalities	9/40 (22.5%)	11/44 (25.0%)	0.804

TABLE 103.9B: STUDY 154-103: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova b.i.d. (N=74)	Ciprofloracin (N=75)	Fisher's P-value
At Least One AE	48/74 (64.9%)	42/75 (56.0%)	0.316
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	21 (28.4%)	18 (24.0%)	0.580
Dizziness	15 (20.3%)	5 (6.7%)	0.017
Headache	9 (12.2%)	5 (6.7%)	0.276
At Least One Treatment Related AE	36/74 (48.7%)	21/75 (28.0%)	0.012
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	17 (23.0%)	9 (12.0%)	0.088
Dizziness	8 (10.8%)	6 (8.0%)	0.588
Headache	7 (9.5%)	5 (6.7%)	0.563
Discontinuations Due to an AE	8/74 (10.8%)	2/75 (2.7%)	0.056
Clinically Significant Lab Abnormalities	5/35 (14.3%)	11/44 (25.0%)	0.273

TABLE 103.9C: STUDY 154-103: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova q.d. (N=72)	Trova b.i.d. (N=74)	Fisher's P-value
At Least One AE	40/72 (55.6%)	48/74 (64.9%)	0.310
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	26 (36.1%)	21 (28.4%)	0.377
Dizziness	18 (25.0%)	15 (20.3%)	0.555
Headache	12 (16.7%)	9 (12.2%)	0.486
At Least One Treatment Related AE	26/72 (36.1%)	36/74 (48.7%)	0.135
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	16 (22.2%)	17 (23.0%)	1.000
Dizziness	10 (13.9%)	8 (10.8%)	0.622
Headache	11 (15.3%)	7 (9.5%)	0.322
Discontinuations Due to an AE	3/72 (4.2%)	8/74 (10.8%)	0.209
Clinically Significant Lab Abnormalities	9/40 (22.5%)	5/35 (14.3%)	0.393

No deaths were reported during this study. One of the 74 subjects (1%) in the trovafoxacin 100 mg b.i.d. group had a serious adverse event, however, this event was considered by the investigator to be unrelated to study drug.

Reviewer's Summary and Conclusions: See Section X.

VII.C. STUDY 154-116

VII.C.1. METHODS

In study 154-116, a total of approximately 540 subjects with uncomplicated urinary tract infections were to be enrolled and to be randomized to one of the three treatment groups in a 1:1:1 ratio. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for clinical diagnosis of uncomplicated urinary tract infection, gave informed consent, and met all inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of female outpatients, who were 16 years of age or older with clinically documented uncomplicated urinary tract infection.

Study visits were scheduled for Visit 1 (Day 1, baseline), Visit 2 (Day 12, EOT), and Visit 3 (Day 42, EOS). At Visit 1, baseline assessments and clinical assessments of signs and symptoms of urinary tract infection were performed. At Visit 2, microbiological tests and clinical assessments of signs and symptoms of urinary tract infection were performed. Safety was also assessed. Hematology, chemistry, and urinalysis determinations were repeated. The investigator provided an evaluation of clinical response. At Visit 3, efficacy and safety observations were the same as those performed at Visit 2. The investigator provided a final evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF. At each visit, the investigator obtained information about concomitant illnesses and therapeutic intervention. The reason for a subject discontinuing from the clinical trial was recorded on the CRF. Table 116.1 demonstrates during treatment and post treatment procedures which were specified by the protocol

Study drug was in the form of trovafoxacin tablets or norfloxacin capsules and was packaged in blister cards using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafoxacin 100 mg/day as a single dose (1x100 mg tablet) in the morning for 3 days; 2. trovafoxacin 100 mg/day as a single dose (1x100 mg tablet) in the morning for 7 days; 3. norfloxacin 800 mg/day in two equally divided doses (2x400 mg capsule) in the morning and evening for 3 days. All subjects took combinations of active drug and placebos for active drug.

TABLE 116.1: STUDY 154-116: VISIT TIMING AND PROCEDURES			
Visit Number	Visit 1	Visit 2	Visit 3
Study Day	Day 1	12	Day 42
Allowable Window	-48 hours	11-13	35-49
Treatment Period	Day 1 to Day 7		
Follow-up Period	Day 8 to Day 42		
Informed Consent	X		
Demographic Information	X		
Physical Examination	X		
Concomitant Medication	X	X	X
Vital Signs	X	X	X
Dosing Record		X	
Clinical Signs & Symptoms	X	X	X
Microbiology			
• analysis of unspun urine	X	X	X
• culture & sensitivity	X	X	X
Safety Laboratory Tests			
• hematology	X	X	abn
• biochemistry	X	X	abn
• urinalysis	X	X	abn
Pregnancy test	X		
Adverse Events			
• routine events		X	X
• serious adverse events		X	X
Investigator's Clinical Evaluation		X	X

abn Abnormal at previous visit or clinically significant adverse event.

Efficacy evaluation, safety evaluation, and statistical methods were similar to those described for Study 154-103 in Section VII.B.1.

VII.C.2. RESULTS

A total of 560 subjects were enrolled across centers in the USA (15) and in Europe (19) between March 15, 1995 and November 13, 1995. Of these enrolled subjects, 18 were withdrawn prior to randomization. No subject in any of the three treatment groups was discontinued from treatment due to inadequate response. One hundred eighty two of trovafloxacin 3 days, 182 of trovafloxacin 7 days, and 178 of norfloxacin subjects were included in the clinical intent-to-treat analyses; 147 of trovafloxacin 3 days; 152 of trovafloxacin 7 days, and 130 of norfloxacin subjects were included in the bacteriological intent-to-treat analyses. The Applicant bacteriologically evaluable group at EOT comprised 405 subjects, and there were 334 subjects in the Medical Officer bacteriologically evaluable group. The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline cultures in evaluable windows. The most common reason for exclusion from clinical evaluability was no post-baseline clinical assessment, no post-baseline assessment in evaluable analysis window, insufficient therapy, and concomitant antibiotic therapy.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 116.2. There were no

statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

Treatment Group for Response	Subjects Included		
	Trova 3 Days (N=182)	Trova 7 Days (N=182)	Norfloxacin (N=178)
Clinically ITT	182 (100%)	182 (100%)	178 (100%)
Bacteriologically ITT	147 (80.8%)	152 (83.5%)	130 (73.0%)
Applicant Clinically Evaluable			
Clinically Evaluable at EOT	140 (76.9%)	144 (79.1%)	125 (70.2%)
Clinically Evaluable at EOS	133 (73.1%)	127 (69.8%)	114 (64.0%)
MO Clinically Evaluable			
Clinically Evaluable at EOT	116 (63.7%)	113 (62.1%)	105 (59.0%)
Clinically Evaluable at EOS	107 (58.8%)	101 (55.5%)	98 (55.1%)
Applicant Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	139 (76.4%)	142 (78.0%)	124 (69.7%)
Bacteriologically Evaluable at EOS	122 (70.3%)	118 (64.8%)	109 (61.2%)
MO Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	116 (63.7%)	113 (62.1%)	105 (59.0%)
Bacteriologically Evaluable at EOS	104 (57.1%)	98 (53.8%)	93 (52.2%)

Subject bacteriological responses at EOT and EOS are shown for the Applicant bacteriologically evaluable subjects in Tables 116.3A and 116.3B, respectively. Confidence interval results from analyses show that trovafloxacin 3 days and trovafloxacin 7 days were both therapeutically equivalent to norfloxacin at the two endpoints. Trovafloxacin 3 days was not considered therapeutically equivalent to trovafloxacin 7 days.

Reviewer's Note: The subject eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT and EOS are presented in Tables 116.4A and 116.4B, respectively. Pairwise comparisons (98.3% confidence intervals) of the difference in subject bacteriological eradication rates among the three treatment groups at both EOT and EOS supported equivalence of trovafloxacin 3 days versus norfloxacin, and trovafloxacin 7 days versus norfloxacin, but not trovafloxacin 3 days versus trovafloxacin 7 days.

Subject Bacteriological Response	Trova 3 Days (N=139)	Trova 7 Days (N=142)	Norfloxacin (N=124)
Eradication	120 (86.3%)	132 (93.0%)	109 (87.9%)
Persistent	19 (13.7%)	10 (7.0%)	15 (12.1%)
Trova 3 Days vs Norfloxacin	-1.6%, 98.3% C.I.: -12.2%, 9.1%		
Trova 7 Days vs Norfloxacin	5.1%, 98.3% C.I.: -4.4%, 14.5%		
Trova 3 Days vs Trova 7 Days	-6.6%, 98.3% C.I.: -16.0%, 2.7%		

TABLE 116.3B: STUDY 154-116: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trova 3 Days (N=122)	Trova 7 Days (N=118)	Norfloxacin (N=109)
Eradication	95 (74.2%)	99 (83.9%)	80 (73.4%)
Persistent	33 (25.8%)	19 (16.1%)	29 (26.6%)
Trova 3 Days vs Norfloxacin	0.8%, 98.3% C.I.: -13.7%, 15.4%		
Trova 7 Days vs Norfloxacin	10.5%, 98.3% C.I.: -3.4%, 24.4%		
Trova 3 Days vs Trova 7 Days	-9.7%, 98.3% C.I.: -22.8%, 3.4%		

TABLE 116.4A: STUDY 154-116: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT			
Subject Bacteriological Response	Trova 3 Days (N=116)	Trova 7 Days (N=113)	Norfloxacin (N=105)
Eradication	101 (87.1%)	105 (92.9%)	94 (89.5%)
Persistent	15 (12.9%)	8 (7.1%)	11 (10.5%)
Trova 3 Days vs Norfloxacin	-2.5%, 98.3% C.I.: -13.7%, 8.8%		
Trova 7 Days vs Norfloxacin	3.4%, 98.3% C.I.: -6.7%, 13.5%		
Trova 3 Days vs Trova 7 Days	-5.9%, 98.3% C.I.: -16.2%, 4.5%		

TABLE 116.4B: STUDY 154-116: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trova 3 Days (N=104)	Trova 7 Days (N=98)	Norfloxacin (N=93)
Eradication	77 (74.0%)	81 (82.7%)	69 (74.2%)
Persistent	27 (26.0%)	17 (17.3%)	24 (25.8%)
Trova 3 Days vs Norfloxacin	-0.2%, 98.3% C.I.: -16.1%, 15.8%		
Trova 7 Days vs Norfloxacin	8.5%, 98.3% C.I.: -6.8%, 23.7%		
Trova 3 Days vs Trova 7 Days	-8.6%, 98.3% C.I.: -23.4%, 6.2%		

Analyses of the pathogen eradication rates of the Applicant bacteriologically evaluable subjects at both EOT and EOS are displayed in Tables 116.5A and 116.5B, respectively. Pairwise comparisons (98.3% confidence intervals) of the difference in *E. coli* eradication rates between treatment groups supported the equivalence of both trovafloxacin regimens versus norfloxacin, but not between the two trovafloxacin regimens at both EOT and EOS.

Reviewer's Note: Tables 116.6A and 116.6B show the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at EOT and EOS, respectively. The results were the same as those from the Applicant bacteriologically evaluable subjects, except that the equivalence of trovafloxacin 3 days versus norfloxacin was not shown at EOT.

Tables 116.7A and 116.7B show clinical responses of the Applicant clinically evaluable subjects at EOT and EOS, respectively. Confidence interval results show that the three treatment groups were therapeutically equivalent to each other with respect to the success rates at EOT and EOS, except trovafloxacin 3 days versus trovafloxacin 7 days at EOS.

Reviewer's Note: Analyses of the success rates of the Medical Officer clinically evaluable subjects at

both EOT and EOS are displayed in Tables 116.8A and 116.8B, respectively, which show the same results as those from the Applicant clinically evaluable subjects.

TABLE 116.5A: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
<i>E. coli</i>	105/114 (92.1%)	103/108 (95.4%)	87/97 (89.7%)
Trova 3 Days vs Norfloxacin	2.4%, 98.3% C.I.: -8.1%, 12.9%		
Trova 7 Days vs Norfloxacin	5.7%, 98.3% C.I.: -4.1%, 15.5%		
Trova 3 Days vs Trova 7 Days	-3.3%, 98.3% C.I.: -11.9%, 5.4%		
<i>E. faecalis</i>	3/10 (30%)	4/6 (67%)	4/6 (67%)

TABLE 116.5B: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
<i>E. coli</i>	85/105 (81.0%)	74/89 (83.1%)	62/84 (73.8%)
Trova 3 Days vs Norfloxacin	7.1%, 98.3% C.I.: -8.6%, 22.9%		
Trova 7 Days vs Norfloxacin	9.3%, 98.3% C.I.: -6.7%, 25.4%		
Trova 3 Days vs Trova 7 Days	-2.2%, 98.3% C.I.: -16.4%, 12.1%		
<i>E. faecalis</i>	1/9 (11.1%)	3/5 (60.0%)	3/6 (50.0%)

TABLE 116.6A: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
<i>E. coli</i>	88/96 (91.7%)	85/90 (94.4%)	75/81 (92.6%)
Trova 3 Days vs Norfloxacin	-0.9%, 98.3% C.I.: -11.8%, 9.9%		
Trova 7 Days vs Norfloxacin	1.9%, 98.3% C.I.: -8.4%, 12.1%		
Trova 3 Days vs Trova 7 Days	-2.8%, 98.3% C.I.: -12.7%, 7.2%		
<i>E. faecalis</i>	1/5 (20.0%)	2/3 (66.7%)	3/5 (60.0%)

TABLE 116.6B: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
<i>E. coli</i>	73/90 (81.1%)	64/77 (83.1%)	54/72 (75.0%)
Trova 3 Days vs Norfloxacin	6.1%, 98.3% C.I.: -10.8%, 23.1%		
Trova 7 Days vs Norfloxacin	8.1%, 98.3% C.I.: -9.2%, 25.4%		
Trova 3 Days vs Trova 7 Days	-2.0%, 98.3% C.I.: -17.4%, 13.4%		
<i>E. faecalis</i>	1/5 (20.0%)	0/2 (0%)	3/5 (60.0%)

TABLE 116.7A: STUDY 154-116: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT

Clinical Response	Trova 3 Days (N=140)	Trova 7 Days (N=144)	Norfloxacin (N=125)
Success (cure+improvement)	136 (97.1%)	140 (97.2%)	115 (92.0%)
Failure (failure+relapse)	4 (2.9%)	4 (2.8%)	10 (8.0%)
Trova 3 Days vs Norfloxacin	5.1%, 98.3% C.I.: -2.3%, 12.6%		
Trova 7 Days vs Norfloxacin	5.2%, 98.3% C.I.: -2.2%, 12.6%		
Trova 3 Days vs Trova 7 Days	-0.1%, 98.3% C.I.: -5.5%, 5.3%		

TABLE 116.7B: STUDY 154-116: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trova 3 Days (N=133)	Trova 7 Days (N=127)	Norfloxacin (N=114)
Success (cure+improvement)	114 (85.7%)	115 (90.6%)	93 (81.6%)
Failure (failure+relapse)	19 (14.3%)	12 (9.4%)	21 (18.4%)
Trova 3 Days vs Norfloxacin	4.1%, 98.3% C.I.: -8.0%, 16.3%		
Trova 7 Days vs Norfloxacin	9.0%, 98.3% C.I.: -2.5%, 20.5%		
Trova 3 Days vs Trova 7 Days	-4.8%, 98.3% C.I.: -15.2%, 5.5%		

TABLE 116.8A: STUDY 154-116: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT

Clinical Response	Trova 3 Days (N=116)	Trova 7 Days (N=113)	Norfloxacin (N=105)
Success (cure+improvement)	113 (97.4%)	110 (97.3%)	97 (92.4%)
Failure (failure+relapse)	3 (2.6%)	3 (2.7%)	8 (7.6%)
Trova 3 Days vs Norfloxacin	5.0%, 98.3% C.I.: -3.0%, 13.1%		
Trova 7 Days vs Norfloxacin	5.0%, 98.3% C.I.: -3.1%, 13.1%		
Trova 3 Days vs Trova 7 Days	0.1%, 98.3% C.I.: -5.9%, 6.0%		

TABLE 116.8B: STUDY 154-116: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trova 3 Days (N=107)	Trova 7 Days (N=101)	Norfloxacin (N=98)
Success (cure+improvement)	91 (85.0%)	90 (89.1%)	81 (82.7%)
Failure (failure+relapse)	16 (15.0%)	11 (10.9%)	17 (17.3%)
Trova 3 Days vs Norfloxacin	2.4%, 98.3% C.I.: -10.9%, 15.7%		
Trova 7 Days vs Norfloxacin	6.5%, 98.3% C.I.: -6.3%, 19.2%		
Trova 3 Days vs Trova 7 Days	-4.1%, 98.3% C.I.: -16.1%, 8.0%		

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Tables 116.9A, 116.9B, and 116.9C. The trovafloxacin 7 days group had significantly higher incidence rates of treatment related adverse events in

the central and peripheral nervous system than the norfloxacin group.

TABLE 116.9A: STUDY 154-116: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova 3 Days (N=182)	Norfloxacin (N=178)	Fisher's P-value
At Least One AE	69/182 (37.9%)	60/178 (33.7%)	0.442
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	35 (19.2%)	23 (12.9%)	0.116
Dizziness	18 (9.9%)	8 (4.5%)	0.066
Headache	22 (12.1%)	15 (8.4%)	0.299
At Least One Treatment Related AE	42/182 (23.1%)	36/178 (20.2%)	0.525
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	25 (13.7%)	13 (7.3%)	0.059
Dizziness	16 (8.8%)	7 (3.9%)	0.083
Headache	11 (6.0%)	7 (3.9%)	0.470
Discontinuations Due to an AE	3/182 (1.7%)	4/178 (2.3%)	0.721
Clinically Significant Lab Abnormalities	25/180 (13.9%)	31/170 (18.2%)	0.308

TABLE 116.9B: STUDY 154-116: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova 7 Days (N=182)	Norfloxacin (N=178)	Fisher's P-value
At Least One AE	61/182 (33.5%)	60/178 (33.7%)	1.000
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	37 (20.3%)	23 (12.9%)	0.067
Dizziness	18 (9.9%)	8 (4.5%)	0.066
Headache	20 (11.0%)	15 (8.4%)	0.478
At Least One Treatment Related AE	44/182 (24.2%)	36/178 (20.2%)	0.378
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	27 (14.8%)	13 (7.3%)	0.029
Dizziness	15 (8.2%)	7 (3.9%)	0.122
Headache	12 (6.6%)	7 (3.9%)	0.347
Discontinuations Due to an AE	4/182 (2.2%)	4/178 (2.3%)	1.000
Clinically Significant Lab Abnormalities	25/175 (14.3%)	31/170 (18.2%)	0.381

TABLE 116.9C: STUDY 154-116: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova 3 Days (N=182)	Trova 7 Days (N=182)	Fisher's P-value
At Least One AE	69/182 (37.9%)	61/182 (33.5%)	0.444
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	35 (19.2%)	37 (20.3%)	0.895
Dizziness	18 (9.9%)	18 (9.9%)	1.000
Headache	22 (12.1%)	20 (11.0%)	0.870
At Least One Treatment Related AE	42/182 (23.1%)	44/182 (24.2%)	0.902
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	25 (13.7%)	27 (14.8%)	0.881
Dizziness	16 (8.8%)	15 (8.2%)	1.000
Headache	11 (6.0%)	12 (6.6%)	1.000
Discontinuations Due to an AE	3/182 (1.7%)	4/182 (2.2%)	1.000
Clinically Significant Lab Abnormalities	25/180 (13.9%)	25/175 (14.3%)	1.000

There were no deaths reported during this study. One subject in the trovafoxacin 7 day group and two subjects in the trovafoxacin 3 day group had serious adverse events during this study that required hospitalization and were considered by the investigator to be unrelated to study drug.

Reviewer's Summary and Conclusions: See Section X.

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IX. PROSTATITIS

IX.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-119, as evidence to support oral trovafoxacin regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general design of the study is as follows:

Study 154-119 was a randomized, multicenter, double-blind, double-dummy trial which compared the efficacy and safety of trovafoxacin (200 mg q.d.) administered orally for 28 days versus ofloxacin (300 mg b.i.d.) administered orally for 42 days for treatment of bacterial prostatitis. The study was initiated on July 17, 1995 and completed on May 30, 1996.

IX.B. STUDY 154-119

IX.B.1. METHODS

In study 154-119, a total of approximately 300 subjects with a medical history and clinical and bacteriological findings consistent with bacterial prostatitis were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the screening visit (Day -5), subjects who met the criteria for a presumptive diagnosis of bacterial prostatitis, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for evaluation. At the baseline visit (Visit 1, Day 1), subjects with a confirmed diagnosis of bacterial prostatitis were randomized to receive treatment. Eligible study population consisted of male outpatients, who were 18 years of age or older with presumptive clinical diagnosis of bacterial prostatitis.

At the screening visit (Day -5), baseline assessments were performed. Hematology, serum chemistry, and urinalysis determinations were performed for safety testing. The investigator confirmed the diagnosis of bacterial prostatitis by quantitative bacteriological cultures. At the baseline visit (Visit 1, Day 1), the investigator began treatment as soon as bacterial pathogens were identified from the screening visit cultures. At Visits 2 (Day 4) and 3 (Day 20), efficacy observations and safety assessments were performed. At Visit 4 (Days 25-42, EOT for trovafoxacin), efficacy observations were obtained. A global clinical assessment was made, compared to the screening assessment. A quantitative bacteriological culture was repeated. At Visit 5 (Days 43-59, EOT for ofloxacin), efficacy observations were obtained. A global clinical assessment was made, compared to the screening assessment. Like Visit 4, quantitative bacteriological cultures were repeated. Visit 6 (Days 60-84, EOS) was included to assess rates of recurrent infections in those subjects cured or improved at Visit 5. At this visit, efficacy observations were obtained. A global clinical assessment was made. Like Visit 5, quantitative bacteriological cultures were repeated. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 119.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of tablets, packaged in blister cards, and capsules, packaged in bottles, using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafoxacin 200 mg (2x100 mg tablet) q.d. as a single dose on Days 1-28 and one capsule

twice daily (ofloxacin placebo) on Days 1-42; 2. ofloxacin 300 mg (1x300 mg capsule) b.i.d. on Days 1-42 and two tablets (trovafoxacin placebo) on Days 1-28. All subjects received two tablets and one capsule in the morning and one capsule at night through Day 28 of the treatment period. From Day 29 through Day 42, subjects took one capsule in the morning and one capsule at night in combinations of active drug and placebo for active drug.

TABLE 119.1: STUDY 154-119: VISIT TIMING AND PROCEDURES

Visit Number	Screen	Baseline	Visit 2	Visit 3	Visit 4	EOT	Visit 5	Visit 6
Study Day	Day -5	Day 1	Day 4	Day 20	Day 35	Day 42	Day 49	Day 63-84
Allowable Window	Day -5	Day 1	Day 3-5	Day 18-22	Day 33-37	Day 42	Day 47-51	Day 63-84
Treatment Period	Day 1 to Day 42							
Follow-up Period	Day 43 to Day 84 after EOT							
Compliance Checks			X	X	X		X	
Informed Consent	X							
Demographic Information	X							
Targeted Physical Exam	X							
Concomitant Medication	X		X	X	X		X	X
Vital Signs		X	X	X		X	X	
Assessment								
Clinical	X		X	X	X	X	X	X
Laboratory								
• hematology	X		X	X	X		X	X*
• serum chemistry	X		X	X	X		X	X*
• urinalysis	X		X	X	X		X	X*
• fractionated urine culture	X				X		X	X
• urine culture			X	X				
Adverse Event	X		X	X	X	X	X	

* To be done only if there are significant abnormalities at Visit 5

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically and bacteriologically evaluable subjects. The primary efficacy endpoint was clinical response at EOT, which referred to Visit 4 for trovafoxacin or Visit 5 for ofloxacin. The secondary endpoints were clinical response at EOS, subject bacteriological responses at EOT and EOS, and pathogen outcomes at EOT and EOS.

Clinical response, subject bacteriological response, and pathogen outcome were determined by the sponsor and evaluated at Visit 4 (EOT for trovafoxacin), Visit 5 (EOT for ofloxacin), and Visit 6 (EOS). Clinical response was classified as cure, improvement, or failure. Subject bacteriologic response was classified as eradication (complete or partial), complete persistence, or superinfection. Pathogen outcome was classified as eradication (complete or partial), complete persistence, or superinfection.

Reviewer's Note: The Medical Officer also defined her clinically and bacteriologically evaluable subjects, and assessed clinical and bacteriological efficacy outcomes according to her clinical and bacteriological criteria.

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of physical examinations, clinical laboratory tests, vital sign measurements, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality, and was monitored up to Visit 5 (Days, 47-51). All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between trovafloxacin and ofloxacin.

Efficacy analyses were based on the clinical and bacteriological responses at Visits 4, 5, and 6. The treatment groups were compared with respect to the clinical success rate (cure+improvement), the subject bacteriological eradication rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success rate at EOT in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: All efficacy analyses were conducted for the Medical Officer clinically and bacteriologically evaluable subjects, and the Applicant clinically and bacteriologically evaluable subjects. All of the subjects in these groups were assessed for their clinical or bacteriological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

IX.B.2. RESULTS

A total of 660 subjects were enrolled at 34 centers in the USA between July 17, 1995 and May 30, 1996. Of these enrolled subjects, 385 subjects were withdrawn prior to randomization because they did not meet entrance criteria, the majority of whom had no pathogen at baseline. One hundred forty two subjects were randomized to receive trovafoxacin, and 135 subjects were randomized to receive ofloxacin. One hundred thirty four trovafoxacin and 129 ofloxacin subjects were included in the clinical intent-to-treat analyses; 122 trovafoxacin and 118 ofloxacin subjects were included in the bacteriological intent-to-treat analyses. The Applicant clinically evaluable group at EOT comprised 224 subjects, and there were 126 subjects in the Medical Officer clinically evaluable group at EOT. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy for trovafoxacin subjects, and no post-baseline clinical response in evaluable window for ofloxacin subjects.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 119.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

TABLE 119.2: STUDY 154-119: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP		
Treatment Group for Response	Subjects Included	
	Trovafoxacin (N=142)	Ofloxacin (N=135)
Clinically ITT	134 (94.4%)	129 (95.6%)
Bacteriologically ITT	122 (90.1%)	118 (87.4%)
Applicant Clinically Evaluable		
Clinically Evaluable at EOT	113 (79.6%)	111 (82.2%)
Clinically Evaluable at EOS	107 (75.4%)	103 (76.3%)
MO Clinically Evaluable		
Clinically Evaluable at EOT	68 (47.9%)	58 (43.0%)
Clinically Evaluable at EOS	56 (39.4%)	39 (28.9%)
Applicant Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	98 (69.0%)	98 (72.6%)
Bacteriologically Evaluable at EOS	86 (60.6%)	92 (68.1%)
MO Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	68 (47.9%)	58 (43.0%)
Bacteriologically Evaluable at EOS	54 (38.0%)	35 (25.9%)

Clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 119.3A and 119.3B, respectively. Confidence interval results from analyses show that trovafoxacin was therapeutically equivalent to ofloxacin with respect to the success rates at both EOT and EOS.

Reviewer's Note: The success rates of the Medical Officer clinically evaluable subjects at EOT and EOS are presented in Tables 119.4A and 119.4B, respectively. Comparisons (95% confidence intervals) of the difference in success rates at EOT between the two treatment groups showed marginal equivalence of trovafoxacin versus ofloxacin. Therapeutic equivalence was shown at EOS.

TABLE 119.3A: STUDY 154-119: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Trovafoxacin (N=113)	Ofloxacin (N=111)
Success (cure+improvement)	101 (89.4%)	96 (86.5%)
Failure (failure+relapse)	12 (10.6%)	15 (13.5%)
Trova vs Oflox by Cure	2.9%, 95% C.I.: -6.5%, 12.3%	

TABLE 119.3B: STUDY 154-119: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Trovafoxacin (N=107)	Ofloxacin (N=103)
Success (cure+improvement)	74 (69.2%)	71 (68.9%)
Failure (failure+relapse)	33 (30.8%)	32 (31.1%)
Trova vs Oflox by Cure	0.2%, 95% C.I.: -13.2%, 13.7%	

TABLE 119.4A: STUDY 154-119: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Trovafoxacin (N=68)	Ofloxacin (N=58)
Success (cure+improvement)	62 (91.2%)	52 (89.7%)
Failure (failure+relapse)	6 (8.8%)	6 (10.3%)
Trova vs Oflox by Cure	1.5%, 95% C.I.: -10.4%, 13.5%	

TABLE 119.4B: STUDY 154-119: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Trovafoxacin (N=56)	Ofloxacin (N=39)
Success (cure+improvement)	37 (66.1%)	23 (59.0%)
Failure (failure+relapse)	19 (33.9%)	16 (41.0%)
Trova vs Oflox by Cure	7.1%, 95% C.I.: -14.9%, 29.1%	

Table 119.5 shows bacteriological response of the Applicant bacteriologically evaluable subjects at EOT. Confidence interval results show that the two treatment groups were not therapeutically equivalent with respect to the eradication rates at EOT.

A summary of the pathogen eradication rates at EOT for the most frequent isolated baseline pathogens is presented for the Applicant bacteriologically evaluable subjects in Table 119.7.

Reviewer's Note: Analyses of the eradication rates of the Medical Officer bacteriologically evaluable subjects at both EOT and EOS are displayed in Tables 119.6A and 119.6B, respectively, which failed to show equivalence of trovafoxacin versus ofloxacin at either EOT or EOS.

Table 119.8 shows the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at

EOT.

TABLE 119.5: STUDY 154-119: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT

Subject Bacteriological Response	Trovafoxacin (N=98)	Ofloxacin (N=98)
Eradication	89 (90.8%)	94 (95.9%)
Persistent	9 (9.2%)	4 (4.1%)
Trova vs Oflox by Eradication	-5.1%, 95% C.I.: -13.1%, -2.8%	

TABLE 119.6A: STUDY 154-119: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT

Subject Bacteriological Response	Trovafoxacin (N=68)	Ofloxacin (N=58)
Eradication	57 (83.8%)	52 (89.7%)
Persistent	11 (16.2%)	6 (10.3%)
Trova vs Oflox by Eradication	-5.8%, 95% C.I.: -19.2%, 7.5%	

TABLE 119.6B: STUDY 154-119: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trovafoxacin (N=54)	Ofloxacin (N=35)
Eradication	38 (70.4%)	28 (80.0%)
Persistent	16 (29.6%)	7 (20.0%)
Trova vs Oflox by Eradication	-9.6%, 95% C.I.: -30.0%, 10.7%	

TABLE 119.7: STUDY 154-119: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trovafoxacin	Ofloxacin
<i>S. epidermidis</i>	24/33 (72.7%)	22/34 (64.7%)
<i>C. (-). Staphylococci</i>	28/28 (100%)	33/33 (100%)
<i>S. haemolyticus</i>	14/19 (73.7%)	18/21 (85.7%)
<i>E. faecalis</i>	14/17 (82.4%)	15/18 (83.3%)
<i>E. coli</i>	13/14 (92.9%)	18/18 (100%)

TABLE 119.8: STUDY 154-119: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)		
Pathogen Bacteriological Outcome	Trovafoxacin	Ofloxacin
<i>E. faecalis</i>	11/14 (78.6%)	11/14 (78.6%)
<i>E. coli</i>	12/13 (92.3%)	16/16 (100%)
<i>S. epidermidis</i>	8/10 (80.0%)	5/6 (83.3%)
<i>S. haemolyticus</i>	4/6 (66.7%)	8/8 (100%)
<i>K. pneumoniae</i>	4/6 (66.7%)	1/1 (100%)

Reviewer's Note: For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Tables 119.9. With respect to the subjects reporting adverse events related to study medication and the subjects discontinuing due to adverse events, the rates were significantly higher in the trovafoxacin group than in the ofloxacin group. There were significantly more trovafoxacin subjects who experienced dizziness and headache.

TABLE 119.9 STUDY 154-119: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trovafoxacin (N=142)	Ofloxacin (N=133)	Fisher's P-value
At Least One AE	114/142 (80.3%)	95/133 (71.4%)	0.092
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	66 (46.5%)	21 (15.8%)	<0.001
Dizziness	46 (32.4%)	7 (5.3%)	<0.001
Headache	32 (22.5%)	14 (10.5%)	0.009
At Least One Treatment Related AE	61/142 (43.0%)	39/133 (29.3%)	0.024
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	40 (28.2%)	9 (6.8%)	<0.001
Dizziness	32 (22.5%)	4 (3.0%)	<0.001
Headache	18 (12.7%)	4 (3.0%)	0.003
Discontinuations Due to an AE	25/142 (17.6%)	9/133 (6.8%)	0.009
Clinically Significant Lab Abnormalities	28/140 (20.0%)	23/132 (17.4%)	0.642

No deaths were reported during this study. Four subjects in the trovafoxacin group each had a serious adverse event in the study, all of which were considered unrelated to study drug and attributed to other illnesses. Three subjects in the ofloxacin group each had a serious adverse event in the study, all of which were considered unrelated to study drug and attributed to other illnesses.

Reviewer's Summary and Conclusions: See Section X.

X. SUMMARY AND CONCLUSIONS

(Which May be Conveyed to the Sponsor)

COMPLICATED INTRA-ABDOMINAL INFECTIONS

This indication was supported by one pivotal study, Study 154-124, to demonstrate the efficacy and safety of alatrofloracin/trovafloracin.

The following statements pertain to Study 154-124:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of alatrofloracin/trovafloracin minus imipenem/cilastatin/amoxicillin/clavulanac for the Applicant clinically evaluable subjects at EOS was ^{156, 152} (-9.9%, 8.2%) ^{82.7%, 83.6%}. The result demonstrated that alatrofloracin/ trovafloracin was therapeutically equivalent in efficacy to its comparator in the treatment of complicated intra-abdominal infections.
2. The two treatment groups were not significantly different in safety with respect to the rates of at least one adverse event, the rates of treatment related adverse events, the rates of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. However, significantly more alatrofloracin/trovafloracin subjects experienced adverse events in the central and peripheral nervous system.

REVIEWER CONCLUSIONS: *For the pivotal study 154-124, the efficacy analyses of the clinically evaluable subjects demonstrated that alatrofloracin/trovafloracin was therapeutically equivalent in efficacy to imipenem/cilastatin/amoxicillin/clavulanac in the treatment of complicated intra-abdominal infections. Results from the safety analysis also suggested that alatrofloracin/trovafloracin and its comparator yield nearly comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, alatrofloracin 300 mg q.d. administered intravenously followed by oral trovafloracin 200 mg q.d. administered for a total treatment duration of 14 days is recommended for approval in the treatment of complicated intra-abdominal infections.*

GYNECOLOGIC AND PELVIC INFECTIONS

This indication was supported by one pivotal study, Study 154-144, to demonstrate the efficacy and safety of alatrofoxacin/trovafoxacin.

The following statements pertain to Study 154-144:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at EOS between the treatment groups in the Medical Officer clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of alatrofoxacin/ trovafoxacin minus cefoxitin/amoxicillin/clavulanic acid for the Medical Officer clinically evaluable subjects at EOS was _{96, 107} (-5.2%, 15.9%) _{88.5%, 83.2%}. The result demonstrated that alatrofoxacin/trovafoxacin was therapeutically equivalent in efficacy to its comparator in the treatment of gynecologic and pelvic infections.
2. The rate of at least one adverse event was significantly higher in the alatrofoxacin/trovafoxacin group (51.9%, 83/160) than the cefoxitin/amoxicillin/clavulanic acid group (35.7%, 56/157) (Fisher's exact p-value=0.005); the rate of at least one treatment related adverse event was significantly higher in the alatrofoxacin/trovafoxacin group (23.8%, 38/160) than the cefoxitin/amoxicillin/clavulanic acid group (6.4%, 10/157) (Fisher's exact p-value<0.001); the rate of discontinuations due to adverse events was significantly higher in the alatrofoxacin/trovafoxacin group (18.8%, 30/160) than the cefoxitin/amoxicillin/clavulanic acid group (5.7%, 9/157) (Fisher's exact p-value=0.001). They were not significantly different in the rate of clinical significant laboratory abnormalities. Significantly more subjects experienced dizziness in the alatrofoxacin/trovafoxacin group.

REVIEWER CONCLUSIONS: *For the pivotal study 154-144, the efficacy analyses of the clinically evaluable subjects demonstrated that alatrofoxacin/trovafoxacin was therapeutically equivalent in efficacy to cefoxitin/amoxicillin/clavulanic acid in the treatment of gynecologic and pelvic infections. Results from the safety analysis showed that trovafoxacin had significantly higher rates than its comparator with respect to at least one adverse event and discontinuations due to adverse events, as well as dizziness.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from an efficacy standpoint, alatrofoxacin 300 mg q.d. administered intravenously followed by oral trovafoxacin 200 mg q.d. administered for a maximum of 14 days of total therapy is recommended for approval in the treatment of gynecologic and pelvic infections. However, the Medical Officer will have to determine whether this treatment regimen has an acceptable safety profile.*

SURGICAL PROPHYLAXIS - ELECTIVE COLORECTAL SURGERY

This indication was supported by one pivotal study, Study 154-128, to demonstrate the efficacy and safety of alatrofoxacin.

The following statements pertain to Study 154-128:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in success rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of alatrofoxacin minus cefotetan for the Applicant clinically evaluable subjects at EOS was $_{161, 156} (-10.9\%, 10.1\%)$ $_{72.0\%, 72.4\%}$. The result demonstrated that alatrofoxacin was therapeutically equivalent in efficacy to its comparator in the prophylaxis of primary site infection following elective colorectal surgery.
2. The two treatment groups were not significantly different in safety with respect to the rates of at least one adverse event, the rates of discontinuations due to an adverse event, and the rate of clinical significant laboratory abnormalities. However, significantly more subjects in the alatrofoxacin group (10.2%, 26/256) experienced treatment related adverse events than those in the cefotetan group (2.5%, 6/236) (Fisher's exact p-value=0.001).

REVIEWER CONCLUSIONS: For the pivotal study 154-128, the efficacy analyses of the clinically evaluable subjects demonstrated that alatrofoxacin was therapeutically equivalent in efficacy to cefotetan in the prophylaxis of primary site infection following elective colorectal surgery. Results from the safety analysis also suggested that alatrofoxacin and its comparator yield nearly comparable safety results.

RECOMMENDED REGULATORY ACTION: Based on the above analyses, from a statistical standpoint, alatrofoxacin 200 mg administered as a single intravenous dose and within 2 hours of surgical incision is recommended for approval in the prophylaxis of primary site infection following elective colorectal surgery.

SURGICAL PROPHYLAXIS - ELECTIVE ABDOMINAL AND VAGINAL HYSTERECTOMY

This indication was supported by one pivotal study, Study 154-146, to demonstrate the efficacy and safety of trovafoxacin.

The following statements pertain to Study 154-146:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of trovafoxacin minus cefoxitin for the Applicant clinically evaluable subjects at EOS was $_{133, 127} (-17.3\%, 0\%)$ $_{83.5\%, 92.1\%}$. The result failed to demonstrate that trovafoxacin was therapeutically equivalent in efficacy to its comparator in the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy. In

fact, the result showed that trovafoxacin was significantly inferior to its comparator.

2. The two treatment groups were not significantly different in safety with respect to the rates of at least one adverse event, the rates of treatment related adverse events, the rates of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities.

REVIEWER CONCLUSIONS: For the pivotal study 154-146, the efficacy analyses of the clinically evaluable subjects failed to demonstrate that trovafoxacin was therapeutically equivalent in efficacy to cefoxitin in the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy. In fact, the result showed that trovafoxacin was significantly worse than cefoxitin. Results from the safety analysis suggested that trovafoxacin and its comparator yield comparable safety results.

RECOMMENDED REGULATORY ACTION: Based on the above analyses, from an efficacy standpoint, an approvable regulatory decision toward trovafoxacin 200 mg administered as a single oral dose and within 45 minutes of surgical incision regarding the indication of the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy can not be made at this time.

NON-GONOCOCCAL URETHRITIS AND CERVICITIS

This indication was supported by two pivotal studies, Studies 154-105 and 154-123, to demonstrate the efficacy and safety of trovafoxacin. The controlled study 154-123 is of primary interest.

The following statements pertain to Study 154-105:

Statistical evaluations of efficacy and safety were described by summarizing data collected on the efficacy and safety variables. The primary efficacy variable was the eradication rate of bacteriologically evaluable subjects at EOS. The Applicant's bacteriologically evaluable populations were used in the analyses. Safety data came from all subjects receiving at least one dose of study medication.

1. Similar bacteriological responses were observed for Applicant bacteriologically evaluable male and female subjects at EOS. The subject bacteriological eradication rates at EOS were as follows: trovafoxacin 200 mg x 7 days, 9/9 (100%) males and 10/11 (90.9%) females; trovafoxacin 200 mg x 5 days, 9/9 (100%) males and 9/9 (100%) females; trovafoxacin 100 mg x 7 days, 5/6 (83.3%) males and 7/8 (87.5%) females; and trovafoxacin 50 mg x 7 days, 10/11 (90.9%) males and 10/10 (100%) females; however, the counts upon which these rates were based were small, especially when subset by gender.
2. The rate of at least one adverse event was 16.1% (5/31) of subjects in the trovafoxacin 200 mg x 7 days group, 17.6% (6/34) of subjects in the trovafoxacin 200 mg x 5 days group, 21.4% (6/28) of subjects in the trovafoxacin 100 mg x 7 days group, and 13.5% (5/37) of subjects in the trovafoxacin 50 mg x 7 days group. The percentage of subjects reporting at least one treatment-related adverse event was 3.2% (1/31) of subjects in the trovafoxacin 200 mg x 7 days group, 14.7% (5/34) of subjects in the trovafoxacin 200 mg x 5 days group, 10.7% (3/28) of subjects in the trovafoxacin 100 mg x 7 days group, and 8.1% (3/37) of subjects in the trovafoxacin 50 mg x 7 days group. No subject in any of the four treatment regimens was discontinued from treatment due to an adverse event. Clinically significant post-baseline laboratory abnormalities were observed for 20.0% (4/20), 11.8% (2/17), 22.2% (2/9), and 5.9% (1/17) of subjects in the trovafoxacin 200 mg x 7 days, 200 mg x 5 days, 100 mg x 7 days, and 50 mg x 7 days groups, respectively.

The following statements pertain to Study 154-123:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in subject bacteriological eradication rates at EOS between the treatment groups in the Medical Officer bacteriologically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence intervals of the subject bacteriological eradication rate of the Medical Officer bacteriologically evaluable subjects at EOS were $_{85, 94} (-12.9\%, 1.1\%)$ $_{92.9\%, 98.9\%}$ $_{150, 123} (-5.4\%, 5.5\%)$ $_{96.0\%, 95.9\%}$ and $_{235, 217} (-6.3\%, 1.7\%)$ $_{94.9\%, 97.2\%}$ for male subjects, female subjects, and all subjects combined, respectively. The results demonstrated that trovafloxacin was therapeutically equivalent in efficacy to doxycycline in the treatment of female subjects and all subjects combined with uncomplicated chlamydial urethritis/cervicitis, however, trovafloxacin was not shown to be equivalent to doxycycline at EOS in male subjects.
2. The rate of at least one adverse event was significantly higher in the trovafloxacin group (45.4%, 222/489) than the doxycycline group (38.5%, 185/481) (Fisher's exact p-value=0.032); the rate of at least one treatment related adverse event was significantly higher in the trovafloxacin group (39.9%, 195/489) than the doxycycline group (30.4%, 146/481) (Fisher's exact p-value=0.002). They were not significantly different in either the rate of discontinuations due to adverse events or the rate of clinical significant laboratory abnormalities. Significantly more subjects experienced dizziness and headache in the trovafloxacin group.

REVIEWER CONCLUSIONS: For the pivotal study 154-123, the efficacy analyses of the bacteriologically evaluable subjects supported equivalence of trovafloxacin and doxycycline for the treatment of uncomplicated chlamydial urethritis/cervicitis in female subjects and all subjects combined, but failed to demonstrate equivalence of the two treatments in male subjects. Results from the safety analysis showed that trovafloxacin had significantly higher rates than its comparator with respect to at least one adverse event and at least one treatment related adverse event, as well as dizziness and headache.

RECOMMENDED REGULATORY ACTION: Based on the above analyses, from an efficacy standpoint, trovafloxacin 200 mg q.d. administered for 5 days is recommended for approval in the treatment of uncomplicated chlamydial urethritis/cervicitis only for female subjects. However, the Medical Officer will have to determine whether this treatment regimen has an acceptable safety profile.

PELVIC INFLAMMATORY DISEASE

This indication was supported by two pivotal studies, Studies 154-122 and 154-125, to demonstrate the efficacy and safety of trovafloxacin or alatrofoxacin/trovafoxacin.

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical cure rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's

exact test.

The following statements pertain to Study 154-122:

1. The 95% confidence interval of the difference in clinical cure rates of alatrofoxacin/trovafoxacin minus cefoxitin/doxycycline for the Applicant clinical evaluable subjects at EOS was $_{53, 55} (-24.6\%, 5.1\%)$ $_{81.1\%, 90.9\%}$, failing to demonstrate therapeutic equivalence of alatrofoxacin/trovafoxacin to cefoxitin/doxycycline in the treatment of pelvic inflammatory disease.
2. With respect to all safety parameters, there were no significant differences between alatrofoxacin/trovafoxacin and cefoxitin/doxycycline.

The following statements pertain to Study 154-125:

1. The 95% confidence interval of the difference in clinical cure rates of trovafoxacin minus ofloxacin/clindamycin for the Applicant clinical evaluable subjects at EOS was $_{101, 97} (-9.5\%, 8.1\%)$ $_{91.1\%, 91.8\%}$, demonstrating that trovafoxacin was therapeutically equivalent in efficacy to ofloxacin/clindamycin in the treatment of pelvic inflammatory disease.
2. Trovafoxacin and ofloxacin/clindamycin were not significantly different in safety with respect to the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. However, the trovafoxacin subjects had significantly higher incidence rates of dizziness and headache than the ofloxacin/clindamycin subjects.

REVIEWER CONCLUSIONS: For the pivotal study 154-125, the efficacy analyses of the clinically evaluable subjects demonstrated that trovafoxacin 200 mg q.d. was therapeutically equivalent in efficacy to ofloxacin/clindamycin in the treatment of pelvic inflammatory disease for ambulatory subjects. Study 154-125 also suggests that trovafoxacin and ofloxacin/clindamycin yield nearly comparable safety results. For the pivotal study 154-122, efficacy analysis of the clinically evaluable subjects failed to demonstrate that alatrofoxacin/trovafoxacin was therapeutically equivalent to cefoxitin/doxycycline.

RECOMMENDED REGULATORY ACTION: Based on the above analyses, from a statistical standpoint, trovafoxacin 200 mg q.d. administered for 14 days is recommended for approval in the treatment of pelvic inflammatory disease for ambulatory subjects. Alatrofoxacin 200 mg q.d. followed by trovafoxacin 200 mg q.d., administered for a total of 14 days, is not recommended for approval.

UNCOMPLICATED URINARY TRACT INFECTIONS

This indication was supported by two pivotal studies, Studies 154-103 and 154-116, to demonstrate the efficacy and safety of trovafoxacin. Study 154-103 was not powered to demonstrate therapeutic equivalence of the three treatment regimens studied, thus study 154-116 is of primary interest.

Statistical evaluation of efficacy is primarily based upon the two-sided 98.3% confidence interval of the difference in subject bacteriological eradication rates at EOT between the treatment groups in the Medical Officer bacteriologically evaluable subjects, where Bonferroni's adjustment for the multiple comparison is applied and a 95% family confidence interval is constructed.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the

treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

The following statements pertain to Study 154-103:

1. Subject bacteriological eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT were 95.5% (21/22), 86.4% (19/22), and 93.1% (27/29) for trovafloracin q.d., trovafloracin b.i.d., and ciprofloracin, respectively.
2. Fisher's exact test (p-value=0.012) indicates a significantly higher rate of subjects in trovafloracin b.i.d. experienced at least one treatment related adverse even (48.6%, 36/74) than in ciprofloracin (28.0%, 21/75). Significantly more subjects experienced dizziness in both trovafloracin groups compared to ciprofloracin.

The following statements pertain to Study 154-116:

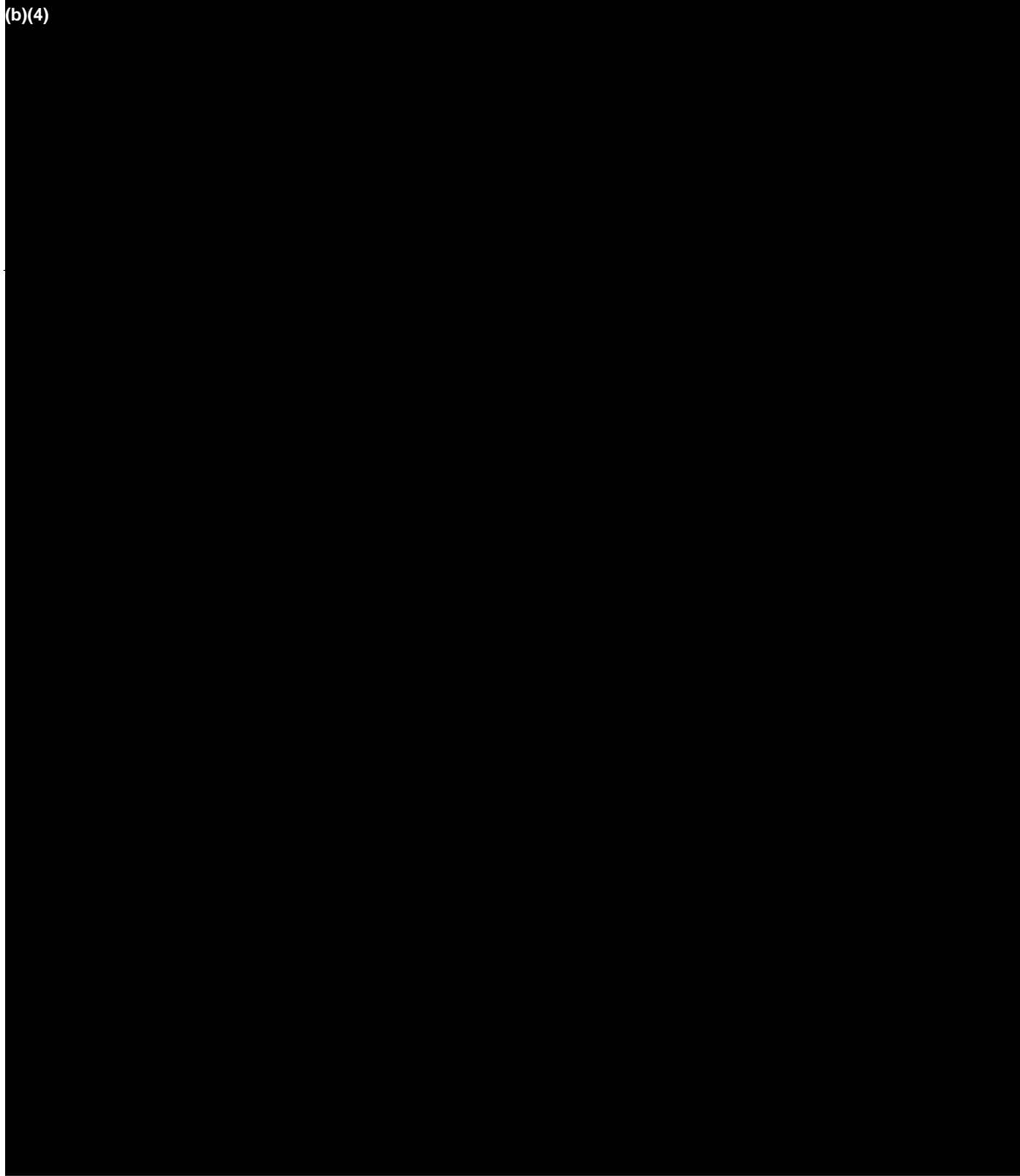
1. The 98.3% confidence interval of the difference in subject bacteriological eradication rates of trovafloracin 3 days minus norfloracin for the Medical Officer bacteriologically evaluable subjects at EOT was $_{116, 105} (-13.7\%, 8.8\%)$ $_{87.1\%, 89.5\%}$, demonstrating that trovafloracin 3 days was therapeutically equivalent in efficacy to norfloracin in the treatment of female subjects with uncomplicated urinary tract infections.
2. The 98.3% confidence interval of the difference in subject bacteriological eradication rates of trovafloracin 7 days minus norfloracin for the Medical Officer bacteriologically evaluable subjects at EOT was $_{113, 105} (-6.7\%, 13.5\%)$ $_{92.9\%, 89.5\%}$, demonstrating that trovafloracin 7 days was therapeutically equivalent in efficacy to norfloracin in the treatment of female subjects with uncomplicated urinary tract infections.
3. The 98.3% confidence interval of the difference in subject bacteriological eradication rates of trovafloracin 3 days minus trovafloracin 7 days for the Medical Officer bacteriologically evaluable subjects at EOT was $_{116, 113} (-16.2\%, 4.5\%)$ $_{87.1\%, 92.9\%}$, demonstrating that trovafloracin 3 days was not therapeutically equivalent in efficacy to trovafloracin 7 days in the treatment of female subjects with uncomplicated urinary tract infections.
4. Trovafloracin 3 days, trovafloracin 7 days, and norfloracin were not significantly different in safety with respect to the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to an adverse events, and the rate of clinical significant laboratory abnormalities. However, the trovafloracin 7 day group had significantly higher incidence rates of treatment related adverse events in the central and peripheral nervous system than the norfloracin group.

REVIEWER CONCLUSIONS: *For the pivotal study 154-116, the efficacy analyses of the bacteriologically evaluable subjects demonstrated that both 3 days and 7 days of trovafloracin 100 mg q.d. were therapeutically equivalent in efficacy to 3 days of norfloracin 250 mg b.i.d. in the treatment of female subjects with uncomplicated urinary tract infections. Three days of trovafloracin was not shown to be therapeutically equivalent to 7 days of trovafloracin. Study 154-116 also suggested that both trovafloracin regimens and its comparator yield nearly comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, both trovafloracin regimens of 100 mg q.d. 3 days and 100 mg q.d. 7 days are recommended for approval in the treatment of female subjects with uncomplicated urinary tract infections. It is noteworthy that the 7 days trovafloracin regimen appeared to be slightly more efficacious than the 3 days trovafloracin regimen*

although this difference was not statistically significantly.

(b)(4)



(b)(4)

PROSTATITIS

This indication was supported by one pivotal study, Study 154-119, to demonstrate the efficacy and safety of trovafloracin.

The following statements pertain to Study 154-119:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of difference in clinical success rates at EOT between the treatment groups in the Medical Officer clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of trovafloracin minus ofloxacin for the Medical Officer clinically evaluable subjects at EOT was $_{68, 58} (-10.4\%, 13.5\%)_{91.2\%, 89.7\%}$. The result demonstrated that trovafloracin was marginally equivalent in efficacy to ofloxacin in the treatment of bacterial prostatitis.
2. The rate of at least one treatment related adverse event was significantly higher in the trovafloracin group (43.0%, 61/142) than the ofloxacin group (29.3%, 39/133) (Fisher's exact p-value=0.024); the rate of discontinuations due to adverse events was significantly higher in the trovafloracin group (17.6%, 25/142) than the ofloxacin group (6.8%, 9/133) (Fisher's exact p-value=0.009). The two treatment groups were not significantly different with respect to the rate of at least one adverse event and the rate of clinically significant laboratory abnormalities. Significantly more subjects experienced dizziness and headache in the trovafloracin group.

REVIEWER CONCLUSIONS: For the pivotal study 154-119, the efficacy analyses of the clinically evaluable subjects demonstrated that trovafloracin was therapeutically equivalent in efficacy to ofloxacin in the treatment of bacterial prostatitis. Results from the safety analysis showed that trovafloracin had significantly higher rates than its comparator with respect to at least one treatment related adverse event and discontinuations due to adverse events, as well as dizziness and headache.

RECOMMENDED REGULATORY ACTION: Based on the above analyses, from an efficacy standpoint,

trovaflloxacin 200 mg q.d. administered for 28 days is recommended for approval in the treatment of bacterial prostatitis. However, the Medical Officer will have to determine whether this treatment regimen has an acceptable safety profile.

/S/ *-12/8/97*

Jóel Jiang, Ph.D.
Statistician, DBIV

/S/

12/8/97

Concur: Nancy Paul Silliman, Ph.D.
Statistician, DBIV

/S/ *12/10/97*

Mohammad Huque, Ph.D.
Acting Division Director, DBIV

cc:

Archival: NDA20759 and NDA20760

HFD-590

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HFD-590/Dr. Albrecht

HFD-590/Dr. Leissa

HFD-590/Dr. Alivisatos

HFD-590/Dr. Davis

HFD-520/Dr. Makhene

HFD-590/Ms. Fogarty

HFD-725/Dr. Huque

HFD-725/Dr. Lin

HFD-725/Dr. Silliman

HFD-725/Dr. Jiang

HFD-725/Chron.

This review contains 102 pages and 103 tables.

MicrosoftWord 7.0/NDA20760

12/8/97

Fogarty

STATISTICAL REVIEW AND EVALUATION

NOV 29 1997

NDA#: 20-759 and 20-760

Name of Drug: TROVAN® tablets (trovafloxacin mesylate) and
TROVAN® I.V. (alatrofloxacin mesylate injection)

Applicant: Pfizer Central Research, Medical Research Laboratory

Indication(s): 17 total, the following 6 by this reviewer:
(1) nosocomial pneumonia,
(2) community acquired pneumonia,
(3) acute exacerbation of chronic bronchitis,
(4) acute sinusitis,
(5) uncomplicated skin and skin structure infections, &
(6) complicated skin and skin structure infections.
(b)(4)

The statistical review of the remaining nine indications was completed by Joel Jiang, Ph.D.

Documents Reviewed: Volumes 1.1 through 1.9 and electronic submission.

Review Type: Clinical.

Statistical Reviewer: Nancy Paul Silliman, Ph.D., HFD-725

Medical Officers: Regina Alivisatos, MD, Philip Coyne, MD, and
Rigoberto Roca, MD, HFD-590

Project Manager: Pauline Fogarty, HFD-590

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ADP 154-101

Reviewer's Note: Much of the following is taken directly from the sponsor's electronic submission. Reviewer comments and analyses will either be given in italics or distinguished as such (e.g., by table headings which indicate "FDA" or "Medical Officer" populations and/or analyses).

The following abbreviations are used throughout this document:

EOT = End of Treatment visit

EOS = End of Study visit

MO = (Reviewing) Medical Officer

ITT = Intent-to-Treat (analysis or population)

CI = confidence interval.

I. INTRODUCTION

Clinical Program

The clinical program was designed to support a claim of effectiveness for (a) oral trovafloxacin 100 or 200 mg once daily, (b) intravenous (IV) alatrofloxacin equivalent to 200 mg trovafloxacin (single dose), or (c) IV alatrofloxacin equivalent to 200 or 300 mg trovafloxacin once daily followed by oral trovafloxacin 200 mg once daily (IV-to-oral regimen) in the treatment of the following conditions:

- respiratory tract infections, including acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, nosocomial pneumonia, and acute sinusitis;
- surgical infections including complicated intra-abdominal infections and acute gynecologic and pelvic infections;
- pelvic inflammatory disease;
- skin and skin structure infections, uncomplicated and complicated (including diabetic foot infections);
- urinary tract infections (UTI), uncomplicated (b)(4)
- bacterial prostatitis;
- sexually transmitted diseases, including acute, uncomplicated gonorrhea and nongonococcal urethritis/cervicitis;
-
- prophylaxis of infection associated with elective surgical procedures, including colorectal surgery, vaginal and abdominal hysterectomy.

The clinical program included 45 Phase I studies of oral trovafloxacin or IV alatrofloxacin. These studies examined the pharmacokinetics, bioavailability and bioequivalence, food and drug interactions, pharmacokinetic characteristics in special patient populations, and safety

issues associated with quinolone compounds, as well as tissue concentrations of trovafloxacin after administration of trovafloxacin or alatrofloxacin.

The Phase II/III clinical program included 33 studies which assessed the efficacy and safety of oral trovafloxacin, IV alatrofloxacin, or the IV-to-oral regimen for the indications described above as follows:

Table 1a. Clinical Studies

Indication	Protocol Numbers of Studies
Community-acquired pneumonia	154-102, 154-110, 154-111, 154-112, 154-134
Nosocomial pneumonia	154-113, 154-137
Acute bacterial exacerbation of chronic bronchitis	154-101, 154-109, 154-141
Acute sinusitis	154-114, 154-115, 154-138
Complicated intra-abdominal infection	154-124
Acute pelvic infection	154-144
Pelvic inflammatory disease	154-122, 154-125
Uncomplicated skin and skin structure infection	154-129, 154-130
Complicated skin and skin structure infection	154-131, 154-132, 154-139
Prostatitis	154-119
Surgical prophylaxis, elective colo-rectal surgery	154-128
Surgical prophylaxis, elective hysterectomy	154-146

Table 1b. Bacteriological Studies

Indication	Protocol Numbers of Studies
Uncomplicated UTI	154-103, 154-116
Sexually transmitted disease, chlamydia	154-105, 154-123
Sexually transmitted disease, gonorrhea	154-120

Clinical efficacy and safety data are presented for four additional studies: one supportive study of gonorrheal infection (154-107), one supportive study of acute bacterial exacerbation of chronic bronchitis (154-108)

and one study of *Helicobacter pylori* infection (154-106). No claims of efficacy are made in this submission relative to these four studies.

Reviewer's Note: Nineteen studies are reviewed here: the eighteen studies listed in Table 1 above for the six specific indications assigned to this reviewer (nosocomial pneumonia, community acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinusitis, uncomplicated skin and skin structure infections, & complicated skin and skin structure infections), plus the one additional supportive study of acute bacterial exacerbation of chronic bronchitis (154-108).

The number of subjects evaluated for each indication is summarized for the oral trovafloxacin trials in Table 1c below.

Table 1c. Number of Subjects Treated in Phase II/III Clinical Development Program by Indication: Oral Trovafloxacin Trials				
Indication	All Trovafloxacin^a	Trovafloxacin 100 mg	Trovafloxacin 200 mg	Oral Comparators
Acute bacterial exacerbation of chronic bronchitis	768	559	134	530
Community-acquired pneumonia	430	0	378	379
Sinusitis	662	0	662	423
Urinary tract infection (UTI)	510	436	0	253
Prostatitis	142	0	142	133
Chlamydia	619	28	554	481
Gonorrhea	350	325	14	314
Pelvic inflammatory disease	149	0	149	156
Prophylaxis: hysterectomy	188	0	188	175
Skin and skin structure infection	361	361	0	363
Diabetic foot infection	225	0	225	0
Complicated skin and skin structure infection	160	0	160	156
<i>Helicobacter pylori</i>	39	17	10	0
a Includes 50 mg, 100 mg, 100 mg BID, 200 mg, and 300 mg oral dose regimens.				

The number of subjects evaluated for each indication is summarized for the IV alatrofloxacin to oral trovafloxacin trials (adult indications only) in Table 1d below.

Table 1d. Number of Subjects Treated in Phase II/III Clinical Development Program by Indication: IV Alatrofloxacin or IV-to-oral Trials			
Indication	Alatrofloxacin 200 mg → Trovafloxacin^{a, b}	Alatrofloxacin 300 mg → Trovafloxacin^a	IV → Oral Comparators
Community-acquired pneumonia	411	0	422
Nosocomial pneumonia	0	262	277
Pelvic inflammatory disease	79	0	79
Abdominal infection	0	201	207
Acute pelvic infection	0	160	157
Prophylaxis: colo-rectal surgery	256	0	236
Complicated skin and skin structure infection	144	0	142
a Trovafloxacin dose was 200 mg for both IV-to-oral regimens.			
b Includes 200 mg alatrofloxacin single dose IV (no oral component) from study number 154-128.			

Efficacy

In general, subjects were required to have clinical signs and/or symptoms of bacterial infection prior to treatment along with bacteriological assessment of infection as appropriate. Bacteriologic evaluation was not required in two of the three acute sinusitis studies (154-115, 154-138). Subjects were evaluated at baseline, at the end of treatment, and at a follow-up visit or end of study visit. Assessments included clinical examinations, collection of samples for bacteriologic/serologic evaluation, and/or radiologic examinations as specified in the study protocol. The clinical response of each subject was assessed by the investigator. The sponsor then evaluated the clinical outcomes, primarily based on the investigator's assessments but also taking into account conditions that superseded the investigator's assessment such as administration of concomitant antibiotics. Both the investigator's original assessments and the sponsor-defined clinical outcomes are presented for each study.

Reviewer's Note: Results corresponding to sponsor-defined outcomes are presented in this review. Sponsor-defined outcomes tended to be more conservative than the investigators' original assessments. Results will be presented for the investigators' original assessments only if they differ substantially from those corresponding to sponsor-defined outcomes.

The analyses of efficacy were based on the sponsor's assessment of subject clinical response (success [cure or improvement] or failure) and/or subject bacteriological response (eradication, presumed eradication, persistence, or presumed persistence) or pathogen eradication rate. Generally, clinical response was classified as:

- 1 Cure - Resolution of all signs and symptoms to the level that existed before baseline.
- 2 Improvement - Incomplete resolution of signs and symptoms.
- 3 Failure - Lack of resolution or progression of any of the signs and symptoms and other indication specific rules such as taking a concomitant antibiotic for insufficient response or carrying forward a previous failure.

and clinical success rates were calculated as:

$$\text{Success Rate} = \frac{\text{Number of Cures and Improvements}}{\text{Number of patients in subset}}$$

For most indications, there were three categories for pathogen outcomes:

- 1 Eradication - Baseline organism is absent.
- 2 Persistence - Baseline organism is present.
- 3 Presumed Persistence - Included indication specific rules such as taking a concomitant antibiotic for insufficient response or in the absence of adequate culture material, a clinical response of failure.

In addition, for some of the indications, there was a fourth category:

- 4 Presumed Eradication - In the absence of adequate culture material, clinical response was a cure or improvement.

Eradication rates were calculated as:

$$\text{Pathogen Eradication Rate} = \frac{\text{Number of patients with baseline pathogens with outcomes of Eradication and Presumptive Eradication}}{\text{Number of patients in subset with the baseline pathogen identified}}$$

For all of the adult treatment studies, analyses were performed for both intent-to-treat (ITT) and evaluable subject groups. For all indications except sexually transmitted diseases, the clinical ITT subject group included all randomized subjects who had a baseline diagnosis of the condition under study regardless of whether study medication was received. The bacteriologic ITT subject group included all subjects in the clinical ITT subset who had at least one pathogen identified at baseline or, in the case of the UTI studies, all clinical ITT subjects who met disease-specific criteria for bacteriologic diagnoses. The clinically evaluable and bacteriologically evaluable subject groups included subjects in the respective ITT subsets who received study medication unless one or more of the criteria in Table 1e applied.

Table 1e. Evaluability Criteria

Clinical Evaluable Group

Criteria	Indications	
	Respiratory	Skin
Insufficient Therapy	✓	✓
Antibiotic Prior to Baseline for > 24 hours	✓	✓
Concomitant Antibiotic for Intercurrent Illness	✓	✓
Intercurrent Illness	✓	✓
Post-Baseline Clinical Assessment Not in Evaluable Window	✓	✓
Less than 80% compliant - Phase II Only (a)	✓	
Lost to Follow-Up - Phase II Only (a)	✓	

(a) protocols 101 and 102 ✓ = evaluability criteria applies

Bacteriological Evaluable Group

Criteria	Indications	
	Respiratory	Skin
Baseline Culture Not in Window	✓	✓
Post-Baseline Culture Not in Evaluable Window	✓	✓

✓ = evaluability criteria applies

For the analysis of the clinical intent-to-treat group, a 'last observation carried forward' strategy was used for subjects who were lost to follow-up before the End of Study visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment was treated as missing data.

***Reviewer's Note:** We usually do not recommend carrying forward successes when patients are lost to follow-up. All patients lost to follow-up are usually treated as failures in the ITT analysis. However, since the ITT population is not of primary interest here, due to the fact that all of the controlled trials reviewed in this submission use an active control arm instead of placebo, this difference in "estimating" missing data is not of great concern.*

Results are presented in this review for the evaluable patient groups. Results will be presented for the intent-to-treat groups only if they differ substantially from those for the evaluable groups.

Analyses were performed at the primary time point defined for each protocol and, in some cases, at secondary time points. Table 1f lists the time points and endpoints used in the clinical studies. The shaded areas of the table indicate that the time point or endpoint is primary. For example, the primary analysis for the skin studies consisted of analyzing sponsor-defined subject clinical response at the end-of-treatment.

Table 1f. Analysis Time Points and Endpoints

Time Points	Clinical Studies	
	Respiratory	Skin
Primary	EOT	EOT
Secondary	EOS	EOS
Endpoints		
Sponsor-Defined Subject Clinical Response	✓	✓
Investigator-Defined Subject Clinical Response	✓	✓
Pathogen Specific Eradication Rates	✓	✓

EOT = end of treatment visit, EOS = end of study visit

shaded area = primary time point / endpoint

Each endpoint was analyzed for every time point.

The primary analysis consisted of the combination of the primary endpoint and the primary time point.

The End of Treatment (EOT) and End of Study (EOS) windows for the evaluable and intent-to-treat analyses were defined as shown in Table 1g.

Table 1g. Analysis Windows

Indication	Protocol	Evaluable Analysis Windows		Intent-to-treat Analysis Windows	
		End of Treatment	End of Study	End of Treatment	End of Study
Sinusitis	114	3 to 18	19 to 40	1 to 18	19 to 45
	115	5 to 21	22 to 40	1 to 21	22 to 45
	138	5 to 18	19 to 40	1 to 18	19 to 45
Bronchitis	101	9 to 15	21 to 35	9 to 15	16 to 45
	All Others	3 to 18	19 to 40	1 to 18	19 to 45
CAP	All	5 to 20	21 to 40	1 to 20	21 to 45
NOS	All	7 to 20	21 to 40	1 to 20	21 to 45
Skin	All	5 to 20	21 to 40	2 to 20	21 to 41

Statistical Methods: Comparative Studies

The objective of each comparative study was to demonstrate that trovafloxacin, or alatrofloxacin followed by trovafloxacin, is "equivalent" to the comparative therapy. The definition of equivalence used in all trials was that suggested by the Division of Anti-Infective Drug Products in their "Points to Consider" guidance document. For example, assuming the primary clinical or microbiological effectiveness rate of the reference drug is 90%, the number of subjects for each treatment group required to ensure with 80% probability that the lower limit of the 95% confidence interval for the true difference in efficacy does not fall below -10% is 142 subjects per treatment group. If 10% of the subjects are expected to be non-evaluable then 158 subjects per group are required to protect the power of the study. The calculations are based on Makuch and Simon, Cancer Treatment Reports, Vol. 62, no. 7, July 1978, pp. 1037-1040 (modified to account for the 2-sided confidence interval).

The primary analysis for determination of equivalence of treatment groups was based on 95% confidence intervals (CI) for each pairwise difference in success rates (cure/improvement vs. failure) or eradication rates (eradication vs. persistence) between treatments. The calculation of CI was based on the normal approximation to the binomial distribution with no correction for continuity.

***Reviewer's Note:** Confidence intervals presented for FDA analyses will be produced by this reviewer using the normal approximation to the binomial distribution incorporating the correction for continuity.*

Success rates or eradication rates between treatment groups were also compared by 1 degree of freedom (d.f.) chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment to account for investigator differences.

The distribution of clinical cures, successes, and failures among treatment groups was compared by a chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment to account for investigator differences. For the End of Study analysis, the categories of failure and relapse were collapsed into one category: failure.

Investigators with fewer than five evaluable subjects per treatment arm were pooled together (within country) until one or more investigator 'group(s)' were formed with at least five evaluable subjects per treatment arm. For the intent-to-treat analyses, any investigator with no evaluable subjects was randomly assigned to an existing investigator group. Pooling of small centers was based on the primary patient subset only, which, for example, would be the clinically evaluable subset for studies where the clinical endpoint was primary.

***Reviewer's Note:** Since all of the comparative trials reviewed here are active-controlled trials (i.e., the comparator is another drug, not a placebo), the Cochran-Mantel-Haenszel (CMH) test is inappropriate and results are not presented in this review. The CMH test assumes that outcome rates in the two treatment groups are equal and then attempts to show otherwise. Failure to show a significant difference, however, does not then imply that outcome rates are, in fact, similar in the two treatment groups.*

For pathogen eradication rate, no inferential statistics were presented if fewer than 15 subjects per treatment group had a particular baseline pathogen.

The baseline comparability of the treatment groups in the primary intent-to-treat subjects and primary evaluable subjects subsets was assessed by examining the age, gender, weight (within gender), race and disease characteristics of the subjects at baseline. If applicable, other risk factors such as duration of baseline condition and tobacco use was also compared among the treatment groups. Only descriptive statistics were used to compare baseline characteristics of the treatment groups. No inferential statistics were presented.

Safety

All treated subjects were included in the analysis of safety. Safety analyses included summaries of the incidence and severity of adverse events, the proportions of subjects who prematurely discontinued treatment or study, and the incidence of clinically significant laboratory abnormalities. Serious adverse events, including deaths, which occurred within 30 days after the last dose of study medication were summarized separately. Safety data were also analyzed by demographic subsets, including age, race, and gender.

Adverse events (excluding objective test findings) were summarized by body system and by severity. Three separate summaries included adverse events (all causality), adverse events determined by the investigator to be treatment related, and treatment emergent signs and symptoms (TESS). Assessment of relationship to treatment and TESS were independent of each other.

An adverse event was defined as a sign or symptom, intercurrent illness, or clinically important test abnormality that occurred during the trial. The analyses of adverse events are based on the investigators' assessments of severity and relationship to study drug. Adverse events classified by the sponsor as treatment-related include those considered by the investigator to be related or possibly related to study drug as well as those with unknown relationship and those for which no comment regarding causality was made. All adverse events occurring either during study drug treatment or within 7 days after the end of treatment were included in analysis.

The analysis of clinical laboratory abnormalities includes clinical laboratory tests performed during treatment and up to 7 days after the end of treatment. In order to be included in the analysis of clinical laboratory data, a subject must have had at least one post-baseline value, either during treatment or during the 7-day post-treatment period. For all clinical laboratory tests, post-treatment values were assessed according to one or two criteria for clinical significance depending on whether the test value was normal (Criteria 1) or abnormal (Criteria 1 and 2) at baseline. *Reviewer's Note: Please refer to the MO's review for a definition of these criteria.*

No statistical inference was made for any summary of adverse events.

Reviewer's Note: During the course of this review, it became obvious that dizziness is one of the more common adverse events associated with the use of alatrofloxacin/trovafloxacin. In fact, in seven of the seventeen controlled trials reviewed here, the rate of dizziness was significantly higher in the alatrofloxacin/trovafloxacin arm than in the comparator arm.

The number and percent of patients experiencing dizziness ("all causalities", i.e., regardless of whether the investigator considered the dizziness to be treatment related or not) is summarized in the following table by treatment arm and protocol for the indications covered by this review.

**Number and Percent of Patients Experiencing Dizziness
by Treatment Arm and Protocol**

Indication	Protocol	Trovan Dose: n (%)	Comparator Drug: n (%)
Sinusitis	154-114	200 mg: 51 (20%)	N/A
	154-115*	200 mg: 69 (34%)	Clarithromycin: 5 (2%)
	154-138*	200 mg: 34 (17%)	Amoxicillin/Clavulanate: 2 (<1%)
Bronchitis	154-101*	100 mg: 4 (5%) 300 mg: 30 (40%)	Ofloxacin: 7 (10%)
	154-109	100 mg: 12 (6%)	Clarithromycin: 6 (3%)
	154-141	100 mg: 5 (4%)	Ciprofloxacin: 7 (6%)
Community-Acquired Pneumonia	154-102*	200 mg: 2 (4%) 300 mg: 16 (31%)	Cefaclor: 3 (6%)
	154-110	200 mg: 12 (6%)	Ciprofloxacin: 3 (2%)
	154-111*	200 mg: 21 (10%)	Ceftriaxone: 3 (1%)
	154-112	200 mg: 6 (4%)	Amoxicillin: 2 (1%)
	154-134*	200 mg: 24 (13%)	Clarithromycin: 8 (4%)
Nosocomial Pneumonia	154-113	300IV/200PO: 5 (4%)	Ciprofloxacin: 2 (1%)
	154-137	300IV/200PO: (<3%)	Ceftazidime/Ciprofloxacin: (<3%)
Uncomplicated Skin	154-129	100 mg: 4 (3%)	Flucloxacillin: 1 (<1%)
	154-130	100 mg: 9 (4%)	Vantin: 6 (3%)
Complicated Skin	154-131	200 mg: (<5%)	Zosyn/Vantin: (<5%)
	154-132	200 mg: 20 (9%)	N/A
	154-139*	200 mg: 12 (8%)	Augmentin: 1 (<1%)

n = number of patients experiencing dizziness
 N/A = not applicable (i.e., no comparator arm)
 *Difference in rates was statistically significant (p < 0.05 using Fisher's exact test) and observed rates were higher in the trovafloxacin arm; for protocols 154-101 and 154-102, only the comparison between the 300 mg trovafloxacin arm and the comparator was significant.

II. NOSOCOMIAL PNEUMONIA

The efficacy and safety of the IV-to-oral regimen in the treatment of nosocomial pneumonia was assessed in two comparative trials, one double-blind (154-113) and one open-label (154-137). The comparator regimens were ciprofloxacin (IV-to-oral; 154-113) and IV ceftazidime followed by oral ciprofloxacin (154-137).

***Reviewer's Note:** The sponsor assessed whether efficacy differed in various subgroups in the nosocomial pneumonia trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, and race. A trend towards a lower clinical response rate was observed in elderly subjects (≥ 75 years of age versus subjects < 75 years of age) in both the trovafloxacin and comparator treatment groups at EOT and EOS.*

II.A. Protocol 154-113

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CIPROFLOXACIN FOLLOWED BY ORAL CIPROFLOXACIN FOR THE TREATMENT OF NOSOCOMIAL PNEUMONIA.

Study Dates: 3 February 1995 - 13 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin (with optional aztreonam and/or vancomycin) compared to intravenous ciprofloxacin followed by oral ciprofloxacin (with optional aztreonam, vancomycin, clindamycin, and/or metronidazole) for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

***Reviewer's Note:** Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional aztreonam or vancomycin to treat documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, respectively, if approved it will need to be labeled this way.*

Study Design: Study 154-113 was a randomized, multicenter, double-blind trial of alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment versus intravenous ciprofloxacin (1500 mg daily administered as 750 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (800 mg daily administered as 400 mg twice daily) to complete 10 to 14 days of total treatment for the treatment of nosocomial pneumonia requiring initial intravenous therapy. In addition, in subjects with documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, aztreonam or vancomycin, respectively, may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added in blinded fashion to the ciprofloxacin treatment regimen.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented nosocomial pneumonia requiring initial intravenous therapy were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia and a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

***Reviewer's Note:** The reviewing medical officer, Dr. Regina Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.*

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Sponsor Efficacy Results:**Analysis Groups**

Table 2a.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Reviewer's Note: Somewhat fewer trovafloxacin patients completed treatment and were considered clinically evaluable, however these differences were not statistically significant ($p=0.08$ and 0.28 , respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 2a.1. Evaluation Groups

Evaluation Groups ^a :	Alatrofloxacin	Ciprofloxacin
	↓ Trovfloxacin	↓ Ciprofloxacin
Randomized	129	138
All Treated	127 (100%)	137 (100%)
Completed Treatment	74 (58%)	94 (69%)
Completed Study	86 (68%)	90 (66%)
Evaluated for Efficacy ^b		
Clinical Intent-to-Treat	127 (98%)	135 (98%)
Clinically Evaluable ^c	88 (68%)	103 (75%)
Bacteriologically Intent-to-Treat	71 (55%)	68 (49%)
Bacteriologically Evaluable	47 (36%)	52 (38%)
Assessed for Safety ^d		
Adverse Events	127 (100%)	137 (100%)
Laboratory Tests	115 (91%)	126 (92%)

a The daily dose of alatrofloxacin was 300 mg and that of trovafloxacin was 200 mg. The daily dose of oral ciprofloxacin was 800 mg (400 mg administered twice daily) and the daily dose of intravenous ciprofloxacin was 1500 mg (750 mg administered twice daily).

b Percentages based on number of randomized subjects.

c Based on End of Treatment assessment.

d Percentages based on number of all treated subjects.

Of the 129 alatrofloxacin/trovafloxacin and 138 ciprofloxacin randomized subjects, two alatrofloxacin/trovafloxacin subjects and three ciprofloxacin subjects had an inappropriate baseline diagnosis (i.e., no clinical signs and symptoms of nosocomial pneumonia at baseline as defined by protocol) and were excluded from all intent-to-treat and evaluable analyses.

Of the 127 alatrofloxacin/trovafloxacin and 135 ciprofloxacin clinically ITT subjects, 39 in the alatrofloxacin/trovafloxacin group and 32 in the ciprofloxacin/ ciprofloxacin group were not clinically evaluable; therefore, 88 subjects in the alatrofloxacin/trovafloxacin group and 103 subjects in the ciprofloxacin group were clinically evaluable. The most common reasons for exclusion from clinical efficacy analyses were no post-baseline clinical assessments (20/129 [16%], alatrofloxacin/trovafloxacin and 16/138 [12%], ciprofloxacin), no post-baseline clinical assessments in evaluable window (20/129 [16%], alatrofloxacin/trovafloxacin and 16/138 [12%], ciprofloxacin) and insufficient therapy due to early discontinuation from treatment or study (27/129 [21%], alatrofloxacin/trovafloxacin and 23/138 [17%], ciprofloxacin). Other

reasons were randomized but not treated, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, and inappropriate use of optional study antibiotics against baseline pathogens.

Of the 127 alatrofloxacin/trovafloxacin and 135 ciprofloxacin clinically ITT subjects, 56 subjects in the alatrofloxacin/trovafloxacin group and 67 subjects in the ciprofloxacin group had negative baseline cultures; therefore, 71 subjects in the alatrofloxacin/trovafloxacin group and 68 subjects in the ciprofloxacin/ ciprofloxacin group were included in the bacteriological ITT analysis.

Of the 88 alatrofloxacin/trovafloxacin and 103 ciprofloxacin clinically evaluable subjects, 41 subjects in the alatrofloxacin/trovafloxacin group and 51 subjects in the ciprofloxacin group were not included in the bacteriologically evaluable analyses; therefore, 47 subjects in the alatrofloxacin/trovafloxacin group and 52 subjects in the ciprofloxacin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (41/129 [32%], alatrofloxacin/trovafloxacin and 51/138 [37%], ciprofloxacin). The other reason was no post-baseline cultures (the subjects [Subject 5175-0719, alatrofloxacin/trovafloxacin; Subject 5407-0349, ciprofloxacin] excluded for this reason had no baseline pathogen). (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 127 alatrofloxacin/trovafloxacin and 137 ciprofloxacin treated subjects, 53 alatrofloxacin/trovafloxacin and 43 ciprofloxacin subjects were prematurely discontinued from treatment as summarized in Table 2a.2.

Table 2a.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=137)	
	Number and Percentage (%) of Subjects			
Total Discontinued	53	(42%)	43	(31%)
Discontinuations Related to Study Drug:	17	(13%)	9	(7%)
Adverse Event	5	(4%)	0	
Insufficient Response	11	(9%)	8	(6%)
Laboratory Abnormality	1	(<1%)	1	(<1%)
Discontinuations Unrelated to Study Drug:	36	(28%)	34	(25%)
Adverse Event	6	(5%)	8	(6%)
Lost to Follow-up	0		1	(<1%)
Other	15	(12%)	12	(9%)
Subject Died	12	(9%)	10	(7%)
Protocol Violation	1	(<1%)	2	(1%)
Withdrawn Consent	2	(2%)	1	(<1%)

Demographics

Seventy-eight (78) of the 127 treated alatrofloxacin/trovafloxacin subjects (61%) were male and 49 (39%) were female and 76 of the 137 treated ciprofloxacin subjects (55%) were male and 61 (45%) were female. Treated subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups were generally comparable with respect to age, race, and weight. The distribution of treated subjects according to smoking classification was also similar between the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups (38% and 39% ex-smoker, 42% and 40% never smoked, and 20% and 21% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinically intent-to-treat subjects was nosocomial-acquired pneumonia. The median duration (range) since onset of pneumonia was 2 days (1-13 days) for subjects in the alatrofloxacin/trovafloxacin group and 2 days (1-12 days) for subjects in the ciprofloxacin group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups with respect to medical history at baseline.

Of clinically evaluable subjects, 29 in the alatrofloxacin/trovafloxacin group (33%) and 35 in the ciprofloxacin group (34%) required high fractional oxygen and/or mechanical ventilation at baseline. The mean APACHE II score at baseline for clinically evaluable subjects in both treatment groups was 13.09. Similar results were noted for clinically intent-to-treat subjects.

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 2a.3. Alatrofloxacin/trovafloxacin was considered therapeutically equivalent to ciprofloxacin at both EOT and EOS.

Table 2a.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovfloxacin (N=88)		Ciprofloxacin ↓ Ciprofloxacin (N=103)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	88	(100%)	101	(100%)	
Success (Cure + Improvement)	68	(77%)	79	(78%)	(-12.8%, 10.9%)
Distribution of Clinical Response:					
Cure	42	(48%)	51	(50%)	
Improvement	26	(30%)	28	(28%)	
Failure	20	(23%)	22	(22%)	
End of Study:					
Number of Subjects Assessed	72	(100%)	79	(100%)	
Success (Cure + Improvement)	50	(69%)	54	(68%)	(-13.7%, 15.9%)
Distribution of Clinical Response:					
Cure	42	(58%)	53	(67%)	
Improvement	8	(11%)	1	(1%)	
Failure	20	(28%)	22	(28%)	
Relapse	2	(3%)	3	(4%)	

The number of clinically evaluable subjects with mild/moderate and severe nosocomial pneumonia at baseline was similar between the alatrofloxacin/trovfloxacin and ciprofloxacin treatment groups (mild/moderate pneumonia at baseline: 59 and 68 subjects, respectively; severe pneumonia at baseline : 29 and 35 subjects, respectively). Subjects were defined as having severe nosocomial pneumonia if they required mechanical ventilation or a fractional inspired oxygen concentration ≥ 0.35 to maintain an arterial oxygen tension of 60 mmHg.

Sponsor-defined clinical success rates (cure + improvement) were comparable for clinically evaluable subjects in the alatrofloxacin/trovfloxacin and ciprofloxacin treatment groups at EOT (49/59, 83% and 56/66, 85%, respectively) and at EOS (39/51, 76% and 40/53, 75%, respectively) for subjects with mild/moderate pneumonia at baseline and for subjects with severe pneumonia at baseline (EOT: 19/29, 66% and 23/35, 66%; EOS: 11/21, 52% and 14/26, 54%, respectively).

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 2a.4.

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**Table 2a.4. Summary of Clinical Success Rates at EOT and EOS
For the Most Frequently Isolated Baseline Pathogens^a
(Clinically Evaluable Subjects)**

	Alatrofloxacin ↓ Trovafoxacin (N=47)	Ciprofloxacin ↓ Ciprofloxacin (N=52)	Alatrofloxacin ↓ Trovafoxacin (N=39)	Ciprofloxacin ↓ Ciprofloxacin (N=38)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>P. aeruginosa</i>	10/15 (67%)	6/11	8/13	2/8
<i>S. aureus</i>	7/11	8/10	4/8	4/6
<i>H. influenzae</i>	7/8	8/9	5/6	6/7
<i>E. coli</i>	5/7	4/5	3/6	4/5
<i>S. pneumoniae</i>	2/4	5/6	2/4	3/4
<i>K. pneumoniae</i>	3/4	3/7	2/4	1/5
<i>H. parainfluenzae</i>	5/5	2/3	5/5	1/2

^a Includes ≥5 isolates of a given pathogen in either treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 2a.5.

**Table 2a.5. Summary of Sponsor-Defined Pathogen Eradication Rates
at EOT and EOS
For the Most Frequently Isolated Baseline Pathogens^a
(Bacteriologically Evaluable Subjects)**

	Alatrofloxacin ↓ Trovafoxacin (N=47)	Ciprofloxacin ↓ Ciprofloxacin (N=52)	Alatrofloxacin ↓ Trovafoxacin (N=39)	Ciprofloxacin ↓ Ciprofloxacin (N=38)
	Number and Percentage (%) of Pathogens			
Pathogen	End of Treatment		End of Study	
<i>P. aeruginosa</i>	9/15 (60%)	3/11	10/13	2/8
<i>S. aureus</i>	6/11	6/9	3/8	4/6
<i>H. influenzae</i>	7/8	9/9	5/6	7/7
<i>E. coli</i>	4/6	5/5	3/4	5/5
<i>S. pneumoniae</i>	2/4	6/6	2/4	4/4
<i>K. pneumoniae</i>	2/4	3/7	2/4	1/4
<i>H. parainfluenzae</i>	5/5	2/3	5/5	1/2

^a Includes ≥5 isolates of a given pathogen in either treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

MO Efficacy Results: *The medical officer reassessed patients' evaluability and clinical outcome status. Table 2a.6 presents clinical response for the MO clinically evaluable patient group at EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, alatrofloxacin/trovafloxacin was considered therapeutically equivalent to ciprofloxacin at both EOT and EOS.*

Table 2a.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)			
	Alatrofloxacin ↓ Trovafloxacin	Ciprofloxacin ↓ Ciprofloxacin	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	70 (100%)	76 (100%)	
Success (Cure + Improvement)	50 (71%)	54 (70%)	(-15.7, 16.4)
End of Study:			
Number of Subjects Assessed	70 (100%)	77 (100%)	
Success (Cure + Improvement)	48 (69%)	52 (68%)	(-15.4, 17.5)

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events and clinically significant laboratory values is presented in Table 2a.7. Tables 2a.8 and 2a.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced adverse events (all causalities) and discontinued treatment due to adverse events ($p < 0.001$ and $p = 0.047$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 2a.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values			
	Alatrofloxacin ↓ Trovafloxacin	Ciprofloxacin ↓ Ciprofloxacin	
Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	121/127 (95%)	111/137 (81%)	
Treatment-Related Adverse Events	28/127 (22%)	23/137 (17%)	
Discontinuations From Treatment Due to an Adverse Event	19/127 (15%)	10/137 (7%)	
Discontinuations From Treatment Due to a Treatment-Related Adverse Event	5/127 (4%)	0	
Clinically Significant Laboratory Values	90/115 (78%)	98/126 (78%)	

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Table 2a.8. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)

	Alatrofloxacin ↓ Trovfloxacin (N=127)	Ciprofloxacin ↓ Ciprofloxacin (N=137)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	121 (95%)	111 (81%)
BODY SYSTEM		
WHO Term		
APPL./INJ./INCISION/INSERTION SITE	29 (23%)	24 (18%)
Appl./Inj./Incision/Insertion Site Infection/Inflammation	5 (4%)	8 (6%)
Appl./Inj./Incision/Insertion Site Pain	3 (2%)	5 (4%)
Appl./Inj./Incision/Insertion Site Reaction	11 (9%)	8 (6%)
Appl./Inj./Incision/Insertion/Device Complication	13 (10%)	11 (8%)
CARDIOVASCULAR	47 (37%)	42 (31%)
Cardiac Arrest	5 (4%)	6 (4%)
Cardiac Failure	6 (5%)	3 (2%)
Circulatory Failure	5 (4%)	6 (4%)
Edema Peripheral	8 (6%)	4 (3%)
Hypotension	7 (6%)	1 (<1%)
Phlebitis	6 (5%)	6 (4%)
CENTRAL AND PERIPHERAL NERVOUS	30 (24%)	25 (18%)
Confusion	10 (8%)	7 (5%)
Dizziness	5 (4%)	2 (1%)
Headache	10 (8%)	8 (6%)
GASTROINTESTINAL	61 (48%)	47 (34%)
Abdominal Pain	5 (4%)	2 (1%)
Constipation	15 (12%)	9 (7%)
Diarrhea	15 (12%)	12 (9%)
Nausea	16 (13%)	11 (8%)
Vomiting	19 (15%)	12 (9%)
GENERAL	30 (24%)	32 (23%)
Fever	3 (2%)	9 (7%)
Moniliasis	3 (2%)	6 (4%)
Pain	5 (4%)	2 (1%)
Sepsis	9 (7%)	5 (4%)
HEMATOPOIETIC	8 (6%)	2 (1%)
Purpura	5 (4%)	2 (1%)
OTHER ADVERSE EVENTS	9 (7%)	8 (6%)
Accidental Injury	7 (6%)	3 (2%)
PSYCHIATRIC	26 (20%)	20 (15%)
Agitation	8 (6%)	5 (4%)
Anxiety	6 (5%)	2 (1%)
Insomnia	3 (2%)	9 (7%)
RESPIRATORY	43 (34%)	47 (34%)
Aspiration	5 (4%)	3 (2%)
Dyspnea	7 (6%)	9 (7%)
Pleural Effusion	4 (3%)	6 (4%)
Pneumonia	7 (6%)	13 (9%)
Respiratory Insufficiency	11 (9%)	5 (4%)
SKIN/APPENDAGES	26 (20%)	30 (22%)
Rash	5 (4%)	11 (8%)
Rash Erythematous	7 (6%)	6 (4%)
Skin Disorder	6 (5%)	5 (4%)
URINARY SYSTEM	19 (15%)	13 (9%)
Urinary Tract Infection	9 (7%)	4 (3%)

a ≥4% of subjects in either treatment group.

b Includes data up to 7 days after last dose of active study medication

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Table 2a.9. Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=137)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	28	(22%)	23	(17%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	6	(5%)	7	(5%)
Appl./Inj./Incision/Insertion Site Reaction	4	(3%)	3	(2%)
Appl./Inj./Incision/Insertion/Device Complication	2	(2%)	1	(<1%)
CARDIOVASCULAR	5	(4%)	2	(1%)
Phlebitis	5	(4%)	2	(1%)
CENTRAL AND PERIPHERAL NERVOUS	4	(3%)	2	(1%)
Headache	2	(2%)	1	(<1%)
GASTROINTESTINAL	11	(9%)	6	(4%)
Diarrhea	2	(2%)	2	(1%)
Nausea	6	(5%)	1	(<1%)
Vomiting	2	(2%)	1	(<1%)
GENERAL	4	(3%)	3	(2%)
Moniliasis	3	(2%)	3	(2%)
REPRODUCTIVE	1	(<1%)	0	
Vaginitis	1	(2%)	0	
RESPIRATORY	0		6	(4%)
Respiratory Tract Infection	0		4	(3%)
a ≥2% of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				

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- Thirty-five (35) subjects in the alatrofloxacin/trovafloxacin group and 38 subjects in the ciprofloxacin group died during this study, as follows:
- Six (6) subjects in the alatrofloxacin/trovafloxacin group and 6 subjects in the ciprofloxacin died while receiving therapy. All deaths were considered by the investigator to be unrelated to study drug.
- Twenty-five (25) subjects in the alatrofloxacin/trovafloxacin and 29 subjects in the ciprofloxacin group died within 30 days after the last dose of study drug. None of these deaths was considered by the investigator to be related to study drug.
- Four (4) subjects in the alatrofloxacin/trovafloxacin group and 3 subjects in the ciprofloxacin group died >30 days after the last dose of study drug. None of these deaths was considered by the investigator to be related to study drug.

Fifty-six (56) subjects in the alatrofloxacin/trovafloxacin group and 57 subjects in the ciprofloxacin group had serious adverse events. One subject in the alatrofloxacin/trovafloxacin group had a serious adverse event (multifocal myoclonus) that was considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or "other" reasons.

Sponsor's Summary and Conclusion: Alatrofloxacin (300 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for a total treatment duration of 10 to 14 days and intravenous ciprofloxacin (400 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (750 mg twice daily) for a total treatment duration of 10 to 14 days were comparable for the sponsor-defined clinical success rate at the end of treatment for both intent-to-treat and evaluable subjects. Sponsor-defined pathogen eradication rates for many of the most commonly isolated pathogens were comparable among bacteriologically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups at the end of treatment and end of study. The percentage of subjects discontinued from treatment due to adverse events was 15% in the alatrofloxacin/trovafloxacin group and 7% in the ciprofloxacin group. Five (5) subjects in the alatrofloxacin/trovafloxacin group and no subjects in the ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all and treatment-related adverse events was 95% and 22%, respectively, for subjects in the alatrofloxacin/trovafloxacin group and 81% and 17%, respectively, for subjects in the ciprofloxacin group. The most commonly reported treatment-related adverse event was nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and respiratory tract infection (3%) for subjects in the ciprofloxacin group.

Reviewer's Summary and Conclusion: Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ciprofloxacin at both EOT and EOS in terms of clinical success rate for clinically evaluable patients for both the sponsor and the MO analysis. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional aztreonam or vancomycin to treat documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, respectively, if approved it will need to be labeled this way.

A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced adverse events, 95% versus 81% for ciprofloxacin patients, and discontinued treatment due to adverse events, 15% versus 7% for ciprofloxacin patients ($p < 0.001$ and $p = 0.047$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

II.B. Protocol 154-137

A RANDOMISED, MULTICENTRE, OPEN TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CEFTAZIDIME FOLLOWED BY ORAL CIPROFLOXACIN WITH OPTIONAL GENTAMYCIN AND VANCOMYCIN FOR THE TREATMENT OF NOSOCOMIAL PNEUMONIA.

Reviewer's Note: "Open" is used here to indicate that the trial is unblinded.

Study Dates: 6 September 1995 - 21 August 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin (with optional vancomycin) compared to intravenous ceftazidime followed by oral ciprofloxacin (with optional

vancomycin, gentamycin, clindamycin, and/or metronidazole) for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

Study Design: Study 154-137 was a randomized, unblinded, comparative, multicenter trial of alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment versus intravenous ceftazidime (4000 mg daily administered as 2000 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (1500 mg daily administered as 750 mg twice daily) to complete 10 to 14 days of total treatment for the treatment of nosocomial pneumonia requiring initial intravenous therapy. In addition, in subjects with documented methicillin-resistant *S. aureus*, vancomycin may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added to the ceftazidime/ciprofloxacin treatment regimen. For subjects with documented *Pseudomonas* infection, gentamycin may have been added to the ceftazidime/ciprofloxacin treatment regimen. Although not specified by protocol, subjects in the alatrofloxacin/trovafloxacin group with documented *P. aeruginosa* at baseline who were subsequently treated with gentamycin were considered to be evaluable for efficacy by the sponsor.

Reviewer's Note: *Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional gentamycin or vancomycin to treat documented Pseudomonas infection or methicillin-resistant S. aureus, respectively, if approved it will need to be labeled this way.*

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented nosocomial pneumonia requiring initial intravenous therapy were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of nosocomial pneumonia to the baseline level that existed prior to the occurrence of nosocomial pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of nosocomial pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of nosocomial pneumonia or a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

***Reviewer's Note:** The reviewing medical officer, Dr. Regina Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.*

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Sponsor Efficacy Results:

Analysis Groups

Table 2b.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

***Reviewer's Note:** A lower percentage of alatrofloxacin/trovafloxacin patients completed treatment, were included in the bacteriological ITT analysis group, and were considered bacteriologically evaluable. None of these differences were statistically significant, however ($p=0.21$, 0.14 , and 0.15 , respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).*

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01/01/2004

Table 2b.1. Evaluation Groups

Evaluation Groups ^a :	Alatrofloxacin	Ceftazidime
	↓ Trovafoxacin	↓ Ciprofloxacin
Randomized	135	140
All Treated	135 (100%)	140 (100%)
Completed Treatment	88 (65%)	101 (72%)
Completed Study	86 (64%)	89 (64%)
Evaluated for Efficacy ^b		
Clinical Intent-to-Treat	132 (98%)	139 (>99%)
Clinically Evaluable ^c	103 (76%)	109 (78%)
Bacteriologically Intent-to-Treat	66 (49%)	81 (58%)
Bacteriologically Evaluable	52 (39%)	66 (47%)
Assessed for Safety ^d		
Adverse Events	135 (100%)	140 (100%)
Laboratory Tests	119 (88%)	124 (89%)

- a The daily dose of alatrofloxacin was 300 mg and that of trovafoxacin was 200 mg. The daily dose of oral ciprofloxacin was 1500 mg (750 mg administered twice daily) and the daily dose of intravenous ceftazidime was 4000 mg (2000 mg administered twice daily).
- b Percentages based on number of randomized subjects.
- c Based on end of treatment assessment.
- d Percentages based on number of all treated subjects.

Of the 135 alatrofloxacin/trovafoxacin and 140 ceftazidime/ciprofloxacin randomized subjects, 3 alatrofloxacin/trovafoxacin subjects and 1 ceftazidime/ciprofloxacin subject had an inappropriate baseline diagnosis (i.e., no clinical signs and symptoms of nosocomial pneumonia at baseline as defined by protocol) and were excluded from all intent-to-treat and evaluable analyses.

Of the 132 alatrofloxacin/trovafoxacin and 139 ceftazidime/ciprofloxacin clinically ITT subjects, 29 in the alatrofloxacin/trovafoxacin group and 30 in the ceftazidime/ciprofloxacin group were not clinically evaluable; therefore, 103 subjects in the alatrofloxacin/trovafoxacin group and 109 subjects in the ceftazidime/ciprofloxacin group were clinically evaluable. The most common reasons for exclusion from clinical efficacy analyses were insufficient therapy (21/135 [16%], alatrofloxacin/trovafoxacin and 11/140 [8%], ceftazidime/ciprofloxacin), no post-baseline clinical assessments and no post-baseline clinical assessments in evaluable window (18/135 [13%], alatrofloxacin/trovafoxacin and 16/140 [11%], ceftazidime/ciprofloxacin). Other reasons included inappropriate use of optional study antibiotics (no baseline *Pseudomonas*), inappropriate use of optional study antibiotic active against baseline pathogen, concomitant antibiotic for "other" infection during therapy, and chest x-ray negative for nosocomial pneumonia.

Of the 132 alatrofloxacin/trovafoxacin and 139 ceftazidime/ciprofloxacin clinically ITT subjects, 66 subjects in the alatrofloxacin/trovafoxacin group and 58 subjects in the ceftazidime/ciprofloxacin group had negative baseline cultures; therefore, 66 subjects in the alatrofloxacin/trovafoxacin group and 81 subjects in the ceftazidime/ciprofloxacin group were included in the bacteriological ITT analysis.

Of the 103 alatrofloxacin/trovafoxacin and 109 ceftazidime/ciprofloxacin clinically evaluable subjects, 51 subjects in the alatrofloxacin/trovafoxacin group and 43 subjects in the ceftazidime/ciprofloxacin group were not included in the bacteriologically evaluable analyses; therefore, 52 subjects in the alatrofloxacin/trovafoxacin group and 66 subjects in the ceftazidime/ciprofloxacin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (50/135 [37%], alatrofloxacin/trovafoxacin and 43/140 [31%], ceftazidime/ciprofloxacin). The other reasons were no post-baseline cultures (the subject [Subject 5800-0581, alatrofloxacin/trovafoxacin] excluded for this reason had no baseline pathogen and baseline culture outside evaluable window). (Subjects may have had more than one reason for exclusion from clinical and bacteriological analyses.)

Discontinuations

Of the 135 alatrofloxacin/trovafoxacin and 140 ceftazidime/ciprofloxacin treated subjects, 47 alatrofloxacin/trovafoxacin and 39 ceftazidime/ciprofloxacin subjects were prematurely discontinued from treatment as summarized in Table 2b.2.

Table 2b.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Alatrofloxacin ↓ Trovafoxacin (N=135)	Ceftazidime ↓ Ciprofloxacin (N=140)
Number and Percentage (%) of Subjects		
Total Discontinued	47 (35%)	39 (28%)
Discontinuations Related to Study Drug:	19 (14%)	16 (11%)
Adverse Event	7 (5%)	1 (<1%)
Insufficient Response	11 (8%)	15 (11%)
Laboratory Abnormality	1 (<1%)	0
Discontinuations Unrelated to Study Drug:	28 (21%)	23 (16%)
Adverse Event	8 (6%)	4 (3%)
Does Not Meet Randomization Criteria	1 (<1%)	2 (1%)
Laboratory Abnormality	4 (3%)	2 (1%)
Other	5 (4%)	3 (2%)
Patient Died	9 (7%)	12 (9%)
Protocol Violation	1 (<1%)	0

Demographics

Eighty-eight (88) of the 135 treated alatrofloxacin/trovafoxacin subjects (65%) were male and 47 (35%) were female. Ninety-nine (99) of the 140 ceftazidime/ciprofloxacin subjects (71%) were male and 41 (29%) were female. The subjects in the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin treatment groups were generally comparable with respect to age, race, and weight. The distribution of treated subjects according to smoking classification was also similar between the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin treatment groups (28% and 36% ex-smoker, 37% and 35% never smoked, and 34% and 29% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinically intent-to-treat subjects was nosocomial pneumonia. The median duration (range) since onset of nosocomial pneumonia was 2 days (0-12 days) for subjects in the alatrofloxacin/trovafloxacin group and 2 days (1-19) for subjects in the ceftazidime/ciprofloxacin group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups with respect to medical history at baseline.

The mean APACHE II score at baseline for clinically evaluable subjects in the alatrofloxacin/trovafloxacin group and the ceftazidime/ciprofloxacin group was 12.66 and 13.59, respectively. Similar results were noted for clinically intent-to-treat subjects.

Reviewer's Note: The reviewing medical officer, Dr. Regina Alivisatos, felt that the difference in mean APACHE II scores at baseline was clinically relevant. As a result, clinical success rates will be displayed below for subgroups of mild/moderate versus severely ill patients, in addition to the overall analysis.

Clinical Response

A summary of clinical response for clinically evaluable subjects at EOT and EOS is presented by treatment group in Table 2b.3. Clinical response was considered therapeutically equivalent between alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin at both EOT and EOS.

Table 2b.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloxacin (N=103)		Ceftazidime ↓ Ciprofloxacin (N=109)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	100	(100%)	107	(100%)	
Success (Cure + Improvement)	74	(74%)	75	(70%)	-8.3, 16.1
Distribution of Clinical Response:					
Cure	54	(54%)	52	(49%)	
Improvement	20	(20%)	23	(21%)	
Failure	26	(26%)	32	(30%)	
End of Study:					
Number of Subjects Assessed	85	(100%)	89	(100%)	
Success (Cure + Improvement)	56	(66%)	52	(58%)	-6.9, 21.8
Distribution of Clinical Response:					
Cure	54	(64%)	48	(54%)	
Improvement	2	(2%)	4	(4%)	
Failure	26	(31%)	32	(36%)	
Relapse	3	(4%)	5	(6%)	

The number of clinically evaluable subjects with mild/moderate and severe nosocomial pneumonia at baseline was similar between the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin treatment groups (mild/moderate nosocomial pneumonia at baseline: 47 and 49 subjects, respectively; severe nosocomial pneumonia at baseline: 56 and 60 subjects, respectively). Subjects were defined as having severe nosocomial pneumonia if they required mechanical ventilation or a fractional inspired oxygen concentration ≥ 0.35 to maintain an arterial oxygen tension of 60 mmHg.

Sponsor-defined clinical success rates (cure + improvement) were higher for clinically evaluable subjects in the alatrofloxacin/trovafloxacin group compared to the ceftazidime/ciprofloxacin group at the end of treatment (89% and 74%, respectively) and at the end of study (85% and 71%, respectively) for subjects with mild/moderate nosocomial pneumonia at baseline. Among subjects with severe nosocomial pneumonia, sponsor-defined clinical success rates were comparable between the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups at the end of treatment (63% and 67%, respectively) and at the end of study (49% and 47%, respectively).

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 2b.4.

	Alatrofloxacin ↓ Trovafloxacin (N=103)		Ceftazidime ↓ Ciprofloxacin (N=109)		Alatrofloxacin ↓ Trovafloxacin (N=103)		Ceftazidime ↓ Ciprofloxacin (N=109)	
	Number of Subjects							
Pathogen	End of Treatment				End of Study			
<i>S. aureus</i>	14/17	(82%)	12/20	(60%)	10/13	6/15	(40%)	
<i>P. aeruginosa</i>	4/8		9/17	(53%)	1/5	5/14		
<i>E. coli</i>	6/6		5/11		5/6	5/11		
<i>H. influenzae</i>	7/7		5/7		4/5	4/6		
<i>S. pneumoniae</i>	5/6		0/3		3/4	0/3		

^a Includes ≥ 5 isolates of a given pathogen in either treatment group; percents displayed only when denominator is ≥ 15 .
A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 2b.5.

Table 2b.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens* (Bacteriologically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=52)	Ceftazidime ↓ Ciprofloxacin (N=66)	95% CI	Alatrofloxacin ↓ Trovafloxacin (N=52)	Ceftazidime ↓ Ciprofloxacin (N=66)
Number and Percentage (%) of Pathogens					
Pathogen	End of Treatment			End of Study	
<i>S. aureus</i>	12/16 (75%)	12/20 (60%)	(-15.2, 45.2)	11/12	6/12
<i>P. aeruginosa</i>	2/8	9/17 (53%)	ND	1/5	7/13
<i>E. coli</i>	6/6	9/11	ND	6/6	9/9
<i>H. influenzae</i>	6/7	6/7	ND	4/5	5/6
<i>S. pneumoniae</i>	5/5	0/3	ND	3/3	0/2
<i>E. cloacae</i>	1/4	6/6	ND	2/4	5/5

ND = Not Determined
 a Includes ≥5 isolates of a given pathogen in either treatment group; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

MO Efficacy Results: *The medical officer reassessed patients' evaluability and clinical outcome status. Table 2b.6 presents clinical response for the MO clinically evaluable patient group at EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, alatrofloxacin/trovafloxacin was considered therapeutically equivalent to ceftazidime/ciprofloxacin at both EOT and EOS.*

Table 2b.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin	Ceftazidime ↓ Ciprofloxacin	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	80 (100%)	86 (100%)	
Success (Cure + Improvement)	54 (68%)	54 (63%)	(-11.0, 20.4)
End of Study:			
Number of Subjects Assessed	85 (100%)	89 (100%)	
Success (Cure + Improvement)	54 (64%)	51 (57%)	(-9.4, 21.9)

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events and clinically significant laboratory values is presented in Table 2b.7. Tables 2b.8 and 2b.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: *A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced treatment-related adverse events, discontinued treatment due to an adverse event, and discontinued treatment due to a treatment-related adverse event (p = 0.01, 0.02 and 0.03, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution for the first two comparisons and Fisher's exact test for the third comparison).*

Table 2b.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Alatrofloxacin ↓ Trovafoxacin	Ceftazidime ↓ Ciprofloxacin
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	88/135 (65%)	79/140 (56%)
Treatment-Related Adverse Events	16/135 (12%)	5/140 (4%)
Discontinuations From Treatment Due to an Adverse Event	16/135 (12%)	6/140 (4%)
Discontinuations From Treatment Due to a Treatment-Related Adverse Event	7/135 (5%)	1/140 (<1%)
Clinically Significant Laboratory Values	95/119 (80%)	109/124 (88%)

Table 2b.8. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)		
	Alatrofloxacin ↓ Trovafoxacin (N=135)	Ceftazidime ↓ Ciprofloxacin (N=140)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	88 (65%)	79 (56%)
BODY SYSTEM		
WHO Term		
APPL./INJ./INCISION/INSERTION SITE	2 (1%)	8 (6%)
Insertion Site Infection/Inflammation	1 (<1%)	4 (3%)
Device Complication	1 (<1%)	6 (4%)
CARDIOVASCULAR	23 (17%)	25 (18%)
Cardiac Arrest	6 (4%)	4 (3%)
Circulatory Failure	6 (4%)	3 (2%)
CENTRAL AND PERIPHERAL NERVOUS	17 (13%)	9 (6%)
Headache	4 (3%)	2 (1%)
GASTROINTESTINAL	24 (18%)	25 (18%)
Abdominal Pain	0	6 (4%)
Constipation	4 (3%)	7 (5%)
Diarrhea	5 (4%)	2 (1%)
Vomiting	6 (4%)	2 (1%)
OTHER ADVERSE EVENTS	5 (4%)	7 (5%)
Multi-Organ Failure	3 (2%)	4 (3%)
PSYCHIATRIC	5 (4%)	13 (9%)
Agitation	0	7 (5%)
Anxiety	1 (<1%)	5 (4%)
RESPIRATORY	25 (19%)	22 (16%)
Dyspnea	4 (3%)	3 (2%)
Pneumonia	7 (5%)	6 (4%)
Pulmonary Edema	4 (3%)	0
Sinusitis	4 (3%)	1 (<1%)
SKIN AND APPENDAGES	7 (5%)	6 (4%)
Rash	4 (3%)	4 (3%)

a ≥3% of subjects in either treatment group.

b Includes data up to 7 days after last dose of active study medication

Table 2b.9. Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=135)	Ceftazidime ↓ Ciprofloxacin (N=140)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	16 (12%)	5 (4%)
BODY SYSTEM		
WHO Term		
AUTONOMIC NERVOUS	3 (2%)	0
Flushing	3 (2%)	0
GASTROINTESTINAL	10 (7%)	1 (<1%)
Vomiting	6 (4%)	0
SKIN AND APPENDAGES	3 (2%)	1 (<1%)
Rash	3 (2%)	1 (<1%)

a ≥2% of subjects in either treatment group.
b Includes data up to 7 days after last dose of active study medication.

Thirty-seven (37) subjects in the alatrofloxacin/trovafoxacin and 30 subjects in the ceftazidime/ciprofloxacin died during this study. No death was considered to be treatment-related. Forty-nine (49) subjects in the alatrofloxacin/trovafoxacin group and 47 subjects in the ceftazidime/ciprofloxacin group had serious adverse events. One subject in the ceftazidime/ciprofloxacin group had a serious adverse event (elevated international normalized ratio and bruising) that was considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, "other" reasons, or concomitant treatment.

Sponsor Summary and Conclusion: Alatrofloxacin (equivalent to 300 mg trovafoxacin once daily) administered intravenously for 2 to 7 days followed by oral trovafoxacin (200 mg once daily) for a total treatment duration of 10 to 14 days was statistically equivalent to intravenous ceftazidime (2000 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (750 mg twice daily) for a total treatment duration of 10 to 14 days for sponsor-defined clinical success rate at the end of treatment. Sponsor-defined pathogen eradication rates were generally comparable among subjects in the alatrofloxacin/trovafoxacin and ceftazidime/ciprofloxacin groups at the end of treatment and end of study for all pathogens isolated. All isolates of *S. pneumoniae*, including two penicillin-resistant isolates, had pathogen outcomes of eradication in subjects receiving alatrofloxacin/trovafoxacin, while all isolates of *S. pneumoniae* in the ceftazidime/ciprofloxacin group had pathogen outcomes of persistent. The percentage of subjects discontinued from treatment due to adverse events was 12% in the alatrofloxacin/trovafoxacin group and 4% in the ceftazidime/ciprofloxacin group. Seven (7) subjects in the alatrofloxacin/trovafoxacin group and one subject in the ceftazidime/ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all causality and treatment-related adverse events was 65% and 12%, respectively, for subjects in the alatrofloxacin/trovafoxacin group and 56% and 4%, respectively, for subjects in the ceftazidime/ciprofloxacin group. The most commonly reported treatment-related adverse event was vomiting in the

alatrofloxacin/trovafloxacin group; all treatment-related adverse events in the ceftazidime/ciprofloxacin were reported by <1% of subjects.

Reviewer's Summary and Conclusion: Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ceftazidime/ciprofloxacin at both EOT and EOS in terms of the clinical success rate for clinically evaluable patients for both the sponsor and the MO analysis. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional gentamycin or vancomycin to treat documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, respectively, if approved it will need to be labeled this way.

A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced treatment-related adverse events, 12% versus 4% for ceftazidime/ciprofloxacin patients, discontinued treatment due to an adverse event, 12% versus 4% for ceftazidime/ciprofloxacin patients, and discontinued treatment due to a treatment-related adverse event, 5% versus <1% for ceftazidime/ciprofloxacin patients ($p=0.01$, 0.02 and 0.03 , respectively, using the test of equal proportions based on the normal approximation to the binomial distribution for the first two comparisons and Fisher's exact test for the third comparison).

III. COMMUNITY-ACQUIRED PNEUMONIA

The efficacy and safety of oral trovafloxacin in the treatment of community-acquired pneumonia was assessed in three double-blind, comparative trials. The comparator agents were cefaclor (154-102), amoxicillin with optional erythromycin (154-112), and clarithromycin (154-134). The use of the IV-to-oral regimen in the treatment of community-acquired pneumonia was assessed in two additional double-blind, comparative trials versus IV ciprofloxacin plus IV ampicillin followed by oral ciprofloxacin plus oral amoxicillin (154-110) or IV ceftriaxone followed by oral cefpodoxime with optional erythromycin (154-111).

***Reviewer's Note:** The sponsor assessed whether efficacy differed in various subgroups in the community-acquired pneumonia trials as part of the Integrated Summary of Efficacy. This was done separately for the oral and IV-to-oral trials.*

For the oral trials, results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, and race. A trend towards a lower clinical response rate was observed in elderly subjects (≥ 75 years of age versus subjects < 75 years of age) in both the trovafloxacin and comparator treatment groups at EOT and EOS.

For the IV-to-oral trials, results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, and race. A trend towards a lower clinical response rate was observed in elderly subjects (≥ 75 years of age versus subjects < 75 years of age) in both the trovafloxacin and comparator treatment groups at EOT and EOS.

III.A. Protocol 154-102

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (200 MG OR 300 MG DAILY) OR CEFACTOR (1500 MG DAILY) FOR THE TREATMENT OF UNCOMPLICATED COMMUNITY-ACQUIRED PNEUMONIA.

Study Dates: 07 December 1993 - 11 November 1994

Study Objectives: The objective of this study was to compare the safety and efficacy of two doses of trovafloxacin and cefaclor in the treatment of subjects with uncomplicated community-acquired pneumonia.

***Reviewer's Note:** This was a Phase II study designed to examine the efficacy and safety of two different doses of trovafloxacin. It was not adequately powered to demonstrate equivalence of either trovafloxacin regimen to cefaclor. The study was also not adequately powered to detect significant treatment differences (e.g., between the two trovafloxacin regimens). As a result, any findings from this study should be interpreted with caution.*

Study Design: Study 154-102 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg or 300 mg daily as a single dose in the morning) versus cefaclor (500 mg in the morning, afternoon, and evening),

administered orally for 10 days for the treatment of uncomplicated community-acquired pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, between the ages _____ at the baseline assessment, with clinically and radiologically documented community-acquired pneumonia were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens).

Clinical response was to be determined by the sponsor and was evaluated at the end of therapy (Day 11) and at the end of study (Day 25). Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point or at the time of discontinuation from the study. The investigator was to classify the clinical response of the subject as cure (resolution of signs and symptoms of pneumonia to a baseline level that existed prior to the occurrence of pneumonia), improved (incomplete resolution of any of the signs and symptoms) or failure (lack of resolution of any of the signs or symptoms).

Bacteriological response was to be determined by the sponsor and evaluated at the end of therapy (Day 11) and at the end of study (Day 25) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as indeterminate (unevaluable), eradication, presumptive eradication, persistence, relapse, superinfection, colonization, eradication with reinfection, or presumed persistence.

The primary efficacy endpoint was the sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS,
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, including serious adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, blood cultures, and urinalysis), physical examinations, concomitant medication use, and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results: One planned and two unplanned interim analyses were done during the course of this study. These were done for administrative reasons only and resulted in no unblinding of individual subject data or modification of the design of the study. No adjustments were made to the nominal p-values to account for these analyses.

Reviewer's Note: As this study is underpowered to begin with, this reviewer also did not make any adjustments to the final analysis.

Analysis Groups

Table 3a.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3a.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (200 mg/day)	Trovafloxacin (300 mg/day)	Cefaclor (500 mg TID)
Entered Study ^a	50	52	47
Completed Treatment	48 (96%)	41 (79%)	40 (85%)
Completed Study	48 (96%)	39 (75%)	40 (85%)
Evaluated for Efficacy			
Clinical Intent-to-treat	50 (100%)	52 (100%)	46 (98%)
Clinically Evaluable	47 (94%)	42 (81%)	42 (89%)
Assessed for Safety			
Adverse Events	50 (100%)	52 (100%)	47 (100%)
Laboratory Tests	50 (100%)	47 (90%)	45 (96%)

a Subjects who were randomized.

Reviewer's Note: *There were significant treatment differences in the proportion of patients who completed both treatment and the study ($p=0.04$ and 0.01 , respectively, using the Chi-square test). Trovafloxacin 300 mg/day patients were the least likely to complete treatment and the study. Somewhat fewer trovafloxacin 300 mg/day patients were considered evaluable for the efficacy analysis, however this difference was not statistically significant ($p=0.11$ using the Chi-square test).*

One subject in the cefaclor group had an inappropriate baseline diagnosis and was excluded from both the clinical intent-to-treat and evaluable analysis. Seventeen (17) additional, of 149 randomized, subjects were not clinically evaluable (3/50 [6%] subjects in the trovafloxacin 200 mg group; 10/52 [19%] subjects in the trovafloxacin 300 mg group; and 4/47 [9%] subjects in the cefaclor group. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (1/50 [2%], trovafloxacin 200 mg; 9/52 [17%], trovafloxacin 300 mg; and 2/47 [4%], cefaclor). Other reasons were noncompliance, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness and lost to follow-up.

Eighty-two (82) of 149 randomized subjects were not bacteriologically evaluable (33/50 [66%] subjects in the trovafloxacin 200 mg group; 22/52 [42%] subjects in the trovafloxacin 300 mg group; and 27/47 [57%] subjects in the cefaclor group). The most common reason for exclusion from bacteriological efficacy analyses was no baseline pathogen (30/50 [60%], trovafloxacin 200 mg; 20/52 [38%], trovafloxacin 300 mg; and 26/47 [55%], cefaclor). Other reasons were baseline culture outside specified visit window, outcome not assessable at end of treatment, and not clinically evaluable.

Discontinuations

Of the 149 treated subjects, 20 subjects were prematurely discontinued from treatment as summarized in Table 3a.2.

Table 3a.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Trovafloxacin 200 mg (N=50)	Trovafloxacin 300 mg (N=52)	Cefaclor 500 mg TID (N=47)	Total (N=149)
Number and Percentage (%) of Subjects				
Total Discontinued	2 (4%)	11 (21%)	7 (15%)	20 (13%)
Discontinuations Related to Study Drug:	1 (2%)	7 (13%)	6 (13%)	14 (9%)
Adverse Event	1 (2%)	6 (12%)	2 (4%)	9 (6%)
Insufficient Clinical Response	0	1 (2%)	3 (6%)	4 (3%)
Laboratory Abnormality	0	0	1 (2%)	1 (<1%)
Discontinuations Unrelated to Study Drug:	1 (2%)	4 (8%)	1 (2%)	6 (4%)
Adverse Event	1 (2%)	1 (2%)	0	2 (1%)
Lost to Follow-up	0	1 (2%)	0	1 (<1%)
Other	0	1 (2%)	1 (2%)	2 (1%)
Withdrawn Consent	0	1 (2%)	0	1 (<1%)

Reviewer's Note: A higher percentage of trovafloxacin 300 mg and cefaclor patients discontinued treatment prematurely (p=0.04 using the Chi-square test). Discontinuations due to study drug appeared higher in the trovafloxacin 300 mg and cefaclor arms (this difference was marginally significant, p=0.07 using Fisher's exact test); within this category, there appeared to be a higher rate of discontinuations due to adverse events on the trovafloxacin 300 mg arm and a higher rate of discontinuations due to insufficient clinical response on the cefaclor arm, however these differences were not statistically significant (p=0.14 and 0.12, respectively, using Fisher's exact test). Discontinuations considered unrelated to study drug also appeared higher on the trovafloxacin 300 mg arm, although this difference was not statistically significant (p=0.37 using Fisher's exact test).

Demographics

The three treatment groups were comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar for the three treatment groups (ex smoker, never smoked, and smoker). The ratio of males to females was approximately 1:2 in the trovafloxacin 200 and cefaclor groups and 1:1 in the trovafloxacin 300 mg group. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for all treated subjects was uncomplicated community-acquired bacterial pneumonia. The median duration since onset of pneumonia was 4.0 days for subjects in both of the trovafloxacin groups and 4.5 days for subjects in the cefaclor group. Similar results were observed for clinically evaluable subjects.

Subjects in the trovafloxacin 300 mg group had a higher percentage (29%) of subjects with chronic obstructive pulmonary diseases at baseline compared to subjects in the trovafloxacin

200 mg (10%) and cefaclor (15%) groups. There were no marked differences among subjects in the three treatment groups with respect to physical examination findings at baseline.

Clinical Response

A summary of clinical response rates for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 3a.3. Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the end of study showed that the three treatment groups were similar. Because this study was not powered to fall within the limits for equivalence, no definitive conclusions regarding equivalency of the three treatments could be drawn.

Table 3a.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)				
	Trovafloxacin 200 mg (N=47)	Trovafloxacin 300 mg (N=42)	Cefaclor 500 mg TID (N=42)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	44 (100%)	40 (100%)	41 (100%)	
Success (Cure + Improvement)	44 (100%)	39 (98%)	38 (93%)	
Trova 200 mg vs Trova 300 mg				(-2.3, 7.3)
Trova 200 mg vs Cefaclor				(-0.7, 15.3)
Trova 300 mg vs Cefaclor				(-4.5, 14.1)
Distribution of Clinical Response:				
Cure	32 (73%)	26 (65%)	22 (54%)	
Improvement	12 (27%)	13 (33%)	16 (39%)	
Failure	0	1 (3%)	3 (7%)	
End of Study:				
Number of Subjects Assessed	45 (100%)	39 (100%)	42 (100%)	
Success (Cure + Improvement)	43 (96%)	36 (92%)	38 (90%)	
Trova 200 mg vs Trova 300 mg				(-7.1, 13.6)
Trova 200 mg vs Cefaclor				(-5.6, 15.8)
Trova 300 mg vs Cefaclor				(-10.4, 14.0)
Distribution of Clinical Response:				
Cure	42 (93%)	34 (87%)	36 (86%)	
Improvement	1 (2%)	2 (5%)	2 (5%)	
Failure	0	1 (3%)	3 (7%)	
Relapse	2 (4%)	2 (5%)	1 (2%)	

Trova = trovafloxacin

Reviewer's Note: Since there are three pairwise treatment comparisons of interest, results should actually be adjusted for multiple comparisons. However, due to the fact that the study is underpowered to demonstrate equivalence for even one pairwise comparison, no adjustments were made by this reviewer.

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 3a.4.

Table 3a.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)						
	Trovafloxacin 200 mg (N=14)	Trovafloxacin 300 mg (N=20)	Cefaclor 500 mg TID (N=15)	Trovafloxacin 200 mg (N=16)	Trovafloxacin 300 mg (N=21)	Cefaclor 500 mg TID (N=16)
	Number of Subjects					
Pathogen	End of Treatment			End of Study		
<i>S. pneumoniae</i>	2/2	7/7	5/5	2/2	5/6	5/5
<i>H. influenzae</i>	5/5	4/4	3/3	4/5	2/3	3/3
<i>K. pneumoniae</i>	4/4	5/5	2/2	6/6	6/6	2/2
<i>C. pneumoniae^b</i>	2/2	4/4	0/1	2/2	4/4	0/1
<i>M. catarrhalis</i>	1/1	3/3	1/1	2/2	2/2	2/2

a ≥3 isolates of a given pathogen in any treatment group.
 b Bacteriological determination made by serology. All other pathogens were isolated from sputum.
 A subject could have had more than one pathogen isolated at baseline.
 Several subjects were not evaluated clinically at the end of treatment.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 3a.5.

Table 3a.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)						
	Trovafloxacin 200 mg (N=14)	Trovafloxacin 300 mg (N=20)	Cefaclor 500 mg TID (N=15)	Trovafloxacin 200 mg (N=13)	Trovafloxacin 300 mg (N=18)	Cefaclor 500 mg TID (N=14)
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>S. pneumoniae</i>	2/2	6/7	5/5	2/2	5/6	5/5
<i>H. influenzae</i>	4/5	3/4	2/3	5/5	2/3	3/3
<i>K. pneumoniae</i>	4/4	5/5	2/2	4/4	5/5	2/2
<i>M. catarrhalis</i>	1/1	3/3	1/1	1/1	2/2	1/1
<i>C. pneumoniae^b</i>	2/2	4/4	0/1	2/2	4/4	0/1

a ≥3 isolates of a given pathogen in any treatment group.
 b Bacteriological determination made by serology. All other pathogens were isolated from sputum.
 A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 3a.6. Tables 3a.7 and 3a.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: A significantly higher proportion of trovafloxacin 300 mg patients experienced adverse events, both all causality and treatment-related ($p=0.01$ and $p<0.001$, respectively, using the Chi-square test). A higher proportion of trovafloxacin 300 mg patients also discontinued treatment due to an adverse event (this was marginally significant; $p=0.07$ using Fisher's exact test).

Table 3a.6. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 200 mg (N=50)	Trovafloxacin 300 mg (N=52)	Cefaclor 500 mg TID (N=47)
Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	17 (34%)	32 (62%)	18 (38%)
Treatment-Related Adverse Events	8 (16%)	23 (44%)	6 (13%)
Discontinuations Due to an Adverse Event ^a	2 (4%)	9 (17%) ^b	3 (6%) ^b
Clinically Significant Laboratory Values	26/50 (52%)	25/47 (53%)	23/45 (51%)
a With the exception of one subject in the trovafloxacin 200 mg group, three subjects in the trovafloxacin 300 mg group, and one subject in the cefaclor group who were discontinued due to unrelated adverse events, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related. b Two subjects in the trovafloxacin 300 mg group and one subject in the cefaclor group experienced adverse events for which the investigator action taken was permanent discontinuation from the study; however, on the subject summary section of the case report form the investigator classified the reasons for withdrawal as either insufficient clinical response or other.			

Table 3a.7. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)

	Trovafloxacin 200 mg (N=50)	Trovafloxacin 300 mg (N=52)	Cefaclor 500 mg TID (N=47)
Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	17 (34%)	32 (62%)	18 (38%)
BODY SYSTEM			
WHO Term			
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	5 (10%)	18 (35%)	5 (11%)
Dizziness	2 (4%)	16 (31%)	3 (6%)
Headache	3 (6%)	3 (6%)	1 (2%)
GASTROINTESTINAL SYSTEM	9 (18%)	17 (33%)	6 (13%)
Nausea	6 (12%)	7 (13%)	5 (11%)
Vomiting	2 (4%)	4 (8%)	1 (2%)
Abdominal Pain	1 (2%)	4 (8%)	0
Gastritis	0	4 (8%)	0
GENERAL	3 (6%)	4 (8%)	6 (13%)
Asthenia	3 (6%)	0	1 (2%)
Back Pain	0	1 (2%)	3 (6%)
REPRODUCTIVE SYSTEM	2 (4%)	1 (2%)	1 (2%)
Prostatic disorder ^d	1 (7%)	0	0

a ≥5 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication

c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

d Preferred term is gender specific; therefore the percentages are based on the number of males or females appropriately.

Table 3a.8. Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)					
	Trovafloxacin 200 mg (N=50)		Trovafloxacin 300 mg (N=52)		Cefaclor 500 mg TID (N=47)
Number and Percentage (%) of Subjects					
Number of Subjects With at Least One Adverse Event^c	8	(16%)	23	(44%)	6 (13%)
BODY SYSTEM					
WHO Term					
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	3	(6%)	14	(27%)	2 (4%)
Dizziness	1	(2%)	13	(25%)	2 (4%)
Headache	1	(2%)	3	(6%)	0
GASTROINTESTINAL SYSTEM	5	(10%)	15	(29%)	2 (4%)
Nausea	5	(10%)	7	(13%)	2 (4%)
Vomiting	1	(2%)	3	(6%)	0
Abdominal Pain	0		4	(8%)	0
Gastritis	0		4	(8%)	0
REPRODUCTIVE SYSTEM	0		1	(2%)	1 (2%)
Vaginitis ^d	0		1	(4%)	1 (3%)

a ≥ 3 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication.

c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.

Two subjects in each of the three treatment groups experienced serious adverse events that were considered by the investigator to be unrelated to study drug. No subjects in any of the three treatment groups died during this study.

Sponsor's Summary and Conclusion: Trovafloxacin 200 mg or 300 mg once daily and cefaclor 500 mg TID were similar with respect to clinical response rates at the end of treatment and at the end of study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment and at the end of study. The incidence of adverse events for subjects in the trovafloxacin 200 mg group was comparable to that of subjects in the cefaclor group (34% and 38%, respectively), as was the incidence of adverse events leading to discontinuation (4% and 6%, respectively). Subjects in the trovafloxacin 300 mg group had a higher incidence of adverse events (62%) and a higher rate of discontinuation due to adverse events (17%) compared to the other two treatment groups. The most commonly reported adverse events for subjects in the trovafloxacin 200 mg and the cefaclor groups were those associated with the gastrointestinal system; nausea was the most commonly reported adverse event for both groups (12% and 11%, respectively). In the trovafloxacin 300 mg group, the most commonly reported adverse events were those associated with the central and peripheral nervous system; dizziness (31%) was the most commonly reported adverse event.

Reviewer's Summary and Conclusions: *This was a Phase II study to examine the efficacy and safety of two different trovafloxacin doses. Clinical response rates for trovafloxacin 200 mg, trovafloxacin 300 mg, and cefaclor appeared similar at both EOT and EOS. However, sample sizes were too small to allow for any definitive conclusions about equivalence.*

A significantly higher proportion of trovafloxacin 300 mg patients experienced adverse events, both all causality and treatment-related ($p=0.01$ and $p<0.001$, respectively, using the Chi-square test). A higher proportion of trovafloxacin 300 mg patients also discontinued treatment due to an adverse event (this was marginally significant; $p=0.07$ using Fisher's exact test).

III.B. Protocol 154-110

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CIPROFLOXACIN AND AMPICILLIN FOLLOWED BY ORAL CIPROFLOXACIN AND AMOXICILLIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Study Dates: 19 January 1995 - 30 January 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ciprofloxacin and ampicillin followed by oral ciprofloxacin and amoxicillin in the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-110 was a randomized, multicenter, double-blind trial of alatrofloxacin (200 mg once daily) administered intravenously for 2-7 days followed by oral trovafloxacin (200 mg once a day) to complete 7-10 days of total treatment versus intravenous ciprofloxacin (400 mg twice daily) and ampicillin (500 mg every 6 hours) for 2-7 days followed by oral treatment with ciprofloxacin (500 mg twice daily) and amoxicillin (500 mg three times daily) to complete 7-10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and initial intravenous therapy were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11) and at the end of study (Visit 4; Day 30) or at the time of

discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia or a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy:

Analysis Groups

Table 3b.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3b.1. Evaluation Groups

Evaluation Groups ^a :	Alatrofloxacin	Ciprofloxacin/Ampicillin
	Trovafloxacin	Ciprofloxacin/Amoxicillin
Entered Study ^b	198	202
All Treated	196 (100%)	200 (100%)
Completed Treatment	147 (75%)	168 (84%)
Completed Study	177 (90%)	180 (90%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	196 (99%)	201 (> 99%)
Clinically Evaluable	169 (85%)	181 (90%)
Bacteriological Intent-to-Treat	89 (45%)	94 (47%)
Bacteriologically Evaluable	76 (38%)	88 (44%)
Assessed for Safety		
Adverse Events	196 (100%)	200 (100%)
Laboratory Tests	192 (98%)	197 (99%)

- a The daily doses of alatrofloxacin and trovafloxacin were each 200 mg. The daily doses of intravenous and oral ciprofloxacin were 400 mg BID and 500 mg BID, respectively. The daily doses of ampicillin and amoxicillin were each 500 mg, administered every 6 hours (ampicillin) or TID (amoxicillin).
- b Subjects who were randomized.

Reviewer's Note: A significantly lower proportion of alatrofloxacin/trovafloxacin patients completed treatment ($p=0.026$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Of the 198 alatrofloxacin/trovafloxacin and 202 ciprofloxacin/ampicillin/amoxicillin randomized subjects, two alatrofloxacin/trovafloxacin subjects (Subjects 5249-0263 and 5501-0329) and one ciprofloxacin/ampicillin/amoxicillin subject (Subject 5046-0327 [*Pneumocystis carinii* pneumonia]) had an inappropriate baseline diagnosis (i.e., no community-acquired pneumonia at baseline as defined by protocol) and were excluded from all clinical and bacteriological ITT and evaluable analyses.

Of the 196 alatrofloxacin/trovafloxacin and 201 ciprofloxacin/ampicillin/amoxicillin clinical ITT subjects, 27 in the alatrofloxacin/trovafloxacin group and 20 in the ciprofloxacin/ampicillin/amoxicillin were not clinically evaluable; therefore, 169 subjects in the alatrofloxacin/trovafloxacin group and 181 subjects in the ciprofloxacin/ampicillin/amoxicillin group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (17/198 [9%], alatrofloxacin/trovafloxacin and 10/202 [5%], ciprofloxacin/ampicillin/amoxicillin). Other reasons were randomized but not treated, no post-baseline clinical assessments, no post-baseline clinical response in evaluable window, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness. In addition, one subject in the alatrofloxacin/trovafloxacin group received only placebo dosing on the first day of treatment and was not considered to be clinically evaluable.

Of the 196 alatrofloxacin/trovafloxacin and 201 ciprofloxacin/ampicillin/amoxicillin clinical ITT subjects, 107 subjects in each treatment group had negative baseline cultures; therefore, 89

subjects in the alatrofloxacin/trovafloxacin group and 94 subjects in the ciprofloxacin/ampicillin/amoxicillin group were included in the bacteriological ITT analysis.

Of the 169 alatrofloxacin/trovafloxacin and 181 ciprofloxacin/ampicillin/amoxicillin clinically evaluable subjects, 93 subjects in each treatment group were not included in the bacteriologically evaluable analyses; therefore, 76 subjects in the alatrofloxacin/trovafloxacin and 88 subjects in the ciprofloxacin/ampicillin/amoxicillin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (92 subjects, each group). Other reasons were baseline culture outside window and no post-baseline cultures. (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 396 treated subjects, 81 subjects were prematurely discontinued from treatment as summarized in Table 3b.2.

Table 3b.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=196)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=200)	
	Number and Percentage (%) of Subjects			
Total Discontinued	49	(25%)	32	(16%)
Discontinuations Related to Study Drug:	23	(12%)	15	(8%)
Adverse Event	13	(7%)	10	(5%)
Insufficient Response	10	(5%)	5	(3%)
Discontinuations Unrelated to Study Drug:	26	(13%)	17	(9%)
Adverse Event	8	(4%)	5	(3%)
Did Not Meet Randomization Criteria ^a	0		1	(<1%)
Laboratory Abnormality	1	(<1%)	0	
Lost To Follow-Up	2	(1%)	1	(<1%)
Other	11	(6%)	9	(5%)
Subject Died	1	(<1%)	1	(<1%)
Protocol Violation	2	(1%)	0	
Withdrew Consent	1	(<1%)	0	
a Subject 5462-0267 entered the study pending results from an HIV test, which subsequently were positive. This subject had received study drug prior to confirmation of the test results.				

Reviewer's Note: As noted above, a significantly lower proportion of alatrofloxacin/trovafloxacin patients completed treatment, i.e., a significantly higher proportion of alatrofloxacin/trovafloxacin patients discontinued study drug (p = 0.026 using the test of equal proportions based on the normal approximation to the binomial distribution).

Demographics

One hundred-twenty (120) of the 196 treated alatrofloxacin/trovafloxacin subjects (61%) were males and 76 (39%) were females and 118 of the 200 treated ciprofloxacin/ampicillin/amoxicillin subjects (59%) were males and 82 (41%) were females. The males and females in the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin treatment groups were generally comparable with respect

to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin treatment groups (36% and 35% ex-smoker, 26% and 23% never smoked, and 38% and 42% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinical ITT subjects was community-acquired pneumonia. The median (range) duration since onset of pneumonia was 5 days (1-32 days) for subjects in the alatrofloxacin/trovafloxacin group and 4 days (1-30 days) for subjects in the ciprofloxacin/ampicillin/amoxicillin group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin groups with respect to medical history at baseline.

Although the two treatment groups were similar overall with respect to baseline characteristics, the subjects with baseline *S. pneumoniae* in the alatrofloxacin/trovafloxacin group were more elderly and had more severe pneumonias (requiring mechanical ventilation, high fractional oxygen, or bacteremic) compared to subjects in the ciprofloxacin/ampicillin/amoxicillin group. Forty-nine percent (49%) of the 45 subjects in the alatrofloxacin/trovafloxacin group with *S. pneumoniae* were ≥ 65 years of age or had a severe pneumonia versus 33% of the 42 subjects in the ciprofloxacin/ampicillin/amoxicillin group with *S. pneumoniae*. Of the alatrofloxacin/trovafloxacin subjects with *S. pneumoniae*, 24% (11/45) were ≥ 65 years of age, 27% (12/45) were bacteremic, and 13% (6/45) required high fractional oxygen or mechanical ventilation versus 14% (6/42), 16% (7/42), and 5% (2/42), respectively, of subjects in the ciprofloxacin/ampicillin/amoxicillin group.

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 3b.3. Response rates for alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin were considered therapeutically equivalent at both EOT and EOS.

Table 3b.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafoxacin (N=169)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=181)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	168	(100%)	179	(100%)	
Success (Cure + Improvement)	151	(90%)	165	(92%)	(-8.3, 3.7)
Distribution of Clinical Response:					
Cure	75	(45%)	74	(41%)	
Improvement	76	(45%)	91	(51%)	
Failure	17	(10%)	14	(8%)	
End of Study:					
Number of Subjects Assessed	140	(100%)	165	(100%)	
Success (Cure + Improvement)	120	(86%)	145	(88%)	(-9.8, 5.5)
Distribution of Clinical Response:					
Cure	106	(76%)	130	(79%)	
Improvement	14	(10%)	15	(9%)	
Failure	17	(12%)	14	(8%)	
Relapse	3	(2%)	6	(4%)	

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 3b.4.

Table 3b.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)								
	Alatrofloxacin ↓ Trovafoxacin (N=77)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=89)		Alatrofloxacin ↓ Trovafoxacin (N=66)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=75)	
Number of Subjects								
Pathogen	End of Treatment				End of Study			
<i>S. pneumoniae</i>	35/39	(90%)	41/42	(98%)	31/35	(89%)	31/34	(91%)
<i>H. influenzae</i>	19/20	(95%)	21/22	(95%)	15/16	(94%)	20/21	(95%)
<i>S. aureus</i>	4/4		6/6		3/3		4/4	
<i>K. pneumoniae</i>	1/1		6/7		1/1		5/6	
<i>C. pneumoniae</i>	2/4		9/9		2/4		9/9	
<i>L. pneumophila</i>	2/2		4/4		2/2		4/4	
<i>M. pneumoniae</i>	8/8		8/9		8/8		7/8	

a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 3b.5.

Table 3b.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens ^a (Bacteriologically Evaluable Subjects)								
	Alatrofloxacin ↓ Trovafoxacin (N=76)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=88)		Alatrofloxacin ↓ Trovafoxacin (N=64)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=75)	
			95% CI				95% CI	
Number and Percentage (%) of Pathogens								
Pathogen	End of Treatment				End of Study			
<i>S. pneumoniae</i>	35/39 (90%)	38/39 (97%)	-18.4, 3.0		30/33 (91%)	32/34 (94%)	-15.8, 9.4	
<i>H. influenzae</i>	18/19 (95%)	20/21 (95%)	-14.1, 13.1		14/16 (88%)	20/21 (95%)	-26.3, 10.9	
<i>S. aureus</i>	4/4	6/6	ND		3/3	4/4	ND	
<i>K. pneumoniae</i>	1/1	7/7	ND		1/1	6/6	ND	
<i>C. pneumoniae</i>	2/4	9/9	ND		2/4	9/9	ND	
<i>L. pneumophila</i>	2/2	4/4	ND		2/2	4/4	ND	
<i>M. pneumoniae</i>	8/8	8/9	ND		8/8	7/8	ND	

ND = Not Determined

a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15.

A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 3b.6. Tables 3b.7 and 3b.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 3b.6. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Alatrofloxacin ↓ Trovafoxacin		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin	
	Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	140/196	(71%)	133/200	(67%)
Treatment-Related Adverse Events	53/196	(27%)	47/200	(24%)
Discontinuations Due to an Adverse Event	26/196	(13%)	19/200	(10%)
Clinically Significant Laboratory Values	101/192	(53%)	108/197	(55%)

a For five subjects in the alatrofloxacin/trovafoxacin group and four subjects in the ciprofloxacin/ampicillin/amoxicillin group, the investigator indicated the study drug discontinuation on the adverse event page on the CRF; however, study drug discontinuation was not checked off on the subject summary page of the CRF.

Table 3b.7. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)			
	Alatrofloxacin ↓ Trovafloxacin (N=196)	Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=200)	
Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	140	(71%)	133 (67%)
BODY SYSTEM			
WHO Term			
APPL./INJ./INCISION/INSERTION SITE	24	(12%)	27 (14%)
Appl./Inj./Incision/Insertion Site Pain	7	(4%)	9 (5%)
Appl./Inj./Incision/Insertion Site Reaction	14	(7%)	11 (6%)
Appl./Inj./Incision/Insertion/Device Complication	3	(2%)	6 (3%)
CARDIOVASCULAR	26	(13%)	26 (13%)
Chest Pain	9	(5%)	4 (2%)
Edema Peripheral	8	(4%)	6 (3%)
Hypotension	6	(3%)	0
Phlebitis	1	(<1%)	5 (3%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	53	(27%)	33 (17%)
Dizziness	12	(6%)	3 (2%)
Headache	31	(16%)	21 (11%)
GASTROINTESTINAL SYSTEM	59	(30%)	63 (32%)
Abdominal Pain	8	(4%)	11 (6%)
Constipation	17	(9%)	19 (10%)
Diarrhea	5	(3%)	9 (5%)
Dyspepsia	8	(4%)	7 (4%)
Nausea	18	(9%)	19 (10%)
Vomiting	10	(5%)	9 (5%)
GENERAL	31	(16%)	32 (16%)
Back Pain	8	(4%)	6 (3%)
Pain	4	(2%)	7 (4%)
PSYCHIATRIC	32	(16%)	32 (16%)
Anxiety	5	(3%)	4 (2%)
Insomnia	21	(11%)	24 (12%)
REPRODUCTIVE SYSTEM	1	(<1%)	3 (2%)
Vaginitis ^d	1	(<1%)	3 (4%)
RESPIRATORY SYSTEM	30	(15%)	28 (14%)
Dyspnea	6	(3%)	2 (1%)
Pleural Effusion	8	(4%)	7 (4%)
Pneumonia	5	(3%)	6 (3%)
Respiratory Insufficiency	5	(3%)	2 (1%)
SKIN/APPENDAGES	22	(11%)	17 (9%)
Pruritus	5	(3%)	1 (<1%)
Rash	5	(3%)	5 (3%)

APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion/Site
a ≥3 % of subjects in either treatment group.
b Includes data up to 7 days after last dose of active study medication.
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.
d Preferred term is gender-specific, and the percentages are based on the number of males and females appropriately.

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Table 3b.8. A Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafoxacin (N=196)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=200)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	53	(27%)	47	(24%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	12	(6%)	16	(8%)
Appl./inj./Incision/Insertion Site Pain	1	(<1%)	8	(4%)
Appl./inj./Incision/Insertion Site Reaction	10	(5%)	10	(5%)
CARDIOVASCULAR SYSTEM	1	(<1%)	5	(3%)
Phlebitis	0		4	(2%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	18	(9%)	3	(2%)
Dizziness	3	(2%)	0	
Headache	12	(6%)	2	(1%)
GASTROINTESTINAL SYSTEM	12	(6%)	19	(10%)
Constipation	1	(<1%)	3	(2%)
Diarrhea	3	(2%)	5	(3%)
Dyspepsia	0		5	(3%)
Nausea	6	(3%)	4	(2%)
GENERAL	5	(3%)	6	(3%)
Moniliasis	2	(1%)	4	(2%)
PSYCHIATRIC	6	(3%)	4	(2%)
Anxiety	3	(2%)	0	
Insomnia	1	(<1%)	4	(2%)
REPRODUCTIVE SYSTEM	1	(<1%)	3	(4%)
Vaginitis ^d	1	(<1%)	3	(4%)
SKIN/APPENDAGES	12	(6%)	8	(4%)
Pruritus	3	(2%)	1	(<1%)
Rash	3	(2%)	2	(1%)
Rash Erythematous	3	(2%)	0	
Rash Maculo-Papular	3	(2%)	1	(<1%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion/Site				
a ≥ 2 % of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.				
d Preferred term is gender-specific, and the percentages are based on the number of males and females appropriately.				

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Six (6) subjects in the alatrofloxacin/trovafoxacin group and 14 subjects in the ciprofloxacin/ampicillin/amoxicillin group died during this study, of which two in the alatrofloxacin/trovafoxacin group and 10 in the ciprofloxacin/ampicillin/amoxicillin group occurred in the first 35 days. All deaths were considered by the investigator to be unrelated to study drug.

Thirty-six (36) subjects in the alatrofloxacin/trovafloxacin group and 29 subjects in the ciprofloxacin/ampicillin/amoxicillin group had serious adverse events. With the exception of one subject in the alatrofloxacin/trovafloxacin group who had serious adverse events (nausea/vomiting) that were considered by the investigator to be related to study drug, all serious adverse events were attributed to other events or illnesses or to the disease under study.

Sponsor's Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy were statistically equivalent for clinical success rate at the end of treatment and at the end of study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable for the most frequently isolated baseline pathogens (*S. pneumoniae* and *H. influenzae*) between the two treatment groups at the end of treatment and at the end of study.

The percentage of subjects discontinued from treatment due to adverse events was 13% in the alatrofloxacin/trovafloxacin group and 10% in the ciprofloxacin/ampicillin/amoxicillin group. The overall percentage of all and treatment-related adverse events for subjects in the alatrofloxacin/trovafloxacin group was comparable to that of subjects in the ciprofloxacin/ampicillin/amoxicillin group (71% and 27% versus 67% and 24%, respectively). The most commonly reported treatment-related adverse events were headache in the alatrofloxacin/trovafloxacin group and diarrhea and dyspepsia in the ciprofloxacin/ampicillin/amoxicillin group. Injection site reactions were comparable between the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin groups (6% and 8%, respectively). Mortality (Day 1 - 35) was lower in the alatrofloxacin/trovafloxacin group compared to the ciprofloxacin/ampicillin/amoxicillin group (1% and 5%, respectively).

Reviewer's Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy was considered therapeutically equivalent to intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy at both EOT and EOS.

The most common adverse events in the alatrofloxacin/trovafloxacin arm were headache (16%), insomnia (11%), constipation (9%), and nausea (9%). The most common adverse events in the ciprofloxacin/ampicillin/amoxicillin arm were insomnia (12%), headache (11%), constipation (10%), and nausea (10%).

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III.C. Protocol 154-111

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CEFTRIAZONE FOLLOWED BY ORAL CEFPODOXIME WITH OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Study Dates: 8 February 1995 - 22 March 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ceftriazone followed by oral cefpodoxime, with optional erythromycin, for the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-111 was a randomized, multicenter, double-blind, double-dummy trial of alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 7 to 10 days of total treatment versus intravenous ceftriazone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg administered twice daily) to complete 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and initial intravenous therapy were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia or a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 3c.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3c.1. Evaluation Groups

Evaluation Groups ^a :	Alatrofloxacin	Ceftriaxone
	Trovafloxacin	Cefpodoxime
Entered Study ^b	218	225
All Treated	215 (100%)	222 (100%)
Completed Treatment	170 (79%)	172 (77%)
Completed Study	182 (85%)	183 (82%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	212 (97%)	221 (98%)
Clinically Evaluable	180 (83%)	187 (83%)
Bacteriologically Intent-to-Treat	92 (42%)	102 (45%)
Bacteriologically Evaluable	80 (37%)	85 (38%)
Assessed for Safety		
Adverse Events	215 (100%)	222 (100%)
Laboratory Tests	203 (94%)	205 (92%)

a The daily doses of alatrofloxacin and trovafloxacin were each 200 mg. The daily dose of ceftriaxone was 1000 mg and the daily dose of cefpodoxime was 400 mg (200 mg administered twice daily).

b Subjects who were randomized.

Of the 218 alatrofloxacin/trovafloxacin and 225 ceftriaxone/cefpodoxime randomized subjects, six alatrofloxacin/trovafloxacin subjects and four ceftriaxone/cefpodoxime subjects

had an inappropriate baseline diagnosis (i.e., no community-acquired pneumonia at baseline) and were excluded from all clinical and bacteriological intent-to-treat and evaluable analyses. Among the subjects with an inappropriate baseline diagnosis, two had a baseline diagnosis of *P. carinii* pneumonia, one had tuberculosis, one had a negative baseline chest X-ray and the remaining subjects did not meet the protocol specific inclusion criteria.

Of the 212 alatrofloxacin/trovafloxacin and 221 ceftriaxone/cefpodoxime clinically ITT subjects, 32 in the alatrofloxacin/trovafloxacin group and 34 in the ceftriaxone/cefpodoxime were not clinically evaluable; therefore, 180 subjects in the alatrofloxacin/trovafloxacin group and 187 subjects in the ceftriaxone/cefpodoxime group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (17/218 [8%], alatrofloxacin/trovafloxacin and 21/225 [9%], ceftriaxone/cefpodoxime). Other reasons were randomized but not treated, no post-baseline clinical assessments, no post-baseline clinical response in evaluable window, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, and other reasons (subjects who were unable to take oral therapy at 7 days and subjects who received incorrect IV drugs).

Of the 212 alatrofloxacin/trovafloxacin and 221 ceftriaxone/cefpodoxime clinical ITT subjects, 119 subjects in each treatment group had negative baseline cultures. Ninety-two (92) subjects in the alatrofloxacin/trovafloxacin group and 102 subjects in the ceftriaxone/cefpodoxime group were included in the bacteriological ITT analysis.

Of the 180 alatrofloxacin/trovafloxacin and 187 ceftriaxone/cefpodoxime clinically evaluable subjects, 100 subjects in the alatrofloxacin/trovafloxacin group and 102 subjects in the ceftriaxone/cefpodoxime group were not included in the bacteriologically evaluable analyses; therefore, 80 subjects in the alatrofloxacin/trovafloxacin and 85 subjects in the ceftriaxone/cefpodoxime group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (99 subjects, each group). Other reasons were baseline culture outside window, no post-baseline cultures (of the 3 subjects in the alatrofloxacin/trovafloxacin group and 19 subjects in the ceftriaxone/cefpodoxime group excluded for this reason, only 1 and 2 subjects, respectively, had baseline pathogens) and *N. meningitidis* in sputum (1 subject). (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 215 alatrofloxacin/trovafloxacin and 222 ceftriaxone/cefpodoxime treated subjects, 45 alatrofloxacin/trovafloxacin and 50 ceftriaxone/cefpodoxime subjects were prematurely discontinued from treatment as summarized in Table 3c.2.

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Table 3c.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Alatrofloxacin ↓ Trovfloxacin (N=215)	Ceftriaxone ↓ Cefpodoxime (N=222)
	Number and Percentage (%) of Subjects	
Total Discontinued	45 (21%)	50 (23%)
Discontinuations Related to Study Drug:		
Adverse Event	19 (9%)	18 (8%)
Insufficient Response	9 (4%)	2 (<1%)
Laboratory Abnormality	10 (5%)	15 (7%)
Laboratory Abnormality	0	1 (<1%)
Discontinuations Unrelated to Study Drug:		
Adverse Event	26 (12%)	32 (14%)
Did not meet Randomization Criteria	8 (4%)	8 (4%)
Lost to Follow-up	5 (2%)	1 (<1%)
Other	4 (2%)	0
Subject Died	4 (2%)	10 (5%)
Protocol Violation	4 (2%)	5 (2%)
Withdrawn Consent	0	1 (<1%)
Withdrawn Consent	1 (<1%)	7 (3%)

Reviewer’s Note: Patients receiving alatrofloxacin/trovfloxacin experienced a significantly higher number of discontinuations due to adverse events considered related to study drug (4% compared to < 1% for ceftriaxone/cefpodoxime patients; $p = 0.03$ using Fisher’s exact test).

Demographics

One hundred twenty-three (123) of the 215 treated alatrofloxacin/trovfloxacin subjects (57%) were male and 92 (43%) were female, and 147 of the 222 treated ceftriaxone/cefpodoxime subjects (66%) were male and 75 (34%) were female. The males and females in the alatrofloxacin/trovfloxacin and ceftriaxone/cefpodoxime treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the alatrofloxacin/trovfloxacin and ceftriaxone/cefpodoxime treatment groups (36% and 40% ex-smoker, 29% and 24% never smoked, and 35% and 36% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinical ITT and evaluable subjects was community-acquired pneumonia. The median duration (range) since onset of pneumonia was 4 days (1-151 days) for subjects in the alatrofloxacin/trovfloxacin group and 4 days (1-31 days) for subjects in the ceftriaxone/cefpodoxime group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Of the clinical ITT subjects, 81 subjects in both treatment groups were initially suspected by the investigator to have atypical pneumonia and seven subjects in the alatrofloxacin/trovfloxacin group and nine subjects in the ceftriaxone/cefpodoxime group had suspected *Legionella* pneumonia. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the alatrofloxacin/trovfloxacin and ceftriaxone/cefpodoxime groups with respect to medical history at baseline.

Reviewer's Note: In fact, a significantly higher proportion of ceftriaxone/cefpodoxime patients had chronic obstructive lung disease (90/222 = 41% of ceftriaxone/cefpodoxime patients compared to 67/215 = 31% alatrofloxacin/trovafloxacin patients; $p=0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution). In addition, a higher proportion of alatrofloxacin/trovafloxacin patients had diabetes mellitus (41/215 = 19% alatrofloxacin/trovafloxacin patients compared to 24/222 = 11% of ceftriaxone/cefpodoxime patients; $p=0.02$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 3c.3. Alatrofloxacin/trovafloxacin and ceftriaxone/cefpodoxime were considered therapeutically equivalent at both EOT and EOS.

Table 3c.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloxacin (N=180)		Ceftriaxone ↓ Cefpodoxime (N=187)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	178	(100%)	184	(100%)	
Success (Cure + Improvement)	160	(90%)	160	(87%)	(-3.6, 9.5)
Distribution of Clinical Response:					
Cure	102	(57%)	108	(59%)	
Improvement	58	(33%)	52	(28%)	
Failure	18	(10%)	24	(13%)	
End of Study:					
Number of Subjects Assessed	159	(100%)	169	(100%)	
Success (Cure + Improvement)	136	(86%)	138	(82%)	(-4.1, 11.9)
Distribution of Clinical Response:					
Cure	128	(81%)	128	(76%)	
Improvement	8	(5%)	10	(6%)	
Failure	19	(12%)	25	(15%)	
Relapse	4	(3%)	6	(4%)	

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 3c.4.

Table 3c.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=180)	Ceftriaxone ↓ Cefpodoxime (N=187)	Alatrofloxacin ↓ Trovafoxacin (N=159)	Ceftriaxone ↓ Cefpodoxime (N=169)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>S. pneumoniae</i>	28/32 (88%)	21/23 (91%)	24/28 (86%)	19/21 (90%)
<i>H. influenzae</i>	16/16 (100%)	25/27 (93%)	13/15 (87%)	24/26 (92%)
<i>S. aureus</i>	4/4	7/8	3/3	6/7
<i>M. catarrhalis</i>	5/5	3/3	3/3	3/3
<i>E. coli</i>	4/5	1/3	3/4	0/2
<i>P. aeruginosa</i>	5/5	1/2	2/2	1/2
<i>C. pneumoniae</i>	4/4	9/9	2/2	7/8
<i>L. pneumophila</i>	7/11	8/10	6/10	8/10
<i>M. pneumoniae</i>	12/12	5/6	9/10	4/6

^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 3c.5.

Table 3c.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=80)	Ceftriaxone ↓ Cefpodoxime (N=85)	95% CI	Alatrofloxacin ↓ Trovafoxacin (N=68)	Ceftriaxone ↓ Cefpodoxime (N=79)	95% CI
	Number and Percentage (%) of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>S. pneumoniae</i>	28/31 (90%)	22/23 (96%)	-18.7, 8.0	25/27 (93%)	19/20 (95%)	-16.1, 11.3
<i>H. influenzae</i>	16/16 (100%)	23/26 (88%)	-0.7, 23.8	13/15 (87%)	22/24 (92%)	-25.5, 15.5
<i>S. aureus</i>	4/4	7/8	ND	3/3	6/7	ND
<i>M. catarrhalis</i>	5/5	3/3	ND	3/3	3/3	ND
<i>P. aeruginosa</i>	5/5	1/2	ND	2/2	0/2	ND
<i>C. pneumoniae</i>	4/4	9/9	ND	2/2	7/8	ND
<i>L. pneumophila</i>	8/11	8/10	ND	7/10	8/10	ND
<i>M. pneumoniae</i>	12/12	5/6	ND	9/10	4/6	ND

ND = Not Determined

^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 3c.6. Tables 3c.7 and 3c.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

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Table 3c.6 A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Alatrofloxacin ↓ Trovafoxacin (N=215)	Ceftriaxone ↓ Cefpodoxime (N=222)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	177/215 (82%)	172/222 (77%)
Treatment-Related Adverse Events	70/215 (33%)	57/222 (26%)
Discontinuations From Treatment Due to an Adverse Event^a	22/215 (10%)	18/222 (8%)
Clinically Significant Laboratory Values	121/203 (60%)	114/205 (56%)

^a With the exception of eight subjects in the alatrofloxacin/trovafoxacin group and eight subjects in the ceftriaxone/cefpodoxime group who were discontinued due to unrelated adverse events, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related.

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Table 3c.7. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)				
	Alatrofloxacin ↓ Trovfloxacin (N=215)		Ceftriaxone ↓ Cefpodoxime (N=222)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	177	(82%)	172	(77%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	43	(20%)	36	(16%)
Appl./Inj./Incision/Insertion Site Pain	15	(7%)	10	(5%)
Appl./Inj./Incision/Insertion Site Reaction	20	(9%)	10	(5%)
Appl./Inj./Incision/Insertion/Device Complication	14	(7%)	18	(8%)
CARDIOVASCULAR	44	(20%)	46	(21%)
Edema Peripheral	14	(7%)	10	(5%)
CENTRAL AND PERIPHERAL NERVOUS	74	(34%)	44	(20%)
Confusion	11	(5%)	8	(4%)
Dizziness	21	(10%)	3	(1%)
Headache	41	(19%)	27	(12%)
GASTROINTESTINAL	85	(40%)	82	(37%)
Abdominal Pain	13	(6%)	7	(3%)
Constipation	23	(11%)	10	(5%)
Diarrhea	20	(9%)	25	(11%)
Dyspepsia	11	(5%)	12	(5%)
Nausea	27	(13%)	27	(12%)
Vomiting	17	(8%)	17	(8%)
GENERAL	39	(18%)	36	(16%)
Moniliasis	7	(3%)	12	(5%)
PSYCHIATRIC	47	(22%)	45	(20%)
Anxiety	13	(6%)	16	(7%)
Insomnia	16	(7%)	18	(8%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site				
a ≥5 % of subjects in any treatment group.				
b Includes data up to 7 days after last dose of active study medication				
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.				

Reviewer's Note: Alatrofloxacin/trovfloxacin patients experienced a significantly higher percentage of the following adverse events than did ceftriaxone/cefpodoxime patients: central and peripheral nervous system events (overall), dizziness, headache, and constipation ($p < 0.001$, $p < 0.001$, $p = 0.046$, and $p = 0.01$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

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Table 3c.8. Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovfloxacin (N=215)		Ceftriaxone ↓ Cefpodoxime (N=222)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event^c	70	(33%)	57	(26%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	18	(8%)	9	(4%)
Appl./Inj./Incision/Insertion Site Pain	7	(3%)	5	(2%)
Appl./Inj./Incision/Insertion Site Reaction	13	(6%)	2	(<1%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	21	(10%)	9	(4%)
Dizziness	11	(5%)	2	(<1%)
Headache	9	(4%)	6	(3%)
GASTROINTESTINAL	22	(10%)	30	(14%)
Diarrhea	7	(3%)	15	(7%)
Nausea	11	(5%)	9	(4%)
Vomiting	1	(<1%)	6	(3%)
GENERAL	11	(5%)	10	(5%)
Moniliasis	6	(3%)	9	(4%)
REPRODUCTIVE	1	(<1%)	2	(<1%)
Vaginitis ^d	1	(1%)	2	(3%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site				
a ≥3 % of subjects in any treatment group.				
b Includes data up to 7 days after last dose of active study medication.				
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.				
d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.				

Eleven (11) subjects in the alatrofloxacin/trovfloxacin group and 20 subjects in the ceftriaxone/cefpodoxime group died during this study. With the exception of one death in the ceftriaxone/cefpodoxime group that occurred > 30 days post-therapy and was considered by the investigator to be treatment related (upper gastrointestinal bleeding and pneumonia), all deaths were considered by the investigator to be unrelated to study drug.

Thirty-four (34) subjects in the alatrofloxacin/trovfloxacin group and 47 subjects in the ceftriaxone/cefpodoxime group had serious adverse events. Two subjects in the alatrofloxacin/trovfloxacin group and two subjects in the ceftriaxone/cefpodoxime group who had serious adverse events that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or concomitant treatment.

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Sponsor Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were statistically equivalent for the sponsor-defined clinical success rate at the end of treatment for both intent-to-treat and evaluable subjects. Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and at the end of study for baseline isolates of *S. pneumoniae* and *H. influenzae*. All subjects who had penicillin-resistant ($\text{MIC} \geq 0.1 \mu\text{g/mL}$) *S. pneumoniae* isolated at baseline (10 in the alatrofloxacin/trovafloxacin group and one in the ceftriaxone/cefpodoxime group) were clinical cures or improvements at the end of treatment and the end of study. No subject in the alatrofloxacin/trovafloxacin group with a clinical outcome of failure had a microbiologically confirmed persistent pathogen.

The percentage of subjects discontinued from treatment due to adverse events was 10% in the alatrofloxacin/trovafloxacin group and 8% in the ceftriaxone/cefpodoxime group. Nine (9) subjects in the alatrofloxacin/trovafloxacin group and two subjects in the ceftriaxone/cefpodoxime group were discontinued from treatment due to treatment-related adverse events. The most frequently occurring treatment-related adverse events that lead to discontinuation were those related to the intravenous insertion site (insertion site reaction, paresthesia, pruritus, thrombophlebitis, phlebitis) among subjects in the alatrofloxacin/trovafloxacin group and colitis and diarrhea among subjects in the ceftriaxone/cefpodoxime group. The overall percentage of all and treatment-related adverse events in the alatrofloxacin/trovafloxacin group was comparable to that of subjects in the ceftriaxone/cefpodoxime group (82% and 33% versus 77% and 26%, respectively). The most commonly reported treatment-related adverse events were dizziness (5%) and nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and diarrhea (7%) for subjects in the ceftriaxone/cefpodoxime group.

Reviewer's Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.

Alatrofloxacin/trovafloxacin patients experienced a significantly higher percentage of the following adverse events than did ceftriaxone/cefpodoxime patients: central and peripheral nervous system events (overall), dizziness, headache, and constipation ($p < 0.001$, $p < 0.001$, $p = 0.046$, and $p = 0.01$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

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III.D. Protocol 154-112

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN WITH AMOXYCILLIN AND OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Study Dates: 9 December 1994 - 12 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to amoxicillin, with optional erythromycin, for the treatment of subjects with community acquired pneumonia.

Study Design: Study 154-112 was a randomized, multicenter, double-blind, double-dummy trial of trovafloxacin (200 mg once daily) administered orally for 7 to 10 days of total treatment versus amoxicillin (500 mg t.i.d.) administered orally for 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia and a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

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Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 3d.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3d.1. Evaluation Groups

Evaluation Groups:	Trovfloxacin (200 mg/day)	Amoxycillin (500 mg TID)
Entered Study ^a	151	152
All Treated	150 (100%)	152 (100%)
Completed Treatment	136 (91%)	139 (91%)
Completed Study	140 (93%)	136 (89%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	148 (98%)	149 (98%)
Clinically Evaluable ^b	138 (91%)	141 (93%)
Bacteriologically Intent-to-Treat	60 (40%)	55 (36%)
Bacteriologically Evaluable	55 (36%)	52 (34%)
Assessed for Safety		
Adverse Events	150 (100%)	152 (100%)
Laboratory Tests	144 (96%)	148 (97%)

a Subjects who were randomized.

b Clinically evaluable at end of treatment.

Of the 151 trovafloxacin and 152 amoxycillin randomized subjects, three trovafloxacin subjects and three amoxycillin subjects had an inappropriate baseline diagnosis (i.e., no clinical signs and symptoms of community-acquired pneumonia at baseline as defined by protocol) and were excluded from all intent-to-treat and evaluable analyses. Among the subjects with an inappropriate baseline diagnosis, two in each treatment group had tuberculosis at baseline and one in each treatment group did not meet the protocol-specific inclusion criteria.

Of the 148 trovafloxacin and 149 amoxycillin clinical ITT subjects, 10 in the trovafloxacin group and 8 in the amoxycillin were not clinically evaluable; therefore, 138 subjects in the trovafloxacin group and 141 subjects in the amoxycillin group were clinically evaluable. The

most common reasons for exclusion from clinical efficacy analyses were no post-baseline clinical assessments (4/151 [3%], trovafloxacin and 6/152 [4%], amoxicillin), no post-baseline clinical response in evaluable window (4/151 [3%], trovafloxacin and 6/152 [4%], amoxicillin), and insufficient therapy due to early discontinuation from treatment or study (7/151 [5%], trovafloxacin and 3/152 [2%], amoxicillin). Other reasons were randomized but not treated, prior antibiotic therapy, and concomitant antibiotic therapy for intercurrent illness.

Of the 148 trovafloxacin and 149 amoxicillin clinical ITT subjects, 88 subjects in the trovafloxacin group and 94 subjects in the amoxicillin group had negative baseline cultures; therefore, 60 subjects in the trovafloxacin group and 55 subjects in the amoxicillin group were included in the bacteriological ITT analysis.

Of the 138 trovafloxacin and 141 amoxicillin clinically evaluable subjects, 83 subjects in the trovafloxacin group and 89 subjects in the amoxicillin group were not included in the bacteriologically evaluable analyses; therefore, 55 subjects in the trovafloxacin and 52 subjects in the amoxicillin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (82/151 [54%], trovafloxacin and 89/152 [59%], amoxicillin). Other reasons were baseline culture outside window and no post-baseline cultures (the subject [Subject 5809-0279] in the trovafloxacin group excluded for this reason had a baseline pathogen). (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 150 trovafloxacin and 152 amoxicillin treated subjects, 14 trovafloxacin and 13 amoxicillin subjects were prematurely discontinued from treatment as summarized in Table 3d.2.

Table 3d.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Trovafloxacin 200 mg (N=150)		Amoxicillin 500 mg TID (N=152)	
	Number and Percentage (%) of Subjects			
Total Discontinued	14	(9%)	13	(9%)
Discontinuations Related to Study Drug:	8	(5%)	7	(5%)
Adverse Event	5	(3%)	2	(1%)
Insufficient Response	3	(2%)	5	(3%)
Discontinuations Unrelated to Study Drug:	6	(4%)	6	(4%)
Adverse Event	2	(1%)	3	(2%)
Lost to Follow-up	0		1	(<1%)
Other	1	(<1%)	0	
Subject Died	2	(1%)	0	
Protocol Violation	0		2	(1%)
Withdrawn Consent	1	(<1%)	0	

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Demographics

Eight-four (84) of the 150 treated trovafloxacin subjects (56%) were male and 66 (44%) were female and 93 of the 152 treated amoxicillin subjects (61%) were male and 59 (39%) were female. The males and females in the trovafloxacin and amoxicillin treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the trovafloxacin and amoxicillin treatment groups (31% and 33% ex-smoker, 33% and 34% never smoked, and 37% and 34% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinical ITT subjects was community-acquired pneumonia. The median duration (range) since onset of pneumonia was 5 days (1-69 days) for subjects in the trovafloxacin group and 5 days (1-42 days) for subjects in the amoxicillin group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Of the clinical ITT subjects, 23 subjects in the trovafloxacin group and 28 subjects in the amoxicillin group were initially suspected by the investigator to have atypical pneumonia. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the trovafloxacin and amoxicillin groups with respect to medical history at baseline.

Reviewer's Note: The proportion of clinical ITT trovafloxacin patients with bilateral pneumonia (as diagnosed by x-ray) was somewhat higher than that for clinical ITT amoxicillin patients; this difference was marginally statistically significant (35/148 = 24% trovafloxacin patients vs. 23/149 = 15% amoxicillin patients; $p = 0.07$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 3d.3. Trovafloxacin and amoxicillin were considered therapeutically equivalent at both EOT and EOS.

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Table 3d.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Trovafloracin 200 mg (N=138)		Amoxycillin 500 mg TID (N=141)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	137	(100%)	140	(100%)	
Success (Cure + Improvement)	128	(93%)	128	(91%)	(-4.2, 8.2)
Distribution of Clinical Response:					
Cure	71	(52%)	75	(54%)	
Improvement	57	(42%)	53	(38%)	
Failure	9	(7%)	12	(9%)	
End of Study:					
Number of Subjects Assessed	122	(100%)	127	(100%)	
Success (Cure + Improvement)	107	(88%)	110	(87%)	(-7.2, 9.4)
Distribution of Clinical Response:					
Cure	98	(80%)	97	(76%)	
Improvement	9	(7%)	13	(10%)	
Failure	9	(7%)	12	(9%)	
Relapse	6	(5%)	5	(4%)	

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 3d.4.

Table 3d.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens ^a (Clinically Evaluable Subjects)								
	Trovafloracin 200 mg (N=56)		Amoxycillin 500 mg TID (N=52)		Trovafloracin 200 mg (N=53)		Amoxycillin 500 mg TID (N=44)	
Number and Percentage (%) of Subjects								
Pathogen	End of Treatment				End of Study			
<i>H. influenzae</i>	21/22	(95%)	19/20	(95%)	18/20	(90%)	11/15	(73%)
<i>M. catarrhalis</i>	5/5		3/3		4/4		3/3	
<i>S. pneumoniae</i>	21/21	(100%)	16/19	(84%)	20/21	(95%)	14/18	(78%)
<i>M. pneumoniae</i>	4/5		2/3		4/5		1/2	
<i>C. pneumoniae</i>	1/1		4/4		1/1		2/2	

^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae* and *M. pneumoniae*); percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

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Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 3d.5.

Table 3d.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens ^a (Bacteriologically Evaluable Subjects)										
	Trovafloracin 200 mg (N=55)		Amoxycillin 500 mg TID (N=52)		95% CI	Trovafloracin 200 mg (N=53)		Amoxycillin 500 mg TID (N=44)		95% CI
Number and Percentage (%) of Pathogens										
Pathogen	End of Treatment					End of Study				
<i>H. influenzae</i>	21/21	(100%)	17/20	(85%)	-0.6, 30.6	19/20	(95%)	10/14	(71%)	ND
<i>S. pneumoniae</i>	21/21	(100%)	17/19	(89%)	-3.3, 24.3	20/21	(95%)	15/18	(83%)	-7.6, 31.4
<i>M. catarrhalis</i>	5/5		3/3		ND	4/4		3/3		ND
<i>C. pneumoniae</i>	1/1		4/4		ND	1/1		2/2		ND
<i>M. pneumoniae</i>	4/5		2/3		ND	4/5		1/2		ND

ND = Not Determined
 a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae* and *M. pneumoniae*); percents and CIs displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events, and clinically significant laboratory values is presented in Table 3d.6. Tables 3d.7 and 3d.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 3d.6. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloracin (200 mg)	Amoxycillin (500 mg TID)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	52/150 (35%)	44/152 (29%)
Treatment-Related Adverse Events	24/150 (16%)	22/152 (14%)
Discontinuations From Treatment Due to Adverse Events ^a	9/150 (6%)	7/152 (5%)
Clinically Significant Laboratory Values	49/144 (34%)	44/148 (30%)

a Five (5) and two discontinuations in the trovafloracin and amoxycillin treatment groups, respectively, were treatment-related.

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Table 3d.7. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)				
	Trovafloxacin 200 mg (N=150)		Amoxicillin 500 mg TID (N=152)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	52	(35%)	44	(29%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS	15	(10%)	7	(5%)
Confusion	3	(2%)	1	(<1%)
Dizziness	6	(4%)	2	(1%)
Headache	5	(3%)	3	(2%)
GASTROINTESTINAL	18	(12%)	18	(12%)
Constipation	3	(2%)	0	
Diarrhea	3	(2%)	9	(6%)
Nausea	7	(5%)	6	(4%)
Vomiting	4	(3%)	1	(<1%)
GENERAL	2	(1%)	4	(3%)
Back Pain	1	(<1%)	3	(2%)
PSYCHIATRIC	6	(4%)	4	(3%)
Somnolence	3	(2%)	1	(<1%)
RESPIRATORY	8	(5%)	7	(5%)
Pneumonia	3	(2%)	2	(1%)
SKIN AND APPENDAGES	1	(<1%)	5	(3%)
Rash	0		3	(2%)
a ≥2% of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication				

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Reviewer's Note: The proportion of trovafloxacin patients experiencing central and peripheral nervous system events (all causalities) was marginally significantly higher than that in the amoxicillin group ($p=0.07$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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Table 3d.8. Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)				
	Trovafloxacin 200 mg/day (N=150)		Amoxicillin 500 mg TID (N=152)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	24	(16%)	22	(14%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	9	(6%)	5	(3%)
Dizziness	5	(3%)	2	(1%)
Headache	2	(1%)	2	(1%)
GASTROINTESTINAL	12	(8%)	14	(9%)
Diarrhea	3	(2%)	7	(5%)
Dyspepsia	2	(1%)	1	(<1%)
Nausea	5	(3%)	5	(3%)
Vomiting	3	(2%)	0	
PSYCHIATRIC	4	(3%)	3	(2%)
Somnolence	2	(1%)	1	(<1%)
SKIN AND APPENDAGES	1	(<1%)	3	(2%)
Rash	0		2	(1%)
a ≥1% of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				

Twelve (12) subjects in the trovafloxacin group and 11 subjects in the amoxicillin group had serious adverse events. One subject in the trovafloxacin group had serious adverse events (sweating, faintness, vomiting, loss of consciousness, and allergic conjunctivitis) that were considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or concomitant treatment.

Five (5) subjects in the trovafloxacin group and 7 subjects in the amoxicillin group died during this study. None of the deaths was considered to be related to study drug.

Sponsor Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxicillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were statistically equivalent for the sponsor-defined clinical success rates at the end of treatment for both intent-to-treat and evaluable subjects. Sponsor-defined eradication rates were comparable between the two treatment groups at the end of treatment for baseline isolates of *S. pneumoniae* and *H. influenzae*. All five trovafloxacin subjects who had penicillin-resistant (MIC ≥0.1 µg/mL) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study. One subject in the amoxicillin group had penicillin-resistant *S. pneumoniae* isolated at baseline and was a clinical failure at the end of treatment and end of study. Of the subjects with a clinical response of failure or relapse, none in the trovafloxacin group and two in the amoxicillin group had an outcome of persistence confirmed by microbiology.

The percentage of subjects discontinued from treatment due to adverse events was 6% in the trovafloxacin group and 5% in the amoxicillin group. The overall percentage of all and

treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the amoxicillin group (35% and 16% versus 29% and 14%, respectively). The most commonly reported treatment-related adverse events were dizziness (3%) and nausea (3%) for subjects in the trovafloxacin group and diarrhea (5%) and nausea (3%) for subjects in the amoxicillin group.

Reviewer's Summary and Conclusions: *Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxicillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were considered therapeutically equivalent in terms of clinical response in clinically evaluable patients at both EOT and EOS.*

The proportion of trovafloxacin patients experiencing central and peripheral nervous system events (all causalities) was marginally significantly higher than that in the amoxicillin group ($p=0.07$ using the test of equal proportions based on the normal approximation to the binomial distribution).

III.E. Protocol 154-134

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN WITH CLARITHROMYCIN FOR THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA.

Study Dates: 28 November 1994 to 13 November 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin and clarithromycin in the treatment of subjects with community-acquired pneumonia appropriate for oral therapy.

Study Design: Study 154-134 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg once daily) versus clarithromycin (500 mg twice daily), administered orally for 7 or 10 days for the treatment of community-acquired pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 16 years of age at the baseline assessment, with clinically and radiologically documented community-acquired pneumonia were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens and blood cultures at baseline).

Clinical response was to be determined by the sponsor and was evaluated at the end of treatment (Visit 3, Day 11) and at the end of study (Visit 4, Day 30), or at the time of discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or

improvement of radiological findings, clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, improvement or resolution of dyspnea, cough, leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia and improvement or lack of progression of acute lung infiltration on chest x-ray), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia and a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of therapy (Visit 3, Day 11) and at the end of study (Visit 4, Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, or relapse.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis) and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 3e.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3e.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (200 mg daily)	Clarithromycin (500 mg BID)
Entered Study ^a	179	180
All Treated	178 (> 99%)	180 (100%)
Completed Treatment	147 (83%)	154 (86%)
Completed Study	157 (88%)	167 (93%)
Evaluated for Efficacy		
Clinical Intent-to-treat	163 (91%)	172 (96%)
Clinically Evaluable ^b	144 (80%)	156 (87%)
Bacteriologically Intent-to-Treat	64 (36%)	72 (40%)
Bacteriologically Evaluable ^b	59 (33%)	67 (37%)
Assessed for Safety		
Adverse Events	178 (100%)	180 (100%)
Laboratory Tests	173 (97%)	174 (97%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Reviewer's Note: Somewhat fewer trovafloxacin patients were considered clinically evaluable, however this difference was not statistically significant ($p = 0.11$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Of the 359 randomized subjects, 16 trovafloxacin subjects and 8 clarithromycin subjects had an inappropriate baseline diagnosis (i.e., no community-acquired pneumonia at baseline) and were excluded from all clinical and bacteriological intent-to-treat and evaluable analyses.

Of the 335 clinical ITT subjects, 35 were not clinically evaluable (19, trovafloxacin and 16, clarithromycin); therefore, 300 subjects (144, trovafloxacin and 156, clarithromycin) were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (15/179 [8%], trovafloxacin and 12/180 [7%], clarithromycin. Other reasons were no post-baseline clinical assessments, no post-baseline assessment in evaluable analysis windows, concomitant antibiotic therapy for intercurrent illness, prior antibiotic therapy, and randomized but not treated.

Of the 335 clinical ITT subjects, 199 had negative baseline cultures (trovafloxacin, 99 subjects and clarithromycin, 100 subjects); therefore, 136 subjects (64, trovafloxacin and 72, clarithromycin) were included in the bacteriological ITT analysis.

Of the 300 clinically evaluable subjects, 174 subjects were not included in the bacteriologically evaluable analyses (trovafloxacin, 85 subjects and clarithromycin, 89 subjects); therefore, 126 subjects (59, trovafloxacin and 67, clarithromycin) were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (trovafloxacin, 85 subjects and clarithromycin, 89 subjects). Other reasons were baseline culture outside specified visit window and no post-baseline cultures. (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 358 treated subjects, 57 subjects were prematurely discontinued from treatment as summarized in Table 3e.2.

Table 3e.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)		
	Trovafloxacin 200 mg (N=178)	Clarithromycin 500 mg BID (N=180)
	Number and Percentage (%) of Subjects	
Total Discontinued	31 (17%)	(14%)
Discontinuations Related to Study Drug:	15 (8%)	(8%)
Adverse Event	14 (8%)	(5%)
Insufficient Response	1 (<1%)	(2%)
Laboratory Abnormality	0	(<1%)
Discontinuations Unrelated to Study Drug:	16 (9%)	(7%)
Adverse Event	4 (2%)	(<1%)
Did Not Meet Randomization Criteria	10 (6%)	(3%)
Lost To Follow-Up	1 (<1%)	(1%)
Other	0	(1%)
Withdrew Consent	1 (<1%)	(<1%)

Demographics

One hundred nine (109) of the 178 treated trovafloxacin subjects were males (61%) and 69 were females (39%) and 79 of the 180 treated clarithromycin subjects were males (44%) and 101 were females (56%). The males and females in the trovafloxacin and clarithromycin treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the trovafloxacin and clarithromycin treatment groups (28% and 27% ex-smoker, 41% and 39% never smoked, and 31% and 33% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinical ITT subjects was community-acquired pneumonia. The median (range) duration since onset of pneumonia was 5 days (1-72 days) for subjects in the trovafloxacin group and 5 days (1-45 days) for subjects in the clarithromycin group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the trovafloxacin and clarithromycin groups with respect to medical history at baseline.

Reviewer's Note: Actually, a significantly higher proportion of clinical ITT trovafloxacin patients had ischemic heart disease at baseline (19/178 = 11% of trovafloxacin patients vs. 5/180 = 3% of clarithromycin patients; p = 0.003 using the test of equal proportions based on the normal approximation to the binomial distribution). In addition, the proportion of males in the trovafloxacin group was significantly higher than that in the clarithromycin group (p = 0.001 using the test of equal proportions based on the normal approximation to the binomial distribution).

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Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 3e.3. Trovafloxacin and clarithromycin were considered therapeutically equivalent at both EOT and EOS.

Table 3e.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Trovafloxacin 200 mg (N=144)		Clarithromycin 500 mg BID (N=156)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	143	(100%)	155	(100%)	
Success (Cure + Improvement)	137	(96%)	146	(94%)	(-3.3, 6.5)
Distribution of Clinical Response:					
Cure	56	(39%)	59	(38%)	
Improvement	81	(57%)	87	(56%)	
Failure	6	(4%)	9	(6%)	
End of Study:					
Number of Subjects Assessed	135	(100%)	144	(100%)	
Success (Cure + Improvement)	120	(89%)	124	(86%)	(-5.0, 10.5)
Distribution of Clinical Response:					
Cure	108	(80%)	113	(78%)	
Improvement	12	(9%)	11	(8%)	
Failure	6	(4%)	9	(6%)	
Relapse	9	(7%)	11	(8%)	

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A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 3e.4.

Table 3e.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)								
	Trovafloxacin 200 mg (N=59)		Clarithromycin 500 mg BID (N=67)		Trovafloxacin 200 mg (N=57)		Clarithromycin 500 mg BID (N=59)	
Number of Subjects								
Pathogen	End of Treatment				End of Study			
<i>M. pneumoniae</i>	17/18	(94%)	18/18	(100%)	16/17	(94%)	17/17	(100%)
<i>H. influenzae</i>	12/12		15/16	(94%)	11/11		14/16	(88%)
<i>S. pneumoniae</i>	12/12		15/16	(94%)	11/12		13/15	(87%)
<i>C. pneumoniae</i>	6/6		10/10		5/6		5/6	

^a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 3e.5.

Table 3e.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)							
	Trovafloxacin 200 mg (N=59)	Clarithromycin 500 mg BID (N=67)	95% CI	Trovafloxacin 200 mg (N=56)	Clarithromycin 500 mg BID (N=59)	95% CI	
Number of Pathogens							
Pathogen	End of Treatment			End of Study			
<i>H. influenzae</i>	12/12	15/16 (94%)	ND	10/10	13/16 (81%)	ND	
<i>S. pneumoniae</i>	10/11	14/15 (93%)	ND	11/12	13/15 (87%)	ND	
<i>C. pneumoniae</i>	6/6	10/10	ND	5/6	5/6	ND	
<i>M. pneumoniae</i>	17/18 (94%)	18/18 (100%)	-16.1, 5.0	16/17 (94%)	17/17 (100%)	-17.1, 5.3	

ND = Not Determined
 a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 3e.6. Tables 3e.7 and 3e.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 3e.6. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg	Clarithromycin 500 mg BID
Number and Percentage (%) of Subjects		
Adverse Events:		
All Causalities	100/178 (56%)	120/180 (67%)
Treatment-Related Adverse Events	57/178 (32%)	71/180 (39%)
Discontinuations Due to an Adverse Event^a	18/178 (10%)	12/180 (7%)
Clinically Significant Laboratory Values	39/173 (23%)	48/174 (28%)

a For two subjects in the clarithromycin group, the investigator indicated study drug discontinuation on the adverse event page of the CRF; however, study drug discontinuation was not checked off on the subject summary page of the CRF.

Reviewer's Note: A higher proportion of clarithromycin patients experienced adverse events (all causalities); $p = 0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 3e.7. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 200 mg (N=178)	Clarithromycin 500 mg BID (N=180)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event ^c	100 (56%)	120 (67%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	47 (26%)	28 (16%)
Dizziness	24 (13%)	8 (4%)
Headache	23 (13%)	21 (12%)
GASTROINTESTINAL SYSTEM	40 (22%)	56 (31%)
Diarrhea	5 (3%)	17 (9%)
Nausea	25 (14%)	28 (16%)
Vomiting	12 (7%)	14 (8%)
GENERAL	15 (8%)	18 (10%)
Back Pain	3 (2%)	5 (3%)
Moniliasis	2 (1%)	6 (3%)
REPRODUCTIVE	1 (<1%)	5 (3%)
Vaginitis ^d	1 (1%)	4 (4%)
RESPIRATORY SYSTEM	16 (9%)	18 (10%)
Sinusitis	3 (2%)	7 (4%)
SKIN/APPENDAGES	13 (7%)	9 (5%)
Rash	5 (3%)	2 (1%)
SPECIAL SENSES	10 (6%)	39 (22%)
Taste Perversion	7 (4%)	34 (19%)

a ≥3 % of subjects in either treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.
 d Preferred term is gender specific and the percentages are based on the number of females.

Reviewer's Note: A higher proportion of trovafloxacin patients experienced dizziness (p=0.003 using the test of equal proportions based on the normal approximation to the binomial distribution). A higher proportion of clarithromycin patients experienced diarrhea and taste perversion (p=0.01 and p<0.001, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

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Table 3e.8. A Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)				
	Trovafloxacin 200 mg (N=178)		Clarithromycin 500 mg BID (N=180)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event^c	57	(32%)	71	(39%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	26	(15%)	7	(4%)
Dizziness	18	(10%)	3	(2%)
Headache	6	(3%)	5	(3%)
GASTROINTESTINAL SYSTEM	27	(15%)	36	(20%)
Abdominal Pain	3	(2%)	2	(1%)
Diarrhea	2	(1%)	13	(7%)
Nausea	21	(12%)	15	(8%)
Vomiting	8	(4%)	8	(4%)
GENERAL	4	(2%)	7	(4%)
Moniliasis	2	(1%)	6	(3%)
REPRODUCTIVE	1	(<1%)	3	(2%)
Vaginitis ^d	1	(1%)	3	(3%)
SKIN AND APPENDAGES	8	(4%)	2	(1%)
Pruritus	4	(2%)	1	(<1%)
SPECIAL SENSES	7	(4%)	35	(19%)
Taste Perversion	7	(4%)	34	(19%)
a ≥ 2 % of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.				

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Eleven subjects in the trovafloxacin group and 13 subjects in the clarithromycin group had serious adverse events. With the exception of the one subject in the clarithromycin group who had a serious adverse event that was considered to be related to study drug, all serious adverse events were attributed to other illnesses or to the disease under study.

There were three deaths (2 trovafloxacin patients and 1 clarithromycin patient) that occurred greater than 30 days after the last treatment dose; all deaths were considered unrelated to study drug.

Sponsor Summary and Conclusion: Trovafloxacin 200 mg once daily for 7 or 10 days was statistically equivalent to clarithromycin 500 mg BID for 7 or 10 days for the treatment of community-acquired pneumonia.

The percentage of subjects discontinued from treatment due to adverse events was 10% in the trovafloxacin group and 7% in the clarithromycin group. The overall percentage of adverse events was lower (56%) in the trovafloxacin group compared to the clarithromycin group (67%); treatment-related adverse events were reported in 32% and 39% of subjects,

respectively. The most commonly reported treatment-related adverse events in the trovafloxacin group were nausea (12%) and dizziness (10%). The most commonly reported treatment-related adverse events in the clarithromycin group were taste perversion (19%), nausea (8%) and diarrhea (7%).

Reviewer's Summary and Conclusions: *Trovafloxacin 200 mg once daily for 7 or 10 days and clarithromycin 500 mg BID for 7 or 10 days were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.*

Overall, a higher proportion of clarithromycin patients experienced adverse events ($p = 0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution). In terms of individual adverse events, a higher proportion of trovafloxacin patients experienced dizziness ($p = 0.003$ using the test of equal proportions based on the normal approximation to the binomial distribution), while a higher proportion of clarithromycin patients experienced diarrhea and taste perversion ($p = 0.01$ and $p < 0.001$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

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IV. ACUTE EXACERBATION OF CHRONIC BRONCHITIS

The efficacy and safety of oral trovafloxacin for the treatment of acute bacterial exacerbation of chronic bronchitis was assessed in three double-blind, comparative trials (154-101, 154-109, and 154-141) and in a supportive study (154-108). The comparator agents were ofloxacin (154-101), clarithromycin (154-109), ciprofloxacin (154-141), and amoxicillin (154-108).

***Reviewer's Note:** The sponsor assessed whether efficacy differed in various subgroups in the bronchitis trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, and race. A trend towards a lower response rate was observed in elderly patients (≥ 75 versus < 75 years of age) in both the trovafloxacin and comparator arms at EOT and EOS.*

IV.A. Protocol 154-101

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG OR 300 MG DAILY) OR OFLOXACIN (800 MG DAILY) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study Dates: 24 November 1993 - 11 July 1994

Study Objectives: The objective of this study was to compare the safety and efficacy of two doses of trovafloxacin and ofloxacin in the treatment of subjects with acute exacerbation of chronic bronchitis.

***Reviewer's Note:** This was a Phase II study to examine the efficacy and safety of two different doses of trovafloxacin. The study was not adequately powered to demonstrate equivalence of either trovafloxacin regimen to ofloxacin. The study was also not adequately powered to detect significant treatment differences. As a result, any findings from this study should be interpreted with caution.*

Study Design: Study 154-101 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg or 300 mg daily as a single dose in the morning) versus ofloxacin (800 mg daily as 400 mg in the morning and evening), administered orally for 10 days for the treatment of acute exacerbation of chronic bronchitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, between the ages of 18 and 72 at the baseline assessment, with clinically documented acute exacerbation of chronic bronchitis were eligible to participate in the study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment of signs and symptoms) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens).

Clinical response was to be determined by the investigator and evaluated at the end of therapy (Day 11) and at the end of study (Day 25), or at the time of discontinuation from study. Clinical response was to be based primarily on the global assessment of the clinical

presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical laboratory signs of infection such as defervescence, disappearance or diminution in purulent sputum production, changes in dyspnea and cough, and stabilization in general physical condition. Additional supporting data to evaluate clinical response was to include reduction in leukocytosis. Clinical response was to be classified as cure, improvement, failure, or indeterminate.

Bacteriological response was to be determined by the sponsor and evaluated at the end of therapy (Day 11) and at the end of study (Day 25), or at the time of discontinuation from the study. Bacteriologic response was to be classified by the sponsor as indeterminate (unevaluable), eradication, presumptive eradication, persistence, relapse, superinfection, colonization, eradication with reinfection, or presumed persistence.

***Reviewer's Note:** Please see the medical officer's review for a more detailed definition of clinical and bacteriologic response.*

The primary efficacy endpoint was the sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS,
- Investigator-defined clinical response at EOT, and sponsor- and investigator-defined clinical response at EOS.

***Reviewer's Note:** The reviewing medical officer, Dr. Regina Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.*

Safety evaluations included assessment of adverse events, including serious adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), physical examinations, concomitant medication use, and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Sponsor Efficacy Results: One planned and two unplanned interim analyses were done during the course of this study. These were done for administrative reasons only and resulted in no unblinding of individual subject data or modification of the design of the study. No adjustments were made to the nominal p-values to account for these analyses.

***Reviewer's Note:** As this study is underpowered to begin with, this reviewer also did not make any adjustments to the final analysis.*

Analysis Groups

Table 4a.1 summarizes the number of patients enrolled, treated, and included in each of the sponsor analysis groups.

Table 4a.1. Evaluation Groups

Evaluation Groups:	Trovafloracin (100 mg/day)	Trovafloracin (300 mg/day)	Ofloxacin (400 mg BID)
Entered Study ^a	74	76	73
All Treated	73 (100%)	75 (100%)	73 (100%)
Completed Study	66 (90%)	55 (73%)	63 (86%)
Completed Treatment	67 (92%)	56 (75%)	64 (88%)
Evaluated for Efficacy			
Clinical Intent-to-treat	74 (100%)	76 (100%)	73 (100%)
Clinically Evaluable	65 (88%)	58 (76%)	62 (85%)
Assessed for Safety			
Adverse Events	73 (100%)	75 (100%)	73 (100%)
Laboratory Tests	72 (99%)	72 (96%)	69 (95%)

a Subjects who were randomized.

Reviewer's Note: *The percent of patients completing study, completing treatment, and evaluable for efficacy was lower in the trovafloxacin 300 mg arm. For patients completing study and completing treatment, the difference was significant ($p=0.01$ using the chi-square test in both cases). For patients evaluable for efficacy, this difference was not statistically significant ($p=0.15$ using the chi-square test).*

Thirty-eight (38) of 223 randomized subjects were not clinically evaluable (9/74 [12%] subjects in the trovafloxacin 100 mg group; 18/76 [24%] subjects in the trovafloxacin 300 mg group; and 11/73 [15%] subjects in the ofloxacin group). The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (4/74 [5%], trovafloxacin 100 mg; 14/76 [18%], trovafloxacin 300 mg; and 7/73 [10%], ofloxacin). Other reasons were noncompliance, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, and lost to follow-up.

Reviewer's Note: *The difference among the three treatment arms with respect to percent of patients excluded from clinical efficacy analyses due to insufficient therapy / early discontinuation is statistically significant ($p=0.04$ using the chi-square test).*

One hundred fifty-eight (158) of 223 randomized subjects were not bacteriologically evaluable (49/74 [66%] subjects in the trovafloxacin 100 mg group; 57/76 [75%] subjects in the trovafloxacin 300 mg group; and 52/73 [71%] subjects in the ofloxacin group). The most common reason for exclusion from bacteriological efficacy analyses was no baseline pathogen (39/74 [53%], trovafloxacin 100 mg; 43/76 [57%], trovafloxacin 300 mg; and 42/73 [58%], ofloxacin). Other reasons were baseline culture outside (specified visit) window, outcome not assessable at end of treatment, and not clinically evaluable.

Discontinuations

Of the 221 treated subjects, 34 subjects were prematurely discontinued from treatment as summarized in Table 4a.2.

Reviewer's Note: *The percent of patients discontinuing due to an adverse event is higher for the trovafloxacin 300 mg arm ($p<0.001$ using the chi-square test).*

Table 4a.2. A Summary of Premature Discontinuations From Treatment (All-Treated Subjects)				
	Trovafloxacin 100 mg (N=73)	Trovafloxacin 300 mg (N=75)	Ofloxacin. 400 mg BID (N=73)	Total (N=221)
Number and Percentage (%) of Subjects				
Total Discontinued	6 (8%)	19 (25%)	9 (12%)	34 (15%)
Discontinuations Related to Study Drug:	5 (7%)	19 (25%)	6 (8%)	30 (14%)
Adverse Event	4 (5%)	19 (25%)	6 (8%)	29 (13%)
Insufficient Clinical Response	1 (1%)	0	0	1 (<1%)
Discontinuations Unrelated to Study Drug:	1 (1%)	0	3 (4%)	4 (2%)
Adverse Event	0	0	1 (1%)	1 (<1%)
Did Not Meet Randomization Criteria	1 (1%)	0	0	1 (<1%)
Lost to Follow-up	0	0	2 (3%)	2 (<1%)

Demographics

The three treatment groups were comparable with respect to age, race, weight, smoking classification and sex distribution. The distribution of subjects according to smoking classification was similar for the three treatment groups (33-39% ex smoker, 28-32% never smoked, and 33-36% smoker). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for all treated subjects was acute exacerbation of chronic bronchitis. The median (range) duration since onset of the exacerbation was 7 days (1-115 days) for subjects in the trovafloxacin 100 mg group, 7 days (1-212 days) for subjects in the trovafloxacin 300 mg group and 6 days (1-110 days) for subjects in the ofloxacin group. Similar results were observed for clinically evaluable subjects. There were no marked differences among subjects in the three treatment groups with respect to medical history or physical examination findings at baseline.

Clinical Response

Sponsor-defined clinical response rates at EOT and EOS are shown for clinically evaluable subjects in Table 4a.3. Pairwise comparisons of the difference between treatment groups at EOT and EOS showed that the three treatments were similar. However, since this study was not powered to demonstrate equivalence, no definitive conclusions regarding equivalency of the three treatments can be drawn.

Reviewer's Note: *Since there are three pairwise treatment comparisons of interest, results should actually be adjusted for multiple comparisons. However, due to the fact that the study is underpowered to demonstrate equivalence for even one pairwise comparison, no adjustments were made by this reviewer.*

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Table 4a.3. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)				
	Trovafloxacin 100 mg (N=65)	Trovafloxacin 300 mg (N=58)	Ofloxacin 400 mg BID (N=62)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	61 (100%)	53 (100%)	58 (100%)	
Success (Cure + Improvement)	59 (97%)	52 (98%)	56 (97%)	
Trova 100 mg vs Trova 300 mg				(-7.2, 4.4)
Trova 100 mg vs Ofloxacin				(-6.3, 6.7)
Trova 300 mg vs Ofloxacin				(-4.4, 7.5)
Distribution of Clinical Response:				
Cure	43 (70%)	34 (64%)	39 (67%)	
Improvement	16 (26%)	18 (34%)	17 (29%)	
Failure	2 (3%)	1 (2%)	2 (3%)	
End of Study:				
Number of Subjects Assessed	64 (100%)	55 (100%)	61 (100%)	
Success (Cure + Improvement)	58 (91%)	54 (98%)	57 (93%)	
Trova 100 mg vs Trova 300 mg				(-15.5, 0.4)
Trova 100 mg vs Ofloxacin				(-12.3, 6.6)
Trova 300 mg vs Ofloxacin				(-2.4, 11.9)
Distribution of Clinical Response:				
Cure	55 (86%)	47 (85%)	50 (82%)	
Improvement	3 (5%)	7 (13%)	7 (11%)	
Failure	3 (5%)	1 (2%)	2 (3%)	
Relapse	3 (5%)	0	2 (3%)	

a Trova=trovafloxacin; CI=confidence interval

A summary of clinical success rates at EOT and EOS for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 4a.4.

Table 4a.4 A Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)						
	Trovafloxacin 100 mg (N=25)	Trovafloxacin 300 mg (N=20)	Ofloxacin 400 mg BID (N=23)	Trovafloxacin 100 mg (N=27)	Trovafloxacin 300 mg (N=22)	Ofloxacin 400 mg BID (N=23)
Number of Subjects						
Pathogen	End of Treatment			End of Study		
	<i>H. influenzae</i>	12/12	7/7	6/6	12/13	9/9
<i>M. catarrhalis</i>	6/6	3/3	9/9	5/6	2/2	9/9
<i>S. pneumoniae</i>	3/3	3/4	3/3	2/3	4/5	3/3
<i>H. parainfluenzae</i>	2/2	4/4	3/3	2/2	4/4	3/3
<i>K. pneumoniae</i>	3/3	-	-	4/4	-	-
<i>P. aeruginosa</i>	1/1	1/1	2/3	1/1	1/1	2/3
<i>C. pneumoniae^b</i>	3/3	2/2	3/3	3/4	2/2	3/3

a ≥3 isolates of a given pathogen in any treatment group.
 b Bacteriological results obtained by serology. All other pathogens were isolated from sputum.
 A subject could have had more than one pathogen isolated at baseline.
 Several subjects were not assessed clinically at the end of treatment.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at EOT and EOS for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 4a.5.

Table 4a.5 A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)						
	Trovafloxacin 100 mg (N=25)	Trovafloxacin 300 mg (N=19)	Ofloxacin 400 mg BID (N=21)	Trovafloxacin 100 mg (N=24)	Trovafloxacin 300 mg (N=15)	Ofloxacin 400 mg BID (N=20)
	Number of Pathogens					
Pathogen ^b	End of Treatment			End of Study		
<i>H. influenzae</i>	12/12	6/6	5/5	10/12	5/5	5/5
<i>M. catarrhalis</i>	6/6	3/3	8/8	5/5	2/2	8/8
<i>S. pneumoniae</i>	3/3	4/4	3/3	2/3	3/3	3/3
<i>H. parainfluenzae</i>	2/2	4/4	3/3	2/2	3/3	3/3
<i>K. pneumoniae</i>	3/3	-	-	3/3	-	-
<i>P. aeruginosa</i>	1/1	1/1	2/3	0/1	1/1	2/2

a ≥3 isolates of a given pathogen in any treatment group.
 b All pathogens were isolated from sputum.
 A subject could have had more than one pathogen isolated at baseline.

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MO Efficacy Results: *The medical officer reassessed patients' evaluability and clinical outcome status. Table 4a.6 presents clinical response for the MO clinically evaluable patient group at EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, results for the three treatment groups appeared similar but sample sizes were too small to allow for any definitive conclusions about equivalence.*

Table 4a.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)				
	Trovafloxacin 100 mg	Trovafloxacin 300 mg	Ofloxacin 400 mg BID	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	61 (100%)	49 (100%)	57 (100%)	
Success (Cure + Improvement)	58 (95%)	48 (98%)	55 (97%)	
Trova 100 mg vs Trova 300 mg				(-16.4, 10.1)
Trova 100 mg vs Ofloxacin				(-15.2, 10.7)
Trova 300 mg vs Ofloxacin				(-11.4, 15.0)
End of Study:				
Number of Subjects Assessed	65 (100%)	54 (100%)	61 (100%)	
Success (Cure + Improvement)	57 (88%)	52 (96%)	57 (93%)	
Trova 100 mg vs Trova 300 mg				(-23.8, 5.1)
Trova 100 mg vs Ofloxacin				(-21.1, 7.9)
Trova 300 mg vs Ofloxacin				(-10.3, 17.1)

a Trova = trovafloxacin

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 4a.7. Tables 4a.8 and 4a.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: The percent of patients experiencing adverse events regardless of relationship to study drug, treatment-related adverse events, and discontinuations due to an adverse event were all significantly higher in the trovafloxacin 300 mg arm (p-values <0.0001, <0.0001, and =0.001, respectively, using the chi-square test). In addition, the rate of dizziness in the trovafloxacin 300 mg arm was rather high (40% of patients experienced dizziness; 37% of patients experienced dizziness that was considered treatment related).

Table 4a.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values			
	Trovafloxacin 100 mg (N=73)	Trovafloxacin 300 mg (N=75)	Ofloxacin 400 mg BID (N=73)
	Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	22 (30%)	52 (69%)	26 (36%)
Treatment-Related Adverse Events	10 (14%)	46 (61%)	21 (29%)
Discontinuations Due to an Adverse Event^a	4 (5%)	19 (25%)	7 (10%)
Clinically Significant Laboratory Values	27/72 (38%)	33/72 (46%)	32/69 (46%)

^a With the exception of one ofloxacin subject who was discontinued due to an unrelated adverse event, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related.

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Table 4a.8. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 100 mg (N=73)	Trovafloxacin 300 mg (N=75)	Ofloxacin 400 mg BID (N=73)
	Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event ^c	22 (30%)	52 (69%)	26 (36%)
BODY SYSTEM			
WHO Term			
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	8 (11%)	38 (51%)	10 (14%)
Dizziness	4 (5%)	30 (40%)	7 (10%)
Headache	4 (5%)	9 (12%)	2 (3%)
Confusion	0	4 (5%)	0
GASTROINTESTINAL SYSTEM	9 (12%)	27 (36%)	10 (14%)
Nausea	4 (5%)	13 (17%)	3 (4%)
Vomiting	2 (3%)	7 (9%)	3 (4%)
Abdominal Pain	1 (1%)	5 (7%)	2 (3%)
PSYCHIATRIC SYSTEM	2 (3%)	4 (5%)	9 (12%)
Insomnia	1 (1%)	1 (1%)	7 (10%)

a ≥5 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication.

c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

Table 4a.9. A Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)

	Trovafloxacin 100 mg (N=73)	Trovafloxacin 300 mg (N=75)	Ofloxacin 400 mg BID (N=73)
Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	10 (14%)	46 (61%)	21 (29%)
BODY SYSTEM			
WHO Term			
AUTONOMIC NERVOUS SYSTEM			
Flushing	0	3 (4%)	0
Sweating Increased	1 (1%)	3 (4%)	0
CARDIOVASCULAR SYSTEM			
Edema Periorbital	0	2 (3%)	0
CENTRAL AND PERIPHERAL NERVOUS SYSTEM			
Dizziness	3 (4%)	28 (37%)	7 (10%)
Headache	2 (3%)	7 (9%)	1 (1%)
Confusion	0	4 (5%)	0
Gait Abnormal	0	2 (3%)	0
Vertigo	0	2 (3%)	0
GASTROINTESTINAL SYSTEM			
Nausea	4 (5%)	11 (15%)	3 (4%)
Vomiting	2 (3%)	7 (9%)	2 (3%)
Abdominal Pain	1 (1%)	4 (5%)	2 (3%)
Dyspepsia	0	3 (4%)	1 (1%)
Diarrhea	1 (1%)	1 (1%)	0
Appetite Increased	2 (3%)	2 (3%)	0
GENERAL			
Fatigue	0	5 (7%)	0
Hot Flashes	0	2 (3%)	0
PSYCHIATRIC SYSTEM			
Insomnia	0	2 (3%)	9 (12%)
Impotence ^d	0	1 (3%)	7 (10%)
REPRODUCTIVE SYSTEM			
Vaginitis ^d	0	0	1 (1%)
SKIN/APPENDAGES			
Pruritus	1 (1%)	4 (5%)	1 (1%)
SPECIAL SENSES			
Tinnitus	0	3 (4%)	0
Vision Abnormal	2 (3%)	7 (9%)	2 (3%)

a ≥3 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication.

c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.

One subject in the trovafloxacin 300 mg group and two subjects in the ofloxacin group experienced serious adverse events that were considered to be unrelated to study drug. No subjects in any of the three treatment groups died during this study.

Sponsor's Summary and Conclusions: Trovafloxacin 100 mg or 300 mg and ofloxacin 400 mg BID were similar with respect to clinical response rates at the end of treatment and at the end of the study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment. At the end of study, bacteriologic relapses were observed in four subjects in the trovafloxacin 100 mg group. However, because of the small number of bacteriologically evaluable subjects in this treatment group (N=24), no definitive conclusions could be drawn. Both trovafloxacin 100 mg and 300 mg once daily were generally well tolerated; however, the incidence of adverse events in the 100 mg group was lower than that observed in the 300 mg group.

Reviewer's Summary and Conclusions: *This was a Phase II study to examine the efficacy and safety of two different trovafloxacin doses. Clinical response rates for trovafloxacin 100 mg, trovafloxacin 300 mg, and ofloxacin appeared similar at both EOT and EOS (perhaps more similar at EOT), but sample sizes were too small to allow for any definitive conclusions about equivalence.*

The percent of patients experiencing adverse events regardless of relationship to study drug, treatment-related adverse events, and discontinuations due to an adverse event were all significantly different across treatment groups (rates were higher in the trovafloxacin 300 mg arm; p-values <0.0001, <0.0001, and =0.001, respectively, using the chi-square test). In addition, the rate of dizziness in the trovafloxacin 300 mg arm was rather high (40% of patients experienced dizziness; 37% of patients experienced dizziness that was considered treatment related).

IV.B. Protocol 154-109

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A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) OR CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study Dates: 16 November 1994 - 22 June 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin with clarithromycin in the treatment of subjects with acute bacterial exacerbation of chronic bronchitis.

Study Design: Study 154-109 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily) versus clarithromycin (500 mg twice daily) administered orally for 7 days for the treatment of acute bacterial exacerbation of chronic bronchitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥ 40 years of age at the baseline visit, with clinically documented acute bacterial exacerbation of chronic bronchitis were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical and laboratory signs of

infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the study. Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection such as disappearance or diminution in purulent sputum production, changes in dyspnea and cough as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of acute bacterial exacerbation chronic bronchitis to the baseline level that existed prior to the occurrence of acute exacerbation), improvement (resolution of sputum purulence but incomplete resolution of the other signs and symptoms of acute bacterial exacerbation of chronic bronchitis and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of acute bacterial exacerbation of chronic bronchitis or a need for additional antibiotic for inadequate response).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, or relapse.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT and;
- Pathogen eradication rates at EOT.

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Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Reviewer's Note: As with study 154-101, the reviewing medical officer, Dr. Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

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Sponsor Efficacy Results:**Analysis Groups**

Table 4b.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Table 4b.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg daily)	Clarithromycin (500 mg BID)
Entered Study ^a	210 (100%)	200 (100%)
All Treated	210 (100%)	200 (100%)
Completed Treatment	201 (96%)	183 (92%)
Completed Study	206 (98%)	188 (94%)
Evaluated for Efficacy		
Clinical ITT	208 (>99%)	199 (>99%)
Clinically Evaluable ^b	203 (97%)	188 (94%)
Bacteriologically ITT	96 (46%)	86 (43%)
Bacteriologically Evaluable ^b	93 (44%)	81 (41%)
Assessed for Safety		
Adverse Events	210 (100%)	200 (100%)
Laboratory Tests	204 (97%)	189 (95%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Of the 410 randomized subjects, two trovafloxacin subjects and one clarithromycin subject had an inappropriate baseline diagnosis due to insufficient symptoms or inappropriate sputum histology and were excluded from all clinical and bacteriological ITT and evaluable analyses.

Of the 407 clinical ITT subjects, 16 were not clinically evaluable (5 subjects in the trovafloxacin group and 11 subjects in the clarithromycin group); therefore 391 (203 trovafloxacin and 188 clarithromycin) subjects were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was prior antibiotic therapy (4 trovafloxacin and 3 clarithromycin subjects). Other reasons were no post-baseline clinical assessment, insufficient therapy, and concomitant antibiotic therapy for intercurrent illness.

Of the 407 clinical ITT subjects, 225 were not included in the bacteriologically ITT analysis due to negative baseline cultures (trovafloxacin, 112 subjects and clarithromycin, 113 subjects); therefore, 182 (96 trovafloxacin and 86 clarithromycin) subjects were included in the bacteriological ITT analysis.

Of the 391 clinically evaluable subjects, 217 subjects were not included in the bacteriologically evaluable analyses (trovafloxacin, 110 subjects and clarithromycin, 107 subjects); therefore 174 subjects (93 trovafloxacin and 81 clarithromycin) were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (trovafloxacin, 108 subjects and clarithromycin, 105 subjects). Other reasons were baseline culture outside specified visit window and no post-baseline cultures.

Discontinuations

Of the 410 treated subjects, 26 subjects were prematurely discontinued from treatment as summarized in Table 4b.2.

Table 4b.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)				
	Trovafloxacin 100 mg (N=210)	Clarithromycin 500 mg BID (N=200)	Total (N=410)	
Number and Percentage (%) of Subjects				
Total Discontinued	9 (4%)	17 (9%)	26	(6%)
Discontinuations Related to Study Drug:	6 (3%)	10 (5%)	16	(4%)
Adverse Event	3 (1%)	6 (3%)	9	(2%)
Insufficient Response	3 (1%)	4 (2%)	7	(2%)
Discontinuations Unrelated to Study Drug:	3 (1%)	7 (4%)	10	(2%)
Adverse Event	1 (<1%)	3 (2%)	4	(<1%)
Did Not Meet Randomization Criteria	1 (<1%)	1 (<1%)	2	(<1%)
Laboratory Abnormality	1 (<1%)	1 (<1%)	2	(<1%)
Protocol Violation	0	2 (1%)	2	(<1%)

Demographics

One hundred eighty-nine (189) of the 410 treated subjects were male (102, trovafloxacin; 87, clarithromycin) and 221 were female (108, trovafloxacin; 113, clarithromycin). The trovafloxacin and clarithromycin treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the trovafloxacin and clarithromycin groups (33% and 37% ex-smoker, 30% and 26% never smoked, and 36% and 38% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinically intent-to-treat subjects was acute bacterial exacerbation of chronic bronchitis. The median duration since onset of acute bacterial exacerbation of chronic bronchitis was 7 days for subjects in both the trovafloxacin and clarithromycin groups (range of 1 to 182 days for trovafloxacin, 1 to 69 days for clarithromycin). Similar results were observed for clinically evaluable subjects.

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 4b.3. Trovafloxacin was considered therapeutically equivalent to clarithromycin at both EOT and EOS.

Reviewer's Note: One of the investigators involved in this study, Dr. Fiddes, has plead guilty to several violations of FDA regulations. Dr. Fiddes enrolled a small number of patients in this study, 12 total (6 trovafloxacin and 6 clarithromycin patients), thus the exclusion of data from his center does not effect conclusions about efficacy.

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Table 4b.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Trovafloxacin 100 mg (N=203)		Clarithromycin 500 mg BID (N=188)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	203	(100%)	188	(100%)	
Success (Cure + Improvement)	181	(89%)	160	(85%)	(-2.6, 10.7)
Distribution of Clinical Response:					
Cure	87	(43%)	75	(40%)	
Improvement	94	(46%)	85	(45%)	
Failure	22	(11%)	28	(15%)	
End of Study:					
Number of Subjects Assessed	197	(100%)	178	(100%)	
Success (Cure + Improvement)	158	(80%)	131	(74%)	(-1.9, 15.1)
Distribution of Clinical Response:					
Cure	140	(71%)	110	(62%)	
Improvement	18	(9%)	21	(12%)	
Failure	22	(11%)	28	(16%)	
Relapse	17	(9%)	19	(11%)	

A summary of clinical success rates at EOT and EOS for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 4b.4.

Table 4b.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)								
	Trovafloxacin 100 mg (N=93)		Clarithromycin 500 mg BID (N=83)		Trovafloxacin 100 mg (N=91)		Clarithromycin 500 mg BID (N=80)	
Number and Percentage (%) of Subjects								
Pathogen	End of Treatment				End of Study			
<i>H. influenzae</i>	24/26	(92%)	16/18	(89%)	24/26	(92%)	7/16	(44%)
<i>M. catarrhalis</i>	14/18	(78%)	16/20	(80%)	12/17	(71%)	14/19	(74%)
<i>S. aureus</i>	13/14		10/12		11/13		9/12	
<i>P. aeruginosa</i>	13/14		8/8		10/14		7/8	
<i>S. pneumoniae</i>	7/7		10/11		6/7		10/11	
^a ≥10 isolates of a given pathogen in any treatment group. A subject could have had more than one pathogen isolated at baseline.								

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 4b.5.

Table 4b.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)										
	Trovafoxacin 100 mg (N=93)		Clarithromycin 500 mg BID (N=81)		95% CI	Trovafoxacin 100 mg (N=87)		Clarithromycin 500 mg BID (N=77)		95% CI
Number of Pathogens										
Pathogen	End of Treatment					End of Study				
<i>H. influenzae</i>	24/26	(92%)	12/16	(75%)	-6.3, 40.9	22/24	(92%)	10/16	(63%)	3.0, 55.3
<i>M. catarrhalis</i>	13/17	(76%)	17/18	(94%)	-40.7, 4.8	13/16	(81%)	16/18	(89%)	-31.7, 16.4
<i>S. aureus</i>	14/14		12/12		ND	13/13		11/12		ND
<i>P. aeruginosa</i>	9/13		6/8		ND	9/14		6/8		ND
<i>S. pneumoniae</i>	6/7		11/11		ND	7/7		11/11		ND

ND = Not Determined
^a ≥10 isolates of a given pathogen in any treatment group. Percents are displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

MO Efficacy Results: *The medical officer reassessed patients' evaluability and clinical outcome status. Table 4b.6 presents clinical response for the MO clinically evaluable patient group at both EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, trovafloxacin was considered therapeutically equivalent to clarithromycin at both EOT and EOS.*

Table 4b.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)			
	Trovafoxacin 100 mg	Clarithromycin 500 mg BID	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	196 (100%)	176 (100%)	
Success (Cure + Improvement)	174 (89%)	148 (84%)	(-2.8, 12.2)
End of Study:			
Number of Subjects Assessed	196 (100%)	176 (100%)	
Success (Cure + Improvement)	157 (80%)	129 (73%)	(-2.3, 15.9)

Reviewer's Note: *One of the investigators involved in this study, Dr. Fiddes, has plead guilty to several violations of FDA regulations. Dr. Fiddes enrolled a small number of patients in this study, 12 total (6 trovafloxacin and 6 clarithromycin patients), thus the exclusion of data from his center does not effect conclusions about efficacy.*

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events, and clinically significant laboratory values is presented in Table 4b.7. Tables 4b.8 and 4b.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: There was a higher incidence of both adverse events, regardless of relationship to study drug, and treatment-related adverse events in the clarithromycin arm ($p = 0.04$ and $p < 0.0001$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 4b.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 100 mg daily (N=210)	Clarithromycin 500 mg BID (N=200)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	85/210 (40%)	101/200 (51%)
Treatment-Related Adverse Events	42/210 (20%)	76/200 (38%)
Discontinuations Due to an Adverse Event ^a	4/210 (2%)	8/200 (4%)
Clinically Significant Laboratory Values	28/204 (14%)	25/189 (13%)
^a With the exception of one subject in the trovafloxacin group and two subjects in the clarithromycin group, all of whom were discontinued due to adverse events that were attributed to other illnesses or to the disease under study, all subjects who were discontinued from treatment had adverse events that were considered by the investigator to be study drug-related.		

Table 4b.8. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)				
	Trovafloxacin 100 mg (N=210)		Clarithromycin 500 mg BID (N=200)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event^c	85	(40%)	101	(51%)
BODY SYSTEM				
WHO Term				
AUTONOMIC-NERVOUS SYSTEM	5	(2%)	6	(3%)
Mouth Dry	1	(<1%)	5	(3%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	36	(17%)	23	(12%)
Dizziness	12	(6%)	6	(3%)
Headache	20	(10%)	9	(5%)
GASTROINTESTINAL SYSTEM	26	(12%)	47	(24%)
Constipation	1	(<1%)	6	(3%)
Diarrhea	6	(3%)	14	(7%)
Nausea	12	(6%)	19	(10%)
Stools Loose	1	(<1%)	5	(3%)
Vomiting	3	(1%)	6	(3%)
PSYCHIATRIC	9	(4%)	17	(9%)
Insomnia	3	(1%)	13	(7%)
RESPIRATORY SYSTEM	20	(10%)	17	(9%)
Rhinitis	8	(4%)	5	(3%)
Sinusitis	6	(3%)	2	(1%)
SPECIAL SENSES	10	(5%)	32	(16%)
Taste Perversion	4	(2%)	31	(16%)
a ≥ 3 % of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.				

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Table 4b.9. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)		
	Trovafloxacin 100 mg (N=210)	Clarithromycin 500 mg BID (N=200)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event ^c	42 (20%)	76 (38%)
BODY SYSTEM		
WHO Term		
AUTONOMIC NERVOUS SYSTEM		
Mouth Dry	4 (2%)	4 (2%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM		
Dizziness	1 (<1%)	3 (2%)
Headache	18 (9%)	12 (6%)
Vertigo	6 (3%)	5 (3%)
	7 (3%)	2 (1%)
	3 (1%)	4 (2%)
GASTROINTESTINAL SYSTEM		
Constipation	15 (7%)	40 (20%)
Diarrhea	0 (0%)	5 (3%)
Nausea	5 (2%)	11 (6%)
Stools Loose	11 (5%)	18 (9%)
Vomiting	1 (<1%)	5 (3%)
	0 (0%)	5 (3%)
GENERAL		
Moniliasis	2 (<1%)	5 (3%)
	1 (<1%)	4 (2%)
PSYCHIATRIC SYSTEM		
Insomnia	7 (3%)	7 (4%)
	2 (<1%)	5 (3%)
SPECIAL SENSES		
Taste Perversion	4 (2%)	31 (16%)
	4 (2%)	31 (16%)

a ≥2 % of subjects in either treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

The most commonly reported treatment-related adverse events in the trovafloxacin group were nausea, headache, and dizziness and the most commonly reported treatment-related adverse events in the clarithromycin group were taste perversion, nausea, and diarrhea.

Fourteen (14) subjects experienced serious adverse events (3 subjects in the trovafloxacin group and 11 subjects in the clarithromycin group). With the exception of one subject in the clarithromycin group, whose serious adverse event (nausea/vomiting) was considered by the investigator to be related to study drug, all serious adverse events were attributed to other illnesses (acute pneumothorax, respiratory failure, atrial fibrillation, angina pectoris, acute exacerbation of COPD, cerebral vascular accident, or fever of unknown origin) or to the disease under study (bronchitis and/or bronchospasm). The serious adverse event(s) resolved for 13 subjects and resulted in death (due to cardiac arrest) for one subject in the clarithromycin group.

No subject in the trovafloxacin group had a clinically significant liver or renal function laboratory abnormality.

Sponsor's Summary and Conclusions: Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to clarithromycin 500 mg twice daily for 7 days for clinical success rates at the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. Pathogen eradication rates for *H. influenzae* at both the end of treatment and the end of study were higher in the trovafloxacin group compared to the clarithromycin group (end of treatment: 92% versus 75%, respectively; end of study: 92% versus 63%, respectively). The overall incidence of all and treatment-related adverse events was lower among subjects in the trovafloxacin group as compared to subjects in the clarithromycin group (40% and 20% versus 51% and 38%, respectively). The percentage of subjects with adverse events leading to discontinuation was comparable between the two treatment groups (2% and 4%, respectively). Subjects in the trovafloxacin group had lower frequencies of gastrointestinal system (12% versus 24%) and special senses (5% versus 16%) adverse events and a higher frequency of central and peripheral nervous system (17% versus 12%) adverse events compared to subjects in the clarithromycin group. The frequency and type of clinically significant laboratory abnormalities were comparable between the two treatment groups.

Reviewer's Summary and Conclusions: Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to clarithromycin 500 mg twice daily for 7 days in terms of clinical success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.

There was a higher incidence of both adverse events, regardless of relationship to study drug, and treatment-related adverse events in the clarithromycin arm ($p=0.04$ and $p<0.0001$, respectively). The most commonly reported adverse events in the trovafloxacin group were headache (10%), dizziness (6%), and nausea (6%) and the most commonly reported adverse events in the clarithromycin group were taste perversion (16%), nausea (10%), diarrhea (7%), and insomnia (7%).

IV.C. Protocol 154-141

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A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND CIPROFLOXACIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study Dates: 21 December 1994 to 21 September 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin with ciprofloxacin in the treatment of subjects with acute bacterial exacerbation of chronic bronchitis.

Study Design: Study 154-141 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily) versus ciprofloxacin

(500 mg twice daily) administered orally for 7 days for the treatment of acute bacterial exacerbation of chronic bronchitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥ 40 years of age at the baseline visit, with clinically documented acute bacterial exacerbation of chronic bronchitis were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the study. Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection such as disappearance or diminution in purulent sputum production, changes in dyspnea and cough as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of chronic bronchitis to the baseline level that existed prior to the occurrence of acute bacterial exacerbation), improvement (resolution of sputum purulence but incomplete resolution of the other signs and symptoms of chronic bronchitis and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of chronic bronchitis or a need for additional antibiotic for inadequate response).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, or relapse.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT and;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

***Reviewer's Note:** As with studies 154-101 and 154-109, the reviewing medical officer, Dr. Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.*

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Sponsor Efficacy Results:

Analysis Groups

Table 4c.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Reviewer's Note: Somewhat fewer trovafloxacin patients were included in the bacteriologically ITT and evaluable analysis groups, due mostly to a higher number of negative baseline cultures in the trovafloxacin group. Neither difference was statistically significant ($p = 0.29$ and 0.13 , respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 4c.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg daily)	Ciprofloxacin (500 mg BID)
Entered Study ^a	131	125
All Treated	131 (100%)	125 (100%)
Completed Treatment	121 (92%)	114 (91%)
Completed Study	123 (94%)	120 (96%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	125 (95%)	121 (97%)
Clinically Evaluable ^b	116 (89%)	115 (92%)
Bacteriologically Intent-to-Treat	70 (53%)	75 (60%)
Bacteriologically Evaluable ^b	60 (46%)	69 (55%)
Assessed for Safety		
Adverse Events	131 (100%)	125 (100%)
Laboratory Tests	124 (95%)	118 (94%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Of the 256 randomized subjects, six trovafloxacin subjects and four ciprofloxacin subjects had an inappropriate baseline diagnosis due to insufficient symptoms or inappropriate sputum histology and were excluded from all clinical and bacteriological intent-to-treat and evaluable analyses.

Of the 246 clinical ITT subjects, 15 were not clinically evaluable (9 subjects in the trovafloxacin group and 6 subjects in the ciprofloxacin group); thus, 231 (116, trovafloxacin and 115, ciprofloxacin) were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (7 trovafloxacin and 5 ciprofloxacin subjects). Other reasons were no post-baseline clinical assessment, no post-baseline assessment in evaluable analysis windows, prior antibiotic therapy, and concomitant antibiotic therapy for intercurrent illness.

Of the 246 clinical ITT subjects, 101 were not included in the bacteriological intent-to-treat analysis due to negative baseline cultures (55, trovafloxacin and 46, ciprofloxacin); thus, 145 (70, trovafloxacin and 75, ciprofloxacin) subjects were included in the bacteriological intent-to-treat analysis.

Of the 231 clinically evaluable subjects, 102 subjects were not included in the bacteriologically evaluable analyses (trovafloxacin 56 subjects and ciprofloxacin 46 subjects); thus, 129 (60, trovafloxacin and 69, ciprofloxacin) were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (trovafloxacin, 52 subjects and ciprofloxacin, 44 subjects). Other reasons were baseline culture outside specified visit window and no post-baseline cultures.

Discontinuations

Of the 256 treated subjects, 21 subjects were prematurely discontinued from treatment as summarized in Table 4c.2.

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Table 4c.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)						
	Trovafloxacin 100 mg (N=131)		Ciprofloxacin 500 mg BID (N=125)		Total (N=256)	
Number and Percentage (%) of Subjects						
Total Discontinued	10	(8%)	11	(9%)	21	(8%)
Discontinuations Related to Study Drug:	2	(2%)	6	(5%)	8	(3%)
Adverse Event	1	(<1%)	5	(4%)	6	(2%)
Insufficient Response	1	(<1%)	1	(<1%)	2	(<1%)
Discontinuations Unrelated to Study Drug:	8	(6%)	5	(4%)	13	(5%)
Adverse Event	2	(2%)	2	(2%)	4	(2%)
Lost to Follow-up	5	(4%)	1	(<1%)	6	(2%)
Other	0		1	(<1%)	1	(<1%)
Withdrawn Consent	1	(<1%)	1	(<1%)	2	(<1%)

Demographics

One hundred fifty-three (153) of the 256 treated subjects were male (76, trovafloxacin; 77, ciprofloxacin) and 103 were female (55, trovafloxacin; 48, ciprofloxacin). The males and females in the trovafloxacin and ciprofloxacin treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the trovafloxacin and ciprofloxacin groups (33% and 43% ex-smoker, 16% and 15% never smoked, and 51% and 42% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinically intent-to-treat subjects was acute bacterial exacerbation of chronic bronchitis. The median duration since onset of acute bacterial exacerbation of chronic bronchitis was 6 days for subjects in both the trovafloxacin and ciprofloxacin

treatment groups (range of 1 to 163 days for trovafloxacin patients, 1 to 81 days for ciprofloxacin patients). Similar results were observed for clinically evaluable subjects.

Clinical Response

A summary of clinical response for clinically evaluable subjects at EOT and EOS is presented by treatment group in Table 4c.3. Clinical response was considered therapeutically equivalent between trovafloxacin and clarithromycin at both EOT and EOS.

Table 4c.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Trovafloxacin 100 mg (N=116)		Ciprofloxacin 500 mg BID (N=115)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	116	(100%)	115	(100%)	
Success (Cure + Improvement)	111	(96%)	106	(92%)	(-2.6, 9.7)
Distribution of Clinical Response:					
Cure	47	(41%)	47	(41%)	
Improvement	64	(55%)	59	(51%)	
Failure	5	(4%)	9	(8%)	
End of Study:					
Number of Subjects Assessed	110	(100%)	102	(100%)	
Success (Cure + Improvement)	95	(86%)	81	(79%)	(-3.2, 17.1)
Distribution of Clinical Response:					
Cure	87	(79%)	62	(61%)	
Improvement	8	(7%)	19	(19%)	
Failure	5	(5%)	9	(9%)	
Relapse	10	(9%)	12	(12%)	

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Table 4c.4 summarizes sponsor clinical success rates for clinically evaluable subjects at both the end of treatment and end of study for the most frequently isolated baseline pathogens.

Table 4c.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)								
	Trovafloxacin 100 mg (N=63)		Ciprofloxacin 500 mg BID (N=71)		Trovafloxacin 100 mg (N=59)		Ciprofloxacin 500 mg BID (N=65)	
Number and Percentage (%) of Subjects								
Pathogen	End of Treatment				End of Study			
	<i>H. influenzae</i>	15/17	(88%)	18/20	(90%)	12/16	(75%)	14/19
<i>M. catarrhalis</i>	13/13		12/13		11/13		9/12	
<i>H. parainfluenzae</i>	7/7		11/12		6/6		8/10	
<i>S. aureus</i>	12/13		9/10		9/11		8/9	

^a ≥10 isolates of a given pathogen in any treatment group. Percents are displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Results

Table 4c.5 presents a summary of sponsor-defined pathogen eradication rates for bacteriologically evaluable subjects at both the end of treatment and end of study for the most frequently isolated baseline pathogens.

Table 4c.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)						
	Trovafloxacin 100 mg (N=60)	Ciprofloxacin 500 mg BID (N=69)	95% CI	Trovafloxacin 100 mg (N=55)	Ciprofloxacin 500 mg BID (N=62)	95% CI
Number of Pathogens						
Pathogen	End of Treatment			End of Study		
<i>H. influenzae</i>	15/16 (94%)	18/19 (95%)	-16.5, 14.6	13/15 (87%)	13/16 (81%)	-20.3, 31.1
<i>M. catarrhalis</i>	12/12	12/12	ND	10/12	9/12	ND
<i>H. parainfluenzae</i>	7/7	11/12	ND	6/6	9/10	ND
<i>S. aureus</i>	11/12	8/9	ND	10/11	7/8	ND

ND = Not Determined
 a ≥10 isolates of a given pathogen in any treatment group. Percents are displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

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MO Efficacy Results: *The medical officer reassessed patients' evaluability and clinical outcome status. Table 4c.6 presents clinical response for the MO clinically evaluable patient group at both EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, trovafloxacin was considered therapeutically equivalent to ciprofloxacin at both EOT and EOS.*

Table 4c.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)			
	Trovafloxacin 100 mg	Ciprofloxacin 500 mg BID	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	109 (100%)	101 (100%)	
Success (Cure + Improvement)	104 (95%)	92 (91%)	(-3.4, 12.1)
End of Study:			
Number of Subjects Assessed	109 (100%)	101 (100%)	
Success (Cure + Improvement)	93 (85%)	79 (78%)	(-4.3, 18.5)

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuations due to adverse events, and clinically significant laboratory values is presented in Table 4c.7. Tables 4c.8 and 4c.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 4c.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 100 mg daily	Ciprofloxacin 500 mg BID
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	51/131 (39%)	50/125 (40%)
Treatment-Related Adverse Events	25/131 (19%)	27/125 (22%)
Discontinuations Due to an Adverse Event ^a	3/131 (2%)	7/125 (6%)
Clinically Significant Laboratory Values	20/124 (16%)	17/118 (14%)

^a With the exception of two subjects in the trovafloxacin group and two subjects in the ciprofloxacin group, all of whom were discontinued due to adverse events that were attributed to other illnesses or to the disease under study, all subjects who were discontinued from treatment had adverse events that were considered by the investigator to be study drug-related.

Table 4c.8. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 100 mg (N=131)	Ciprofloxacin 500 mg BID (N=125)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event ^c	51 (39%)	50 (40%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	10 (8%)	14 (11%)
Dizziness	5 (4%)	7 (6%)
Headache	5 (4%)	4 (3%)
GASTROINTESTINAL SYSTEM	25 (19%)	27 (22%)
Abdominal Pain	4 (3%)	2 (2%)
Constipation	4 (3%)	1 (<1%)
Diarrhea	4 (3%)	6 (5%)
Dyspepsia	1 (<1%)	4 (3%)
Nausea	11 (8%)	13 (10%)
PSYCHIATRIC	8 (6%)	11 (9%)
Insomnia	5 (4%)	5 (4%)

^a ≥3 % of subjects in either treatment group.
^b Includes data up to 7 days after last dose of active study medication.
^c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

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Table 4c.9. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)				
	Trovafloracin 100 mg (N=131)		Ciprofloracin 500 mg BID (N=125)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	25	(19%)	27	(22%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM				
Dizziness	3	(2%)	6	(5%)
Tremor	3	(2%)	5	(4%)
	0	(0%)	3	(2%)
GASTROINTESTINAL SYSTEM				
Abdominal Pain	17	(13%)	19	(15%)
Constipation	2	(2%)	2	(2%)
Diarrhea	2	(2%)	1	(<1%)
Dyspepsia	1	(<1%)	3	(2%)
Flatulence	0	(0%)	3	(2%)
Nausea	2	(2%)	1	(<1%)
Stools Loose	9	(7%)	9	(7%)
Vomiting	2	(2%)	2	(2%)
PSYCHIATRIC SYSTEM				
Insomnia	5	(4%)	4	(3%)
Somnolence	2	(2%)	2	(2%)
	2	(2%)	0	(0%)
REPRODUCTIVE SYSTEM				
Vaginitis ^d	1	(<1%)	1	(<1%)
	1	(2%)	1	(2%)
SPECIAL SENSES				
Taste Perversion	2	(2%)	1	(<1%)
	2	(2%)	1	(<1%)
a ≥2 % of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. d Preferred term is gender specific, and the percentages are based in the number of males or females appropriately.				

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Nausea was the most commonly reported treatment-related adverse event in both groups (each group, 7%).

Four subjects in the trovafloracin group and seven subjects in the ciprofloracin group experienced serious adverse events. Of these, one subject in the trovafloracin group died 20 days post-treatment. This death was considered to be unrelated to study drug and was attributed to the subject's underlying illness (hypertension).

No clinically significant laboratory abnormalities were noted in any trovafloracin subject for liver function tests.

Sponsor's Summary and Conclusions: Trovafloracin 100 mg once daily for 7 days was statistically equivalent to that of ciprofloracin 500 mg twice daily for 7 days for clinical

success rates in subjects with acute bacterial exacerbation of chronic bronchitis. Sponsor-defined pathogen eradication rates were similar between the two treatment groups. The overall incidence of adverse events for subjects in the trovafloxacin group was comparable to that of subjects in the ciprofloxacin group (39% and 40%, respectively), as was the frequency of treatment-related adverse events (19% and 22%, respectively) and adverse events leading to discontinuation (2% and 6%, respectively). The most commonly reported adverse event in both treatment groups was nausea. The frequency and type of adverse laboratory events were comparable between the two treatment groups.

Reviewer's Summary and Conclusions: *Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to ciprofloxacin 500 mg twice daily for 7 days in terms of clinical success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.*

The most commonly reported adverse events in the trovafloxacin group were nausea (8%), dizziness (4%), headache (4%), and insomnia (4%) and the most commonly reported adverse events in the ciprofloxacin group were nausea (10%), dizziness (6%), diarrhea (5%), and insomnia (4%).

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IV.D. Protocol 154-108

Reviewer's Note: *This study is considered supportive by both the sponsor and the review team as it examined two 5 day regimens of trovafloxacin for the treatment of acute bacterial exacerbation of chronic bronchitis. The sponsor wishes to market a 7 day regimen of trovafloxacin for the treatment of acute bacterial exacerbation of chronic bronchitis. Results are summarized briefly below.*

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN WITH AMOXYCILLIN FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS

APPROVED THIS DAY
BY [illegible]

Study Dates: December 8, 1994 - December 19, 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of two regimens of trovafloxacin with amoxicillin in the treatment of subjects with acute bacterial exacerbation of chronic bronchitis.

Study Design: Study 154-108 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily or 200 mg once daily) versus amoxicillin (500 mg three times daily) administered orally for 5 days for the treatment of acute bacterial exacerbation of chronic bronchitis.

	Evaluation Groups:					
	Trovafloracin (100 mg daily)		Trovafloracin (200 mg daily)		Amoxycillin (500 mg TID)	
Entered Study ^a	145		135		132	
All Treated	145	(100%)	134	(100%)	132	(100%)
Completed Treatment	136	(94%)	129	(96%)	128	(97%)
Completed Study	133	(92%)	129	(96%)	126	(95%)
Evaluated for Efficacy						
Clinical Intent-to-Treat	135	(93%)	126	(93%)	116	(88%)
Clinically Evaluable ^b	128	(88%)	118	(87%)	114	(86%)
Bacteriologically Intent-to-Treat	91	(63%)	85	(63%)	80	(61%)
Bacteriologically Evaluable ^b	84	(58%)	79	(59%)	79	(60%)
Assessed for Safety						
Adverse Events	145	(100%)	134	(100%)	132	(100%)
Laboratory Tests	136	(94%)	126	(94%)	126	(95%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥ 40 years of age at the baseline visit, with clinically documented acute bacterial exacerbation of chronic bronchitis were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens). Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results: Sponsor-defined clinical success rates (cure + improvement) were similar among all three treatment groups in both the clinically evaluable and intent-to-treat analyses at the end of treatment and at the end of study.

A Summary of the Sponsor's Assessment of Clinical Response						
(Clinically Evaluable Subjects)						
	End of Treatment			End of Study		
	Trovafloxacin 100 mg (N=128)	Trovafloxacin 200 mg (N=118)	Amoxicillin 500 mg TID (N=114)	Trovafloxacin 100 mg (N=123)	Trovafloxacin 200 mg (N=113)	Amoxicillin 500 mg TID (N=109)
Number and Percentage (%) of Subjects						
Number of Subjects Assessed	128 (100%)	118 (100%)	114 (100%)	123 (100%)	113 (100%)	109 (100%)
Success (Cure + Improvement)	116 (91%)	104 (88%)	101 (89%)	105 (85%)	87 (77%)	86 (79%)
Cure	45 (35%)	30 (25%)	33 (29%)	90 (73%)	69 (61%)	71 (65%)
Improvement	71 (55%)	74 (63%)	68 (60%)	15 (12%)	18 (16%)	15 (14%)
Failure	12 (9%)	14 (12%)	13 (11%)	12 (10%)	14 (12%)	13 (12%)
Relapse	NA	NA	NA	6 (5%)	12 (11%)	10 (9%)
(Clinically Intent-to-Treat Subjects)						
	End of Treatment			End of Study		
	Trovafloxacin 100 mg (N=135)	Trovafloxacin 200 mg (N=126)	Amoxicillin 500 mg TID (N=116)	Trovafloxacin 100 mg (N=135)	Trovafloxacin 200 mg (N=126)	Amoxicillin 500 mg TID (N=116)
Number and Percentage (%) of Subjects						
Number of Subjects Assessed	135 (100%)	126 (100%)	116 (100%)	135 (100%)	126 (100%)	116 (100%)
Success (Cure + Improvement)	121 (90%)	109 (87%)	103 (89%)	115 (85%)	97 (77%)	93 (80%)
Cure	48 (36%)	32 (25%)	33 (28%)	97 (72%)	76 (60%)	75 (65%)
Improvement	73 (54%)	77 (61%)	70 (60%)	18 (13%)	21 (17%)	18 (16%)
Failure	14 (10%)	17 (13%)	13 (11%)	14 (10%)	17 (13%)	13 (11%)
Relapse	NA	NA	NA	6 (4%)	12 (10%)	10 (9%)
Clinical Success Rates For the Most Frequently Isolated Baseline Pathogens ^a						
(Clinically Evaluable Subjects)						
	Trovafloxacin 100 mg (N=86)	Trovafloxacin 200 mg (N=80)	Amoxicillin 500 mg TID (N=79)	Trovafloxacin 100 mg (N=82)	Trovafloxacin 200 mg (N=78)	Amoxicillin 500 mg TID (N=77)
Number of Subjects						
Pathogen	End of Treatment			End of Study		
<i>H. influenzae</i>	38/44 (86%)	41/44 (93%)	31/39 (79%)	31/40 (78%)	36/42 (86%)	25/39 (64%)
<i>M. catarrhalis</i>	15/17 (88%)	14/17 (82%)	18/20 (90%)	15/17 (88%)	11/17 (65%)	17/20 (85%)
<i>S. pneumoniae</i>	21/23 (91%)	22/25 (88%)	19/21 (90%)	21/23 (91%)	22/25 (88%)	16/20 (80%)

^a ≥10 isolates of a given pathogen in any treatment group.
 A subject could have had more than one pathogen isolated at baseline.
 Several subjects were not evaluated clinically at the end of treatment.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events, and clinically significant laboratory values is presented in the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values					
	Trovafoxacin 100 mg daily (N=145)		Trovafoxacin 200 mg daily (N=134)		Amoxicillin 500 mg TID (N=132)
Number and Percentages (% of Subjects)					
Adverse Events: All Causalities	14/145	(10%)	31/134	(23%)	20/132 (15%)
Treatment-Related Adverse Events	9/145	(6%)	16/134	(12%)	12/132 (9%)
Discontinuations From Treatment Due to an Adverse Event	5/145	(3%)	5/134	(4%)	3/132 (2%)
Discontinuations Due to a Treatment- Related Adverse Event	3/145	(2%)	4/134	(3%)	1/132 (1%)
Clinically Significant Laboratory Values	20/136	(15%)	18/126	(14%)	21/126 (17%)

APPENDIX 1
TABLE 1

V. ACUTE SINUSITIS

The efficacy and safety of oral trovafloxacin for the treatment of sinusitis was assessed in two comparative trials, one double-blind (154-115) and one open-label (154-138), and one noncomparative trial with sinus aspirates (154-114). The comparator agents were clarithromycin (154-115) and amoxicillin/clavulanate (154-138). These trials are reviewed below.

***Reviewer's Note:** The sponsor assessed whether efficacy differed in various subgroups in the sinusitis trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, race, and age.*

V.A. Protocol 154-114

AN OPEN NONCOMPARATIVE, MULTI-CENTER TRIAL DESIGNED TO ASSESS THE EFFICACY AND SAFETY OF 10 DAYS ORAL THERAPY WITH TROVAFLOXACIN (200 MG ONCE DAILY) FOR THE TREATMENT OF ACUTE SINUSITIS.

Study Dates: 15 November, 1994 - 3 August, 1995

Study Objectives: The objective of this study was to evaluate the safety and efficacy of trovafloxacin administered as a 200 mg oral dose for 10 days for the treatment of subjects with acute sinusitis.

Study Design: Study 154-114 was an unblinded, non-comparative, multicenter trial.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 16 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection) and bacteriologic response (based on eradication or presumptive eradication of causative organisms isolated from trans-antral aspirations at baseline).

Clinical response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), the end of therapy (Visit 3, Day 11), and at the end of study (Visit 4, Day 24) or at the time of discontinuation from study. The clinical response was to be classified as cure (resolution of signs and symptoms of acute sinusitis to the level that existed before baseline and improvement in x-ray findings), improvement (improvement but incomplete resolution of signs and symptoms of acute sinusitis to the level that existed before baseline and no requirement for additional antibiotic), or failure (lack of resolution or worsening of any signs and symptoms of acute sinusitis or the need for an additional antibiotic for inadequate response).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Day 11) and at the end of study (Day 24), or at the time of discontinuation from the study. Bacteriological response for each pathogen was to be classified by the sponsor as eradication, presumed eradication, persistence, presumed persistence, or relapse.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT and;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 5a.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 5a.1. Evaluation Groups

Evaluation Groups:	Trovanoxacin (200 mg/day)	
Entered Study ^a	255	(100%)
All Treated	254	(> 99%)
Completed Treatment	243	(96%)
Completed Study	242	(95%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	251	(98%)
Clinically Evaluable ^b	235	(92%)
Bacteriological Intent-to-Treat	131	(51%)
Bacteriological Evaluable ^b	125	(49%)
Assessed for Safety		
Adverse Events	254	(100%)
Laboratory Tests	247	(97%)

a Subjects who were enrolled; Percentages for efficacy based on enrolled subjects as the denominator and percentages for safety based on all treated subjects.

b Based on End of Treatment assessment.

Of the 255 enrolled subjects, four subjects had an inappropriate baseline diagnosis and were excluded from all clinical and bacteriological ITT and evaluable analyses.

Of the 251 clinical ITT subjects, 16 were not clinically evaluable; thus, 235 subjects were clinically evaluable. Reasons for exclusion from clinical efficacy analyses were no post-baseline clinical assessments (4 subjects), no post-baseline assessment in evaluable analysis windows (5 subjects), insufficient therapy due to early discontinuation from treatment or

study (4 subjects), prior antibiotic therapy (5 subjects), and concomitant antibiotic therapy for intercurrent illness (3 subjects).

Of the 251 clinical ITT subjects, 120 were not included in the bacteriological ITT analysis due to negative baseline cultures; thus, 131 subjects were included in the bacteriological ITT analysis.

Of the 235 clinically evaluable subjects, 110 subjects were not included in the bacteriologically evaluable analyses; thus, 125 subjects were bacteriologically evaluable. The only reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (110 subjects).

Discontinuations

Of the 254 treated subjects, 11 subjects were prematurely discontinued from treatment as summarized in Table 5a.2.

Table 5a.2 Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Trovafloxacin 200 mg (N=254)	
	Number and Percentage (%) of Subjects	
Total Discontinued	11	(4%)
Discontinuations Related to Study Drug:	6	(2%)
Adverse Event	4	(2%)
Insufficient Response	2	(<1%)
Discontinuations Unrelated to Study Drug:	5	(2%)
Adverse Event	1	(<1%)
Did Not Meet Randomization Criteria	1	(<1%)
Lost to Follow-up	1	(<1%)
Withdrew Consent	2	(<1%)

Demographics

One hundred and twenty-three (123) male and 131 female subjects received treatment. Male and female subjects were generally comparable with respect to age, race, and weight. The distribution of male and female subjects according to smoking classification was (22% and 17% ex-smoker, 48% and 64% never smoked, and 30% and 19% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinically intent-to-treat subjects was acute sinusitis. The median (range) duration since onset of acute sinusitis was 8 days. Similar results were observed for clinically evaluable subjects.

Clinical Response

Sponsor-defined clinical response rates for clinically evaluable subjects at EOT and EOS are presented in Table 5a.3. Table 5a.4 presents clinical response rates by baseline pathogen for clinically evaluable subjects at EOT and EOS.

Table 5a.3 Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)		
	Trovafloxacin 200 mg (N=235)	95% CI
Number and Percentage (%) of Subjects		
End of Treatment:		
Number of Subjects Assessed	235 (100%)	
Success (Cure + Improvement)	213 (91%)	(86.9, 94.4)
Distribution of Clinical Response:		
Cure	110 (47%)	
Improvement	103 (44%)	
Failure	22 (9%)	
End of Study:		
Number of Subjects Assessed	227 (100%)	
Success (Cure + Improvement)	199 (88%)	(83.4, 91.9)
Distribution of Clinical Response:		
Cure	174 (77%)	
Improvement	25 (11%)	
Failure	22 (10%)	
Relapse	6 (3%)	

Table 5a.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens* (Clinically Evaluable Subjects)				
	Trovafloxacin 200 mg (N=235)		Trovafloxacin 200 mg (N=227)	
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>S. pneumoniae</i>	24/25	(96%)	24/25	(96%)
<i>H. influenzae</i>	38/45	(84%)	36/45	(80%)
<i>S. aureus</i>	18/18	(100%)	16/16	(100%)
<i>M. catarrhalis</i>	21/23	(91%)	19/21	(90%)

a ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

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Bacteriologic Response

Table 5a.5 summarizes pathogen eradication rates for bacteriologically evaluable patients at EOT and EOS.

Table 5a.5. Summary of Sponsor-Defined Pathogen Eradication Rates^a (Bacteriologically Evaluable Subjects)		
	Trovafloxacin 200 mg (N=125)	Trovafloxacin 200 mg (N=121)
	Number of Pathogens	
Pathogen^b	End of Treatment	End of Study
<i>S. pneumoniae</i>	24/25 (96%)	24/25 (96%)
<i>H. influenzae</i>	44/45 (98%)	43/45 (96%)
<i>S. aureus</i>	18/18 (100%)	16/16 (100%)
<i>M. catarrhalis</i>	22/23 (96%)	19/21 (90%)

a Includes subjects with presumptive eradication (subjects clinically improved or cured who did not undergo post-treatment transantral aspiration of the sinus).
 b ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed when denominator is ≥15.
 A subject could have more than one pathogen isolated at baseline.

Disqualified Investigator

Reviewer’s Note: One of the investigators involved in this study, Dr. Fiddes, has plead guilty to several violations of FDA regulations. To examine the robustness of results in this study, the data were examined after excluding patients enrolled at Dr. Fiddes’ center.

*A total of 32 patients were enrolled by Dr. Fiddes. Of the 28 patients considered clinically evaluable at EOT, 8 were cures, 19 were improved, and 1 was a failure. At EOS, 25 patients were considered clinically evaluable: 18 patients were cured, 6 improved, 1 a failure, and none had relapsed. Twenty-three patients were considered bacteriologically evaluable at EOT: 2 of 2 patients with *S. pneumoniae* were presumed eradicated, 6 of 7 patients with *H. influenzae* were presumed eradicated (the 7th was presumed persistent), 1 of 1 patient with *S. aureus* was presumed eradicated, 12 of 12 patients with *M. catarrhalis* were presumed eradicated, and 1 of 1 patient with *S. pyogenes* was presumed eradicated (no patient had more than one baseline pathogen isolated). At EOS, 21 patients were considered bacteriologically evaluable: 2 of 2 patients with *S. pneumoniae* were presumed eradicated, 6 of 7 patients with *H. influenzae* were presumed eradicated (the 7th was presumed persistent), 1 of 1 patient with *S. aureus* was presumed eradicated, 10 of 10 patients with *M. catarrhalis* were presumed eradicated, and 1 of 1 patient with *S. pyogenes* was presumed eradicated (again, no patient had more than one baseline pathogen isolated).*

*Results excluding patients from Dr. Fiddes’ center are presented in Tables 5a.6 and 5a.7, respectively, for clinical and bacteriologic outcome. On the whole, results are fairly robust. The most noticeable difference is in the number of patients with *M. catarrhalis* -- approximately half of the patients with *M. catarrhalis* were enrolled at Dr. Fiddes’ center. When these patients are excluded, there are only 11 patients enrolled with *M. catarrhalis* (slightly below the number of 15 recommended in the Division of Anti-Infective Drug*

Products 1992 "Points to Consider" document); the eradication rates are somewhat lower although they still appear acceptable.

Table 5a.6 FDA Analysis of Sponsor-Defined Clinical Response Rates at EOT and EOS, Excluding Patients From Dr. Fiddes' Center (Clinically Evaluable Subjects)		
	Trovafloxacin 200 mg (N=207)	95% CI
Number and Percentage (%) of Subjects		
End of Treatment:		
Number of Subjects Assessed	207 (100%)	
- Success (Cure + Improvement)	186 (90%)	(85.7, 94.0)
Distribution of Clinical Response:		
Cure	102 (49%)	
Improvement	84 (41%)	
Failure	21 (10%)	
End of Study:		
Number of Subjects Assessed	202 (100%)	
Success (Cure + Improvement)	175 (87%)	(82.0, 91.3)
Distribution of Clinical Response:		
Cure	156 (77%)	
Improvement	19 (9%)	
Failure	21 (10%)	
Relapse	6 (3%)	

Table 5a.7. FDA Analysis of Sponsor-Defined Pathogen Eradication Rates^a, Excluding Patients From Dr. Fiddes' Center (Bacteriologically Evaluable Subjects)		
	Trovafloxacin 200 mg (N=102)	Trovafloxacin 200 mg (N=100)
Number of Pathogens		
Pathogen^b	End of Treatment	End of Study
<i>S. pneumoniae</i>	22/23 (96%)	22/23 (96%)
<i>H. influenzae</i>	38/38 (100%)	37/38 (97%)
<i>S. aureus</i>	17/17 (100%)	15/15 (100%)
<i>M. catarrhalis</i>	10/11 (91%)	9/11 (82%)

a Includes subjects with presumptive eradication (subjects clinically improved or cured who did not undergo post-treatment transantral aspiration of the sinus).
 B ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed when denominator is ≥15.
 A subject could have more than one pathogen isolated at baseline.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 5a.8. Tables 5a.9 and 5a.10 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 5a.8. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values	
	Trovafloxacin 200 mg
	Number and Percentage (%) of Subjects
Adverse Events: All Causalities	137/254 (54%)
Treatment-Related Adverse Events	87/254 (34%)
Discontinuations Due to an Adverse Event ^a	5/254 (2%)
Clinically Significant Laboratory Abnormalities	34/247 (14%)

a With the exception of one subject who was discontinued due to unrelated adverse events, all subjects were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related.

Table 5a.9 Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)	
	Trovafloxacin 200 mg (N=254)
	Number and Percentage (%) of Subjects
Number of Subjects With at Least One Adverse Event ^c	137 (54%)
BODY SYSTEM	
WHO Term	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	83 (33%)
Dizziness	51 (20%)
Headache	34 (13%)
Vertigo	7 (3%)
GASTROINTESTINAL SYSTEM	40 (16%)
Nausea	30 (12%)
Vomiting	10 (4%)
Diarrhea	7 (3%)
RESPIRATORY SYSTEM	26 (10%)
Epistaxis	9 (4%)

a ≥ 3 % of subjects in any treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

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Table 5a.10 Summary of the Most Commonly Reported Adverse Events ^{a,b} by Body System - Treatment-Related (All Treated Subjects)		
	Trovafloracin 200 mg (N=254)	
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event ^c	87	(34%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	59	(23%)
Dizziness	45	(18%)
Headache	11	(4%)
Vertigo	6	(2%)
GASTROINTESTINAL SYSTEM	35	(14%)
Nausea	27	(11%)
Vomiting	9	(4%)
Diarrhea	6	(2%)
a ≥2 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.		

Two subjects experienced serious adverse events unrelated to study drug. There were no subject deaths during the study.

Sponsor's Summary and Conclusion: Trovafloracin 200 mg once daily for 10 days was safe and effective in the treatment of acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 2%. The overall percentage of subjects reporting adverse events was 54%; treatment-related adverse events were reported in 34% of subjects. The most commonly reported adverse events were dizziness and headache. No subjects were discontinued due to laboratory abnormalities.

Reviewer's Summary and Conclusion: Trovafloracin 200 mg once daily for 10 days appears to have been effective in the treatment of acute sinusitis in this trial. Caution should be taken in interpreting results, however, due to the fact that this was an uncontrolled trial. Eighteen percent of trovafloracin patients reported dizziness that was considered treatment related. Eleven percent of trovafloracin patients reported nausea that was considered treatment related.

One of the investigators involved in this trial, Dr. Fiddes, has plead guilty to violations of FDA regulations. Results are fairly robust when patients from Dr. Fiddes' center are excluded. The number of evaluable patients with *M. catarrhalis* drops to 11 (slightly below the number of 15 recommended in the Division of Anti-Infective Drug Products 1992 "Points to Consider" document), however eradication rates still appear acceptable (10/11 = 91% patients are eradicated at EOT; 9/11 = 82% patients are eradicated at EOS).

V.B. Protocol 154-115

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (200 MG DAILY) AND 14 DAYS OF ORAL CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE SINUSITIS.

Study Dates: 28 November 1994 - 20 March 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to clarithromycin in the treatment of subjects with acute sinusitis.

Study Design: Study 154-115 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg daily as a single dose) administered orally for 10 days versus clarithromycin (1000 mg daily as 500 mg twice daily), administered orally for 14 days for the treatment of acute sinusitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 16 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). Bacteriologic response was not assessed in this trial (i.e., no subject in either treatment group underwent trans-antral aspiration of the sinus, had a culture of an aspirate, or a blood culture during this study).

Clinical response was to be determined by the investigator and evaluated at Visit 2 (Day 4), the end of therapy (Day 15), and at the end of study (Day 28) or at the time of discontinuation from study. Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of pretreatment clinical signs of infection including post-nasal discharge, facial pain, hyposmia, jaw pain with mastication, and nasal congestion and improvement or resolution of positive sinus x-ray findings. The clinical response was to be classified as cure (resolution of signs and symptoms to the level that existed before baseline), improvement (improvement but incomplete resolution of signs and symptoms to the level that existed before baseline), or failure (lack of resolution or worsening of signs and symptoms or a need for an additional antibiotic).

The primary efficacy endpoint was the sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Investigator-defined clinical response at EOT, and sponsor-defined clinical response and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 5b.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 5b.1. Evaluation Groups

Evaluation Groups:	Trovafoxacin (200 mg/day)	Clarithromycin (500 mg BID)
Entered Study ^a	206	214
All Treated	203 (100%) ^b	214 (100%) ^b
Completed Study	186 (92%)	200 (93%)
Completed Treatment	158 (78%)	181 (85%)
Evaluated for Efficacy		
Clinical Intent-to-treat	193 (94%)	203 (95%)
Clinically Evaluable ^c	162 (79%)	188 (88%)
Assessed for Safety		
Adverse Events	203 (100%)	214 (100%)
Laboratory Tests	197 (97%)	211 (99%)

a Subjects who were randomized.

b Percentages based on treated subjects as the denominator

c Based on End of Treatment assessment.

Reviewer's Note: A lower percentage of patients completed treatment and were evaluable for efficacy in the trovafoxacin arm. The difference in patients completing treatment did not reach statistical significance ($p=0.08$ using the test of equal proportions based on the normal approximation to the binomial distribution), whereas the difference in patients who were evaluable did ($p=0.025$ using the same test as above). The difference in the number of evaluable patients appears to be largely due to the greater number of patients who discontinued treatment due to an adverse event in the trovafoxacin arm (see Table 5b.2).

Since a significantly lower percentage of trovafoxacin patients were included in the evaluable analysis, intent-to-treat efficacy results are presented below (in addition to the usual evaluable efficacy results).

Forty-six (46) of 420 randomized subjects were not clinically evaluable (31/206 [15%] subjects in the trovafoxacin group and 15/214 [7%] subjects in the clarithromycin group). The most common reasons for exclusion from the clinically evaluable efficacy analyses were insufficient therapy due to early discontinuation from treatment or study (23/206 [11%], trovafoxacin and 11/214 [5%], clarithromycin). Other reasons were randomized but not treated, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness.

In addition, 13 randomized subjects (6%) in the trovafoxacin and 11 randomized subjects (5%) in the clarithromycin treatment groups had an inappropriate baseline diagnosis (negative baseline x-ray) and were therefore excluded from both the clinical intent-to-treat and the clinically evaluable analyses.

Discontinuations

Of the 417 treated subjects, 78 subjects were prematurely discontinued from treatment as summarized in Table 5b.2.

Table 5b.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)			
	Trovafloxacin 200 mg (N=203)	Clarithromycin 500 mg BID (N=214)	Total (N=417)
Number and Percentage (%) of Subjects			
Total Discontinued	45 (22%)	33 (15%)	78 (19%)
Discontinuations Related to Study Drug:	32 (16%)	16 (7%)	48 (12%)
Adverse Event	28 (14%)	11 (5%)	39 (9%)
Insufficient Clinical Response	4 (2%)	5 (2%)	9 (2%)
Discontinuations Unrelated to Study Drug:	13 (6%)	17 (8%)	30 (7%)
Adverse Event	4 (2%)	1 (<1%)	5 (1%)
Did Not Meet Randomization Criteria	9 (4%)	9 (4%)	18 (4%)
Laboratory Abnormality	0	1 (<1%)	1 (<1%)
Other	0	1 (<1%)	1 (<1%)
Withdrew Consent	0	5 (2%)	5 (1%)

Reviewer's Note: A significantly higher proportion of trovafloxacin patients discontinued due to adverse events (14% of trovafloxacin patients versus 5% of clarithromycin patients, $p=0.002$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Demographics

The two treatment groups were comparable with respect to age, race, weight, smoking classification and the distribution of males and females. The distribution of subjects according to smoking classification was similar between the trovafloxacin and clarithromycin groups (20% and 23% ex-smoker, 57% and 50% never smoked, and 23% and 27% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for subjects in the intent-to-treat analysis was acute sinusitis. The median (range) duration since onset of acute sinusitis was 8 days (1-29 days) for subjects in the trovafloxacin group and 7 days (1-38 days) for subjects in the clarithromycin group. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the two treatment groups with respect to medical history at baseline.

Clinical Response

A summary of clinical response for clinically evaluable subjects at EOT and EOS is presented by treatment group in Table 5b.3. Clinical response was considered therapeutically equivalent between trovafloxacin and clarithromycin at both EOT and EOS.

Table 5b.3. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 200 mg (N=162)*	Clarithromycin 500 mg BID (N=188)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	161 (100%)	188 (100%)	
Success (Cure + Improvement)	136 (84%)	165 (88%)	(-10.6, 4.0)
Distribution of Clinical Response:			
Cure	67 (42%)	84 (45%)	
Improvement	69 (43%)	81 (43%)	
Failure	25 (16%)	23 (12%)	
End of Study:			
Number of Subjects Assessed	160 (100%)	184 (100%)	
Success (Cure + Improvement)	118 (74%)	138 (75%)	(-10.5, 8.0)
Distribution of Clinical Response:			
Cure	85 (53%)	112 (61%)	
Improvement	33 (21%)	26 (14%)	
Failure	25 (16%)	23 (13%)	
Relapse	17 (11%)	23 (13%)	
CI=confidence interval for the difference in rates, Trovafloxacin minus Clarithromycin a Subject 5077-0052 did not have an end of treatment assessment within the evaluable window.			

A summary of clinical response for ITT subjects at EOT and EOS is presented by treatment group in Table 5b.4. Clinical response was considered therapeutically equivalent between trovafloxacin and clarithromycin at both EOT and EOS.

Reviewer's Note: The intent-to-treat results are similar to the evaluable results, but with slightly lower success rates.

Table 5b.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Intent-to-Treat Subjects)			
	Trovafloxacin 200 mg (N=193)	Clarithromycin 500 mg BID (N=203)^a	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	193 (100%)	202 (100%)	
Success (Cure + Improvement)	154 (80%)	168 (83%)	(-11.0, 4.3)
Distribution of Clinical Response:			
Cure	72 (37%)	84 (42%)	
Improvement	82 (42%)	84 (42%)	
Failure	39 (20%)	34 (17%)	
End of Study Visit:			
Number of Subjects Assessed	193 (100%)	203 (100%)	
Success (Cure + Improvement)	135 (70%)	145 (71%)	(-10.5, 7.5)
Distribution of Clinical Response:			
Cure	94 (49%)	118 (58%)	
Improvement	41 (21%)	27 (13%)	
Failure	39 (20%)	35 (17%)	
Relapse	19 (10%)	23 (11%)	

^a Subject 5078-0238 was not assessed at the end of treatment.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 5b.5. Tables 5b.6 and 5b.7 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 5b.5. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg (N=203)	Clarithromycin 500 mg BID (N=214)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	119 (59%)	124 (58%)
Treatment-Related Adverse Events	76 (37%)	81 (38%)
Discontinuations Due to an Adverse Event^{a, b}	32 (16%)	12 (6%)
Clinically Significant Laboratory Abnormalities	17/197 (9%)	26/211 (12%)
a With the exception of four subjects in the trovafloxacin 200 mg group and one subject in the clarithromycin group who were discontinued due to unrelated adverse events, all subjects were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related. b One additional subject (5132-0426) in the trovafloxacin group had an unrelated adverse event (ischemic colon) for which the investigator action taken was treatment given; hospitalization for surgery; however, on the subject summary section of the case report form the investigator classified the reason for withdrawal from the study as adverse event.		

For subjects in the trovafloxacin group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the central and peripheral nervous system. Twenty-six subjects (26/203, 13%) in this group were discontinued due to dizziness, headache, vertigo, paresthesia, and/or hypoesthesia. Four subjects (4/214, 2%) in the clarithromycin group were discontinued due to headache, dizziness, paresthesia and/or hypertonia.

For subjects in the clarithromycin group, the most frequently occurring adverse events that led to discontinuation from treatment were those associated with the gastrointestinal system. Nine subjects (9/214, 4%) in the clarithromycin group were discontinued due to vomiting, nausea, diarrhea, coated tongue, abdominal pain and/or blood in stool. Thirteen subjects (13/203, 6%) in the trovafloxacin group were discontinued due to nausea, vomiting, tongue edema, diarrhea, abdominal pain, and/or loose stools.

All other adverse events leading to discontinuation were reported by three or less subjects in either treatment group.

One subject in the trovafloxacin group was discontinued from treatment due to interstitial nephritis (allergic) that was considered by the investigator to be related to study drug as described in the following narrative.

Subject 5083-0108, a 61 year-old white male with a history of chronic interstitial nephritis, confirmed by biopsy, proteinuria and mild renal insufficiency and a present diagnosis of acute sinusitis was treated with trovafloxacin 200 mg for 10 days. At baseline the subject's serum creatinine value was found to be elevated

and his urine protein finding Repeat serum creatinine values on Days 3 and 10 showed further increases The subject was discontinued from treatment on Day 14 due to what the investigator defined as mild interstitial nephritis (allergic) which was not confirmed by biopsy or any other procedure. On Day 17, decreases in serum creatinine and urine protein were noted.

Treatment with prednisone was initiated on Day 18 and this event was considered to be resolved on Day 25.

Table 5b.6. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)				
	Trovafloxacin 200 mg (N=203)		Clarithromycin 500 mg BID (N=214)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event^c	119	(59%)	124	(58%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	89	(44%)	36	(17%)
Dizziness	69	(34%)	5	(2%)
Headache	29	(14%)	27	(13%)
GASTROINTESTINAL SYSTEM	39	(19%)	52	(24%)
Nausea	23	(11%)	21	(10%)
Diarrhea	8	(4%)	12	(6%)
Abdominal Pain	5	(2%)	6	(3%)
Flatulence	3	(1%)	7	(3%)
Dyspepsia	1	(<1%)	7	(3%)
PSYCHIATRIC SYSTEM	13	(6%)	10	(5%)
Insomnia	5	(2%)	6	(3%)
REPRODUCTIVE SYSTEM	5	(2%)	5	(2%)
Vaginitis ^d	4	(3%)	3	(2%)
SPECIAL SENSES	12	(6%)	48	(22%)
Taste Perversion	2	(<1%)	44	(21%)
a ≥3 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.				

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Table 5b.7. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - Treatment-Related (All Treated Subjects)

	Trovafloxacin 200 mg (N=203)	Clarithromycin 500 mg BID (N=214)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event ^c	76 (37%)	81 (38%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	60 (30%)	10 (5%)
Dizziness	54 (27%)	4 (2%)
Headache	7 (3%)	4 (2%)
Parästhesia	4 (2%)	1 (<1%)
GASTROINTESTINAL SYSTEM	30 (15%)	39 (18%)
Nausea	19 (9%)	18 (8%)
Diarrhea	4 (2%)	10 (5%)
Abdominal Pain	4 (2%)	6 (3%)
Flatulence	2 (<1%)	5 (2%)
Vomiting	3 (1%)	4 (2%)
Dyspepsia	1 (<1%)	4 (2%)
REPRODUCTIVE SYSTEM	2 (<1%)	4 (2%)
Vaginitis ^d	2 (2%)	3 (2%)
SPECIAL SENSES	5 (2%)	41 (19%)
Taste Perversion	2 (<1%)	41 (19%)
a ≥ 2 % of subjects in any treatment group. b Includes data up to 7 days after last dose of active study medication. c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once. d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.		

Two subjects in each treatment group experienced serious adverse events unrelated to study drug. The outcome of one event (presumed myocardial infarction) in the clarithromycin group was death.

Subject 5090-0129 in the trovafloxacin group and Subject 5079-0219 in the clarithromycin group were discontinued from treatment due to elevated serum glucose values attributed to the subject's underlying diabetic condition and to thrombocytopenia of unknown etiology, respectively.

Sponsor's Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was statistically equivalent to clarithromycin 500 BID for 14 days for the treatment of acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 16% in the trovafloxacin group and 6% in the clarithromycin group. The overall percentage of adverse events was 59% in the trovafloxacin group and 58% in the clarithromycin group; treatment-related adverse events were also reported at similar rates (37% and 38%, respectively). Subjects in the trovafloxacin group had a lower percentage

of adverse events associated with the special senses (6% versus 22%), and a higher percentage of adverse events associated with the central and peripheral nervous system (44% versus 17%) compared to the clarithromycin group; all other adverse events were reported at similar rates for both treatment groups. The most commonly reported adverse events were dizziness and taste perversion in the trovafloxacin and clarithromycin groups, respectively. The frequency and type of adverse laboratory events were comparable between the two treatment groups.

Reviewer's Summary and Conclusion: *A greater number of patients in the trovafloxacin arm were excluded from the evaluable efficacy analysis ($p=0.025$), due largely to the greater number of patients who discontinued treatment due to an adverse event in the trovafloxacin arm ($p=0.002$). However, clinical response for trovafloxacin 200 mg once daily for 10 days was therapeutically equivalent to clarithromycin 500 mg BID for 14 days at both EOT and EQS for both the clinically evaluable and ITT patient group.*

Central and peripheral nervous system adverse events were the most frequently occurring adverse events that led to discontinuation from treatment with trovafloxacin. Twenty-six trovafloxacin subjects (26/203, 13%) were discontinued due to dizziness, headache, vertigo, paresthesia, and/or hypoesthesia, compared to only four clarithromycin subjects (4/214, 2%) who discontinued due to headache, dizziness, paresthesia and/or hypertonia ($p<0.0001$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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V.C. Protocol 154-138

A RANDOMISED, OPEN, MULTI-CENTRE TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (200 MG ONCE DAILY) WITH ORAL AMOXYCILLIN/CLAVULANATE (AUGMENTIN, 500/125 MG TID) FOR THE TREATMENT OF ACUTE SINUSITIS.

Reviewer's Note: *"Open" is used here to indicate that the trial is unblinded.*

Study Dates: 25 May 1995 - 11 April 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to amoxicillin/clavulanate in the treatment of subjects with acute sinusitis.

Study Design: Study 154-138 was a randomized, unblinded, comparative, multicenter trial of trovafloxacin administered orally for 10 days versus amoxicillin/clavulanate administered orally for 10 days for the treatment of acute sinusitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 18 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray, were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection). Bacteriologic response was not uniformly assessed in this trial

(bacteriologic assessment was not required in the protocol, thus data were collected on only a few patients).

Clinical response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), the end of treatment (Visit 3, Day 11), and at the end of study (Visit 4, Day 24) or at the time of discontinuation from study. Clinical evaluation of response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point and compared to the pretreatment assessment. Clinical assessment was to be based upon resolution or improvement of clinical and laboratory signs of infection such as improvement in post-nasal discharge, facial pain, hyposmia, jaw pain with mastication, and nasal congestion and improvement or resolution of positive sinus x-ray findings. The clinical response was to be classified as cure (resolution of signs and symptoms of acute sinusitis to a baseline level that existed prior to the occurrence of the acute illness and improvement in x-ray findings), improvement (improvement but incomplete resolution of signs and symptoms to the level that existed before baseline and no requirement for an additional antibiotic), or failure (lack of resolution or worsening of any of the signs and symptoms of acute sinusitis or a need for an additional antibiotic).

The primary efficacy endpoint was the sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were the investigator-defined clinical response at EOT, and sponsor- and investigator-defined clinical response at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy:

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Analysis Groups

Table 5c.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

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Table 5c.1. Evaluation Groups

Evaluation Groups:	Trovafloracin (200 mg/day)	Amoxicillin/Clavulanate (500/125 mg TID)
Entered Study ^a	207	211
All Treated	205 (100%)	209 (100%)
Completed Study	191 (93%)	201 (96%)
Completed Treatment	189 (92%)	196 (94%)
Evaluated for Efficacy ^b		
Clinical Intent-to-treat	202 (98%)	211 (100%)
Clinically Evaluable	189 (91%)	203 (96%)
Assessed for Safety		
Adverse Events	205 (100%)	209 (100%)
Laboratory Tests	200 (98%)	206 (99%)

a Subjects who were randomized.

b Evaluability was determined at end of treatment.

Reviewer's Note: A significantly lower percentage of trovafloxacin patients were included in the evaluable efficacy analysis ($p = 0.025$ using the test of equal proportions based on the normal approximation to the binomial distribution). Intent-to-treat efficacy results will be presented below, in addition to evaluable efficacy results.

Of the 207 trovafloxacin and 211 amoxicillin/clavulanate randomized subjects, five trovafloxacin subjects (Subjects 5274-0053, 5278-0526, 5703-0338, 5723-0253, and 6462-0160) and no amoxicillin/clavulanate subject had an inappropriate baseline diagnosis (i.e., no acute sinusitis at baseline as defined by the study protocol) and were excluded from all clinical intent-to-treat and evaluable analyses.

Of the 202 trovafloxacin and 211 amoxicillin/clavulanate clinically intent-to-treat subjects, 13 in the trovafloxacin group and 8 in the amoxicillin/clavulanate were not clinically evaluable; therefore, 189 subjects in the trovafloxacin group and 203 subjects in the amoxicillin/clavulanate group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (9/207 [4%], trovafloxacin and 5/211 [2%], amoxicillin/clavulanate). Other reasons were randomized but not treated, no post-baseline clinical assessments, no post-baseline clinical response in evaluable window, prior antibiotic therapy, and concomitant antibiotic therapy for intercurrent illness.

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Discontinuations

Of the 205 trovafloxacin and 209 amoxicillin/clavulanate treated subjects, 16 trovafloxacin subjects and 13 amoxicillin/clavulanate subjects were prematurely discontinued from treatment as summarized in Table 5c.2.

Reviewer's Note: A higher percentage of trovafloxacin patients discontinued due to adverse events, although this difference did not reach statistical significance ($p = 0.09$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 5c.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)		
	Trovafloxacin 200 mg (N=205)	Amoxicillin/Clavulanate 500/125 mg TID (N=209)
	Number and Percentage (%) of Subjects	
Total Discontinued	16 (8%)	13 (6%)
Discontinuations Related to Study Drug:	15 (7%)	6 (3%)
Adverse Event	13 (6%)	6 (3%)
Insufficient Response	2 (<1%)	0
Discontinuations Unrelated to Study Drug:	1 (<1%)	7 (3%)
Adverse Event	1 (<1%)	0
Laboratory Abnormality	0	1 (<1%)
Lost To Follow-Up	0	1 (<1%)
Other	0	2 (<1%)
Withdrawn Consent	0	3 (1%)

Demographics

One hundred-two (102) of the 205 treated trovafloxacin subjects (50%) were males and 103 (50%) were females and 86 of the 209 treated amoxicillin/clavulanate subjects (41%) were males and 123 (59%) were females. The males and females in the trovafloxacin and amoxicillin/clavulanate treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the trovafloxacin and amoxicillin/clavulanate treatment groups (21% and 23% ex-smoker, 45% and 49% never smoked, and 34% and 28% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The median (range) duration since onset of sinusitis was 6 days (1-28 days) for clinically evaluable and intent-to-treat subjects in both the trovafloxacin and amoxicillin/clavulanate groups. There were no marked differences between subjects in the trovafloxacin and amoxicillin/clavulanate groups with respect to medical history at baseline.

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Clinical Response

A summary of sponsor-defined clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 5c.3. Clinical response was considered therapeutically equivalent between trovafloxacin and amoxicillin/clavulanate at both EOT and EOS.

Table 5c.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Trovafloxacin 200 mg (N=189)		Amoxicillin/Clavulanate 500/125 mg TID (N=203)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed ^a	188	(100%)	201	(100%)	
Success (Cure + Improvement)	181	(96%)	186	(93%)	(-0.8, 8.3)
Distribution of Clinical Response:					
Cure	90	(48%)	80	(40%)	
Improvement	91	(48%)	106	(53%)	
Failure	7	(4%)	15	(7%)	
End of Study:					
Number of Subjects Assessed	175	(100%)	196	(100%)	
Success (Cure + Improvement)	158	(90%)	175	(89%)	(-5.2, 7.2)
Distribution of Clinical Response:					
Cure	123	(70%)	125	(64%)	
Improvement	35	(20%)	50	(26%)	
Failure	7	(4%)	15	(8%)	
Relapse	10	(6%)	6	(3%)	
^a Three subjects (1 trovafloxacin; 2 amoxicillin/clavulanate) had a missing assessment at end of treatment but were assessed at end of study.					

A summary of sponsor-defined clinical response for ITT subjects at the end of treatment and at the end of study is presented by treatment group in Table 5c.4. Clinical response was

considered therapeutically equivalent between trovafloxacin and amoxicillin/clavulanate at both EOT and EOS.

Reviewer's Note: The intent-to-treat results are similar to the evaluable results, with slightly lower success rates.

Table 5c.4. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Intent-to-Treat Subjects)

	Trovafloxacin 200 mg (N=202)		Amoxicillin/ Clavulanate 500/125 mg TID (N=211)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed ^a	202	(100%)	210	(100%)	
Success (Cure + Improvement)	191	(95%)	191	(91%)	(-1.4, 8.6)
Distribution of Clinical Response:					
Cure	93	(46%)	82	(39%)	
Improvement	98	(49%)	109	(52%)	
Failure	11	(5%)	19	(9%)	
End of Study Visit:					
Number of Subjects Assessed	202	(100%)	211	(100%)	
Success (Cure + Improvement)	180	(89%)	186	(88%)	(-5.2, 7.1)
Distribution of Clinical Response:					
Cure	136	(67%)	132	(63%)	
Improvement	44	(22%)	54	(26%)	
Failure	11	(5%)	19	(9%)	
Relapse	11	(5%)	6	(3%)	
a One subject in the amoxicillin/clavulanate group had a missing assessment at the end of treatment but was assessed at the end of study.					

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Bacteriologic Response

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Sixteen (16) trovafloxacin and 14 amoxicillin/clavulanate clinically intent-to-treat subjects had trans-antral aspiration of the sinus performed at baseline. All 16 trovafloxacin subjects with pathogens isolated at baseline had a sponsor-defined clinical response of cure or improved at EOT. At EOS, 12 of the 16 subjects were designated as clinically cured or improved and four subjects had a clinical response of relapse. These four subjects had one or more of the following pathogens isolated at baseline: *Staphylococcus aureus*, *H. influenzae*, *Acinetobacter sp.*, *Fusobacterium nucleatum*, *Prevotella sp.*, and/or *Streptococcus anginosus*. The baseline pathogen was not present on repeat culture in three of the four subjects; in the remaining subject *Prevotella sp.* was still present. In the amoxicillin/clavulanate group, ten of the 14 subjects with pathogens isolated at baseline had a sponsor-defined clinical response of cure or improved at EOT and EOS and four subjects were designated as clinical failures at both EOT and EOS. These four subjects had one or more of the following pathogens isolated at baseline: *Fusobacterium sp.*, *Veillonella sp.*, *Acinetobacter sp.*, *E. agglomerans*, *Peptostreptococcus sp.* and/or *K. pneumoniae*. None of the four subjects designated as a clinical failure had a repeat culture.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 5c.5. Tables 5c.6 and 5c.7 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 5c.5. Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 200 mg	Amoxicillin/ Clavulanate 500/125 mg TID
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	77/205 (38%)	62/209 (30%)
Treatment-Related Adverse Events	52/205 (25%)	48/209 (23%)
Discontinuations From Treatment Due to an Adverse Event	15/205 (7%)	7/209 (3%)
Clinically Significant Laboratory Abnormalities	38/200 (19%)	56/206 (27%)

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Reviewer's Note: Trovafloxacin patients reported a higher number of adverse events (all causalities) than did amoxicillin/clavulanate patients, although this difference did not reach statistical significance ($p = 0.09$ using the test of equal proportions based on the normal approximation to the binomial distribution). Amoxicillin/clavulanate patients experienced a significantly higher number of clinically significant laboratory abnormalities ($p = 0.05$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 5c.6. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)		
	Trovafloxacin (N=205)	Amoxicillin/ Clavulanate (N=209)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	77 (38%)	62 (30%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	46 (22%)	9 (4%)
Dizziness	34 (17%)	2 (<1%)
Headache	15 (7%)	4 (2%)
GASTROINTESTINAL SYSTEM	19 (9%)	43 (21%)
Diarrhea	1 (<1%)	19 (9%)
Dyspepsia	0	6 (3%)
Nausea	9 (4%)	9 (4%)
REPRODUCTIVE SYSTEM	1 (<1%)	6 (3%)
Vaginitis ^c	1 (<1%)	5 (4%)

a ≥3% of subjects in either treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Preferred term is gender-specific; the percentages are based on the number of males and females, appropriately.

Table 5c.7. Summary of the Most Commonly Reported Adverse Events ^{a,b} by Body System - Treatment-Related (All Treated Subjects)		
	Trovafloxacin (N=205)	Amoxicillin/ Clavulanate (N=209)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	52 (25%)	48 (23%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM		
Dizziness	36 (18%)	4 (2%)
Headache	30 (15%)	2 (<1%)
	9 (4%)	1 (<1%)
GASTROINTESTINAL SYSTEM	11 (5%)	39 (19%)
Diarrhea	1 (<1%)	19 (9%)
Dyspepsia	0	6 (3%)
Nausea	6 (3%)	9 (4%)
REPRODUCTIVE SYSTEM	1 (<1%)	6 (3%)
Vaginitis ^c	1 (<1%)	5 (4%)
a ≥2% of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication. c Preferred term is gender-specific and the percentages are based on the number of males and females, appropriately.		

No deaths were reported during this study. One subject in the trovafloxacin group had a serious adverse event (intentional overdose with Co-proxamol), which occurred ten days after the last treatment dose and led to hospitalization. This serious adverse event was attributed to reactive depression and was noted as having resolved. No serious adverse events were reported during this study for any subject in the amoxicillin/clavulanate group.

Sponsor’s Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was statistically equivalent to amoxicillin/clavulanate 500/125 mg three times daily for 10 days for clinical success rates at the end of treatment in subjects with acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 7% in the trovafloxacin group and 3% in the amoxicillin/clavulanate group. The overall percentage of all and treatment-related adverse events for subjects in the trovafloxacin group was comparable to that of subjects in the amoxicillin/clavulanate group (38% and 25% versus 30% and 23%, respectively). The most commonly reported treatment-related adverse events were dizziness in the trovafloxacin group and diarrhea in the amoxicillin/clavulanate group.

Reviewer’s Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was therapeutically equivalent to amoxicillin/clavulanate 500/125 mg three times daily for 10 days in terms of clinical success rates at both EOT (the primary efficacy endpoint) and EOS. This was true for both the evaluable and ITT patient group (recall that a significantly higher number of trovafloxacin patients were excluded from the evaluable efficacy analysis, $p = 0.025$).

Safety appears acceptable, although dizziness was noted in a number of patients (17%, regardless of relationship to treatment).

VI. UNCOMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

The efficacy and safety of oral trovafloxacin in the treatment of uncomplicated skin infections was assessed in two double-blind, comparative trials. The comparator agents were flucloxacillin (154-129) and cefpodoxime (154-130).

Reviewer's Note: The sponsor assessed whether efficacy differed in various subgroups in the uncomplicated skin and skin structure infection trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, race, and age.

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VI.A. Protocol 154-129

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND FLUCLOXACILLIN (500 MG QID) FOR THE TREATMENT OF UNCOMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE

Study Dates: 10 July 1995 - 10 January 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to that of flucloxacillin in the treatment of subjects with uncomplicated infections of the skin and skin structure.

Study Design: Study 154-129 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg daily as a single dose) administered orally for 7 days versus flucloxacillin (2000 mg daily as 500 mg every 6 hours), administered orally for 7 days for the treatment of uncomplicated infections of the skin and skin structure.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 16 years of age at the baseline assessment, with clinically documented uncomplicated infection of the skin or skin structure.

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Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical signs and symptoms of infection) and bacteriologic response (individual pathogen response).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment visit (Visit 2, Day 8), and at the end of study (Day 30) or at the time of discontinuation from study. Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection including erythema, pain, induration or swelling and general condition. The clinical response was to be classified as cure (resolution of signs and symptoms to the level that existed before baseline), improvement (incomplete resolution of signs and symptoms to the level that existed before baseline and no

requirement for additional antibiotics), or failure (lack of resolution and or a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment visit (Visit 2, Day 8), and the end of study (Day 30) or at the time of discontinuation from study. Subject bacteriological response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence or relapse; however, the protocol was amended to not include the analysis of subject bacteriological response. Instead, each pathogen was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence or relapse.

For all infections except cellulitis, culturable material was to be obtained at Visit 1. For simple abscesses and minor wound infections, the exudate was to be cultured. For impetiginous lesions, a swab was adequate. For cellulitis, an attempt was to be made to aspirate from the margin of the infected area if no other culturable material (e.g., an exudate from a vesicle) was present. If the location and type of uncomplicated skin or skin structure infection consistent with a possible anaerobic infection, e.g., a perianal abscess, anaerobic cultures were to be performed.

The primary efficacy endpoint was sponsor-defined clinical response at EOT;

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS.
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

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Reviewer's Note: Since the EOT visit is only a day or so after treatment was discontinued, this reviewer will place more emphasis on the clinical response rates at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

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Analysis Groups

Table 6a.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

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Table 6a.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg/day)	Flucloxacillin (500 mg QID)
Entered Study ^a	141 (100%)	139 (100%)
All Treated	140 (>99%)	138 (>99%)
Completed Treatment	128 (91%)	133 (96%)
Completed Study	135 (96%)	135 (98%)
Evaluated for Efficacy		
Clinical Intent-to-treat	141 (100%)	139 (100%)
Clinically Evaluable ^b	130 (92%)	133 (96%)
Bacteriological Intent-to-Treat	81 (57%)	86 (62%)
Bacteriologically Evaluable ^b	76 (54%)	83 (60%)
Assessed for Safety		
Adverse Events	140 (100%)	138 (100%)
Laboratory Tests	128 (91%)	132 (96%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Of the 141 trovafloxacin and 139 flucloxacillin clinical ITT subjects, 11 subjects in the trovafloxacin group and six subjects in the flucloxacillin group were not clinically evaluable; therefore, 130 trovafloxacin and 133 flucloxacillin subjects were clinically evaluable. The most common reason for exclusion from the clinically evaluable efficacy analyses was insufficient therapy (8/141 [6%], trovafloxacin and 4/139 [3%], flucloxacillin). Other reasons were randomized but not treated, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical assessment and no post-baseline clinical assessment within the evaluable window.

Of the 141 trovafloxacin and 139 flucloxacillin clinical ITT subjects, 60 subjects in the trovafloxacin group and 53 subjects in the flucloxacillin group had negative baseline cultures; therefore, 81 trovafloxacin and 86 flucloxacillin subjects were included in the bacteriological ITT analyses.

Of the 130 trovafloxacin and 133 flucloxacillin clinically evaluable subjects, 54 subjects in the trovafloxacin group and 50 subjects in the flucloxacillin group were not included in the bacteriologically evaluable analyses; therefore, 76 trovafloxacin subjects and 83 flucloxacillin subjects were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (54/141 [38%], trovafloxacin and 50/139 [36%], flucloxacillin). Other reasons were no post-baseline culture or baseline culture outside the evaluability window.

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Discontinuations

Of the 140 trovafloxacin and 138 flucloxacillin treated subjects, 12 trovafloxacin and five flucloxacillin subjects were prematurely discontinued from treatment as summarized in Table 6a.2.

Table 6a.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Trovafloxacin 100 mg (N=140)		Flucloxacillin 500 mg QID (N=138)	
	Number and Percentage (%) of Subjects			
Total Discontinued	12	(9%)	5	(4%)
Discontinuations Related to Study Drug:	9	(6%)	4	(3%)
Adverse Event	8	(6%)	3	(2%)
Insufficient Clinical Response	1	(<1%)	1	(<1%)
Discontinuations Unrelated to Study Drug:	3	(2%)	1	(<1%)
Adverse Event	2	(1%)	0	
Lost to Follow-up	1	(<1%)	1	(<1%)

Reviewer's Note: A marginally higher number of trovafloxacin patients discontinued treatment prematurely (p=0.09 using the test of equal proportions based on the normal approximation to the binomial distribution).

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Demographics

Sixty-nine (69) of the 140 treated trovafloxacin subjects (49%) were males and 71 were females (51%) and 70 of the 138 treated flucloxacillin subjects (51%) were males and 68 were females (49%). The males and females in the trovafloxacin and flucloxacillin treatment groups were generally comparable with respect to age, race, and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects. The mean age of subjects in the trovafloxacin and flucloxacillin groups was 44.1 years and 47.3 years, respectively. Sixteen percent of subjects in the trovafloxacin group and 25% of subjects in the flucloxacillin group were ≥65 years of age.

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The primary diagnosis for clinical ITT subjects was uncomplicated skin and skin structure infection. The median duration since onset of infection was 4 days in each treatment group. Subject 5278-0178 in the flucloxacillin group had a reported duration since onset of infection (cellulitis) of 227 days; however, this included multiple episodes of infection. The subject's actual duration for the most recent onset of cellulitis was 46 days.

The most commonly reported type of infection reported among clinical ITT subjects in both treatment groups was simple abscess (28, trovafloxacin and 24, flucloxacillin). Other types of infections included impetiginous lesion, minor wound infection, otitis externa, cellulitis with and without a baseline pathogen, paronychia, leg ulcers and others (including infected burn, ingrown toenail, insect bite, superficial ulcers, dyshidrosis, erysipelas, pyodermal vegetans, infected serbareous cyst or bedsores). All types of infections were reported at similar rates in both treatment groups. Similar results were observed for clinically evaluable subjects.

The majority of clinical ITT subjects in both treatment groups did not require a surgical drainage procedure at baseline or during the study. Fourteen (14) trovafloxacin subjects and nine flucloxacillin subjects had skin infections that required surgical intervention at baseline and five trovafloxacin subjects and four flucloxacillin subjects had skin infections that required surgical intervention post-baseline. Subject 6080-0239 in the flucloxacillin group had a surgical procedure done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report form. Subject 6141-0267 in the trovafloxacin group had a skin infection that required surgical intervention both at baseline and post-baseline. The most commonly reported type of skin infection for subjects requiring surgical intervention in both treatment groups was simple abscess (11/18 [61%], trovafloxacin and 6/13 [60%], flucloxacillin).

A summary of type of skin infection at baseline and number of subjects with a surgical drainage procedure is presented for clinical ITT subjects in Table 6a.3.

Table 6a.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT Subjects)

	Trovafloxacin 100 mg (N=141)	Flucloxacillin 500 mg QID (N=139)
Type of Infection^a	Number and Percentage (%) of Subjects	
Simple Abscess	28 (20%)	24 (17%)
Impetiginous Lesion	23 (16%)	24 (17%)
Minor Wound	17 (12%)	21 (15%)
Cellulitis with a Baseline Pathogen	12 (9%)	19 (14%)
Cellulitis without a Baseline Pathogen	19 (13%)	19 (14%)
Otitis Externa	19 (13%)	19 (14%)
Paronychia	16 (11%)	11 (8%)
Leg Ulcers	8 (6%)	3 (2%)
Other	11 (8%)	12 (9%)
Subjects Requiring Surgical Intervention	18 (12%)	13 ^b (9%)
At Baseline	14 (9%)	9 (6%)
Post-Baseline	5 (3%)	3 (2%)
Before the EOT Assessment	4 (2%)	2 (1%)
After the EOT Assessment	1 (<1%)	1 (<1%)

a A subject may have had more than one type of infection.
 b Subject 6080-0239 had a surgical procedure done post-baseline. The type and timing of the procedure was not listed on the subject's case report form.

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There were no marked differences between subjects in the trovafloxacin and flucloxacillin groups with respect to medical history at baseline. A small percentage of subjects in each treatment group (3%, trovafloxacin; 2%, flucloxacillin) had diabetes mellitus without reported complication at baseline.

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Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 6a.4. Trovafloxacin was considered therapeutically equivalent to flucloxacillin at both EOT and EOS.

Table 6a.4. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 100 mg (N=130)	Flucloxacillin 500 mg QID (N=133)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment			
Number of Subjects Assessed ^a	129 (100%)	133 (100%)	
Success (Cure + Improvement)	117 (91%)	115 (86%)	(-3.4, 11.9)
Distribution of Clinical Response:			
Cure	72 (56%)	60 (45%)	
Improvement	45 (35%)	55 (41%)	
Failure	12 (9%)	18 (14%)	
End of Study			
Number of Subjects Assessed	125 (100%)	123 (100%)	
Success (Cure + Improvement)	106 (85%)	97 (79%)	(-3.6, 15.5)
Distribution of Clinical Response:			
Cure	97 (78%)	92 (75%)	
Improvement	9 (7%)	5 (4%)	
Failure	12 (10%)	18 (15%)	
Relapse	7 (6%)	8 (7%)	

a Subject 5895-0252 in the trovafloxacin group was not assessed at the end of treatment visit.

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogen (*S. aureus*) among clinically evaluable subjects is presented by treatment group in Table 6a.5.

Table 6a.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)				
	Trovafloxacin 100 mg (N=130)	Flucloxacillin 500 mg QID (N=133)	Trovafloxacin 100 mg (N=125)	Flucloxacillin 500 mg QID (N=123)
Number of Subjects				
Pathogen	End of Treatment		End of Study	
<i>S. aureus</i>	39/42 (93%)	42/47 (89%)	34/40 (85%)	33/42 (79%)

a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

When sponsor-defined clinical response was subset by type of baseline infection (simple abscess, impetiginous lesion, minor wound infection, cellulitis with and without a baseline pathogen, otitis externa, paronychia, leg ulcers, or other) in clinical ITT subjects, a trend towards a higher (≥10 percentage points) clinical success rate at EOT and EOS was observed among subjects with a simple abscess in the trovafloxacin group (26/28, 93% and 25/28, 89%, respectively) compared to the flucloxacillin group (19/24, 79% and 19/24, 79%, respectively). In subjects with impetiginous lesion, similar results were observed between the

two treatment groups at the end of treatment (trovafloxacin: 22/23, 96%; flucloxacillin: 22/24, 92%), but a higher clinical success rate was observed in the trovafloxacin group at the end of study (trovafloxacin: 22/23, 96%; flucloxacillin: 19/24, 79%). Similar clinical success rates were observed between the two treatment groups for subjects with the other types of infection (minor wound infection, cellulitis with and without a baseline pathogen, otitis externa, paronychia, leg ulcers, or other); however, due to the small number of subjects in each treatment group no definitive conclusions can be drawn.

A summary of clinical success rates for clinical ITT subjects subset by type of infection at baseline at the end of treatment and at the end of study is presented by treatment group in Table 6a.6.

	Trovafloxacin 100 mg (N=141)		Flucloxacillin 500 mg QID (N=139)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection ^a	EOT	EOS	EOT	EOS
Simple Abscess	26/28 (93%)	25/28 (89%)	19/24 (79%)	19/24 (79%)
Impetiginous Lesion	22/23 (96%)	22/23 (96%)	22/24 (92%)	19/24 (79%)
Minor Wound Infection	14/15 (93%)	15/17 (88%)	20/21 (95%)	19/21 (90%)
Cellulitis Without a Baseline Pathogen	16/19 (84%)	16/19 (84%)	16/19 (84%)	15/19 (79%)
Cellulitis With a Baseline Pathogen	11/12 (92%)	10/12 (83%)	17/19 (89%)	16/19 (84%)
Otitis Externa	15/19 (79%)	14/19 (74%)	16/19 (84%)	13/19 (68%)
Paronychia	15/15 (100%)	14/16 (88%)	10/11 (91%)	10/11 (91%)
Leg Ulcers	3/8 (38%)	1/8 (13%)	2/3 (67%)	2/3 (67%)
Other	9/11 (82%)	8/11 (73%)	8/12 (67%)	7/12 (58%)

^a A subject may have had more than one type of infection at baseline.

Reviewer’s Note: Although the numbers are small, trovafloxacin did not appear very effective against leg ulcers. Only 1 of 8 patients (13%) was considered a clinical success at EOS.

When sponsor-defined clinical response was subset by timing of surgical intervention in clinical ITT subjects, similar success rates were observed between treatment groups at both the end of treatment and at the end of study, for subjects with no surgical intervention. Among subjects with surgical intervention at baseline or surgical intervention before or after the end of treatment, subject subsets were too small for any definitive conclusions to be drawn.

A summary of clinical success rates for clinical ITT subjects subset by timing of surgical intervention at the end of treatment and at the end of study is presented by treatment group in Table 6a.7.

Table 6a.7. Summary of Sponsor-Defined Clinical Success Rates Subset by Timing of Surgical Intervention (Clinical ITT Subjects)

	Trovafloxacin 100 mg (N=141)		Flucloxacillin 500 mg QID (N=139)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Timing of Surgical Intervention ^a	EOT		EOS	
No Surgical Intervention	106/120 (88%)	102/123 (83%)	109/126 (87%)	102/126 (81%)
Surgical Intervention at Baseline	13/14 (93%)	13/14 (93%)	8/9 (89%)	7/9 (78%)
Surgical Intervention Post Baseline				
Before the EOT Assessment	1/4 (25%)	1/4 (25%)	1/2 (50%)	1/2 (50%)
After the EOT Assessment	1/1 (100%)	1/1 (100%)	1/1 (100%)	0

a Subjects may have had surgical intervention at more than one timepoint.

Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects were similar between the two treatment groups for the most frequently isolated pathogen (*S. aureus*) at the end of treatment and the end of study as presented in Table 6a.8.

Table 6a.8. A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Trovafloxacin 100 mg (N=76)	Flucloxacillin 500 mg QID (N=83)	95% CI	Trovafloxacin 100 mg (N=69)	Flucloxacillin 500 mg QID (N=76)	95% CI
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>S. aureus</i>	26/42 (62%)	31/46 (67%)	-25.5, 14.5	32/38 (84%)	33/42 (79%)	-11.3, 22.6

a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuations from treatment due to adverse events and clinically significant laboratory values is presented in Table 6a.9. Tables 6a.10 and 6a.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

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Table 6a.9 A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin 100 mg (N=140)	Flucloxacillin 500 mg QID (N=138)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	31/140 (22%)	27/138 (20%)
Treatment-Related Adverse Events	13/140 (9%)	18/138 (13%)
Discontinuations from Treatment Due to an Adverse Event	12/140 (9%)	3/138 (2%)
Discontinuations Due to a Treatment-Related Adverse Event	8/140 (6%)	3/138 (2%)
Clinically Significant Laboratory Abnormalities	21/128 (16%)	16/132 (12%)

Reviewer's Note: A significantly higher proportion of trovafloxacin patients discontinued treatment due to an adverse event (12/140 = 9% trovafloxacin patients versus 3/138 = 2% flucloxacillin patients; $p = 0.03$ using Fisher's exact test).

Table 6a.10. A Summary of the Most Commonly Reported Adverse Events ^{a,b} by Body System - All Causalities (All Treated Subjects)		
	Trovafloxacin 100 mg (N=140)	Flucloxacillin 500 mg QID (N=138)
Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event	31 (22%)	27 (20%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	9 (6%)	3 (2%)
Dizziness	4 (3%)	1 (<1%)
Headache	5 (4%)	2 (1%)
GASTROINTESTINAL SYSTEM	11 (8%)	16 (12%)
Dyspepsia	1 (<1%)	7 (5%)
Nausea	4 (3%)	4 (3%)
Vomiting	4 (3%)	2 (1%)
URINARY SYSTEM	2 (1%)	5 (4%)
Urinary Tract Infection	0 (0%)	4 (3%)

a ≥ 3 % of subjects in any treatment group.
 b Includes data up to 7 days after last dose of active study medication

Reviewer's Note: Higher proportions of flucloxacillin patients experienced dyspepsia and urinary tract infections; the difference in dyspepsia rates was statistically significant (< 1% trovafloxacin patients vs. 5% flucloxacillin patients; $p = 0.04$ using Fisher's exact test), the difference in urinary tract infection rates was marginally statistically significant (0% trovafloxacin vs. 3% flucloxacillin; $p = 0.06$ using Fisher's exact test).

Table 6a.11. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)		
	Trovafloxacin 100 mg (N=140)	Flucloxacillin 500 mg QID (N=138)
Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event	13 (9%)	18 (13%)
BODY SYSTEM WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	7 (5%)	0
Dizziness	3 (2%)	0
Headache	4 (3%)	0
GASTROINTESTINAL SYSTEM	7 (5%)	15 (11%)
Dyspepsia	1 (<1%)	7 (5%)
Nausea	2 (1%)	3 (2%)
Vomiting	3 (2%)	2 (1%)
a ≥2 % of subjects in any treatment group.		
b Includes data up to 7 days after last dose of active study medication.		

Four subjects, (3 subjects in the trovafloxacin group and 1 subject in the flucloxacillin group) had serious adverse events. All serious adverse events were attributed to other illnesses or the disease under study.

One subject in the trovafloxacin group had acute renal failure during this study as summarized in the following narrative.

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Trovafloxacin 100 mg

Subject 5884-0040, an 82-year-old white male with a history of cerebrovascular disease, asthma, Parkinson's Disease, and Paget's disease, and a primary diagnosis of uncomplicated skin and skin structure infection of the left great toe, received trovafloxacin (100 mg) once daily for 7 days. On Day 8, the subject had elevated creatinine and urea

values; baseline creatinine and urea values were unavailable for this subject. On Day 11, the subject was diagnosed with acute renal failure, which was considered by the investigator to be mild in intensity and not related to study drug. On Day 29, this subject had a repeat creatinine value that was within the normal range and a urea value that had decreased but was still above the normal range. This adverse event (acute renal failure) was listed as still present at the end of study.

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There were no deaths reported during the study.

Sponsor Summary and Conclusion: Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to flucloxacillin 500 mg every six hours for 7 days for clinical success rates at the end of treatment and the end of study for both intent-to-treat and evaluable subjects in subjects with uncomplicated skin and skin structure infection. Pathogen eradication rates were comparable for the most frequently isolated pathogen of (*S. aureus*) between treatment groups at the end of treatment and the end of study.

The percentage of subjects discontinued from treatment due to treatment-related adverse events was 6% in the trovafloxacin group and 2% in the flucloxacillin group. The overall percentage of adverse events was 22% in the trovafloxacin group and 20% in the flucloxacillin group; treatment-related adverse events were reported in 9% and 13% of subjects, respectively. The most commonly reported treatment-related adverse events in the trovafloxacin group were dizziness, headache, and vomiting. The most commonly reported treatment-related adverse events in the flucloxacillin group were dyspepsia and nausea.

Reviewer's Summary and Conclusion: *Trovafloxacin 100 mg once daily for 7 days demonstrated therapeutic equivalence to flucloxacillin 500 mg every six hours for 7 days for clinical success rates at both EOT and EOS. Of note, although the numbers are small, trovafloxacin did not appear very effective against leg ulcers (only 1/8 = 13% patients was considered a clinical success at EOS).*

A significantly higher proportion of trovafloxacin patients discontinued treatment due to an adverse event (12/140 = 9% trovafloxacin patients versus 3/138 = 2% flucloxacillin patients; $p = 0.03$ using Fisher's exact test). Higher proportions of flucloxacillin patients experienced dyspepsia and urinary tract infections; the difference in dyspepsia rates was statistically significant (< 1% trovafloxacin patients vs. 5% flucloxacillin patients; $p = 0.04$ using Fisher's exact test), the difference in urinary tract infection rates was marginally statistically significant (0% trovafloxacin vs. 3% flucloxacillin; $p = 0.06$ using Fisher's exact test).

VI.B. Protocol 154-130

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND ORAL CEFPODOXIME PROXETIL (VANTIN™) (400 MG BID) FOR THE TREATMENT OF UNCOMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE

Study Dates: 1 June 1995 - 18 April 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to that of cefpodoxime proxetil (Vantin™) in the treatment of subjects with uncomplicated infections of the skin and skin structure.

Study Design: Study 154-130 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily) administered orally for 7 to 10 days versus cefpodoxime proxetil (Vantin™) (400 mg bid) administered orally for 7 to 10 days for the treatment of uncomplicated infections of the skin and skin structure.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥ 18 years of age at the baseline visit, with clinically documented uncomplicated skin and skin structure infections were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical of infection) and bacteriological response (based on eradication of causative organisms isolated from culture specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8 or 11) and at the end of study (Visit 4; Day 30), or at the time of discontinuation from the study. A clinical evaluation to determine the length of treatment (7 or 10 days) was to be conducted at Visit 2 (Day 4). Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection such as disappearance or diminution in culturable exudate, the disappearance or reduction of erythema, tenderness, pain, induration, or swelling, and improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of all signs and symptoms of uncomplicated skin and skin structure infection), improvement (incomplete resolution of signs and symptoms of uncomplicated skin and skin structure infection and no requirement for additional antibiotics), or failure (lack of resolution of any of the signs and symptoms of uncomplicated skin and skin structure infection and a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), Visit 3 (Day 8 or 11) and at Visit 4 (Day 30), or at the time of discontinuation from the study. Subject bacteriological response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence or relapse; however, the protocol was amended to not include the analysis of subject bacteriological response. Instead, each pathogen was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection or colonization.

The primary efficacy endpoint was sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS.
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Reviewer's Note: Since the EOT visit is only a day or so after treatment was discontinued, this reviewer will place more emphasis on the clinical response rates at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 6b.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

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Table 6b.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg daily)	Vantin (400 mg BID)
Entered Study ^a	221	225
All Treated	221 (100%)	225 (100%)
Completed Treatment	205 (93%)	205 (91%)
Completed Study	212 (96%)	204 (91%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	221 (100%)	225 (100%)
Clinically Evaluable ^b	211 (95%)	208 (92%)
Bacteriological Intent-to-Treat	176 (80%)	175 (78%)
Bacteriologically Evaluable ^b	167 (76%)	162 (72%)
Assessed for Safety		
Adverse Events	221 (100%)	225 (100%)
Laboratory Tests	210 (95%)	208 (92%)

a Subjects who were randomized.

b Based on End of Treatment assessment.

Of the 221 trovafloxacin and 225 Vantin clinical ITT subjects, 10 subjects in the trovafloxacin group and 17 subjects in the Vantin group were not clinically evaluable; therefore, 211 trovafloxacin and 208 Vantin subjects were clinically evaluable. The most common reason for exclusion from the clinically evaluable efficacy analyses was insufficient therapy (6/221 [3%], trovafloxacin and 13/225 [6%], Vantin). Other reasons were prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical assessment and no post-baseline clinical assessment within the evaluable window.

Of the 221 trovafloxacin and 225 Vantin clinical ITT subjects, 45 subjects in the trovafloxacin group and 50 subjects in the Vantin group had negative baseline cultures; therefore, 176 trovafloxacin and 175 Vantin subjects were included in the bacteriological ITT analyses.

Of the 211 trovafloxacin and 208 Vantin clinically evaluable subjects, 44 subjects in the trovafloxacin group and 46 subjects in the Vantin group were not included in the bacteriologically evaluable analyses; therefore, 167 trovafloxacin subjects and 162 Vantin subjects were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (43/221 [19%], trovafloxacin and 46/225 [20%], Vantin). The other reason was no post-baseline culture.

Discontinuations

Of the 221 trovafloxacin and 225 Vantin treated subjects, 16 trovafloxacin and 20 Vantin subjects were prematurely discontinued from treatment as summarized in Table 6b.2.

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Table 6b.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)

	Trovafoxacin 100 mg (N=221)	Vantin 400 mg BID (N=225)
	Number and Percentage (%) of Subjects	
Total Discontinued	16 (7%)	20 (9%)
Discontinuations Related to Study Drug:	10 (5%)	8 (4%)
Adverse Event	6 (3%)	6 (3%)
Insufficient Response	4 (2%)	2 (<1%)
Discontinuations Unrelated to Study Drug:	6 (3%)	12 (5%)
Adverse Event	0	4 (2%)
Lost to Follow-up	0	5 (2%)
Other	3 (1%)	1 (<1%)
Patient Died	0	1 (<1%)
Protocol Violation	1 (<1%)	0
Withdrew Consent	2 (<1%)	1 (<1%)

Demographics

One hundred twenty-seven (127) of the 221 treated trovafoxacin subjects (57%) were males and 94 were females (43%) and 118 of the 225 treated Vantin subjects (52%) were males and 107 were females (48%). The males and females in the trovafoxacin and Vantin treatment groups were generally comparable with respect to age, race, and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects. The mean age of subjects in the trovafoxacin and Vantin groups was 46.9 years and 45.6 years, respectively. Twenty-one percent of subjects in the trovafoxacin group and 17% of subjects in the Vantin group were ≥ 65 years of age.

The primary diagnosis for clinical ITT subjects was uncomplicated skin and skin structure infection. The median duration since onset of infection was 6.0 days for subjects in both treatment groups. Eleven subjects in each treatment group had a duration since onset of infection of ≥ 50 days. The maximum duration since onset of infection was 135 days (Subject 5643-0321) for subjects in the trovafoxacin group and 190 days (Subject 5643-0326) for subjects in the Vantin group.

The most commonly reported type of infection reported among clinical ITT subjects in the trovafoxacin group was minor wound infection (52/221 [24%], trovafoxacin and 37/225 [16%], Vantin), and the most commonly reported type of infection reported among clinical ITT subjects in the Vantin group was simple abscess (50/221 [23%], trovafoxacin and 56/225 [25%], Vantin). Of note, subjects may have had more than one type of infection at baseline. Other types of infections included impetiginous lesion, furuncle, cellulitis with and without a baseline pathogen and others (including infected paronychia, ulcers, insect bites, cysts, hydradenitis, erysipelas, pyoderma, folliculitis, carbuncle, dermatitis, surgical wounds, boils, complex abscesses and perirectal abscesses). All types of infections were reported at similar rates in both treatment groups. Similar results were observed for clinically evaluable subjects.

The majority of clinical ITT subjects in both treatment groups did not require a surgical drainage procedure at baseline or during the study. Fifty-four (54) trovafloxacin subjects (24%) and 68 Vantin subjects (30%) had skin infections that required surgical intervention at baseline and four trovafloxacin subjects (1%) and seven Vantin subjects (3%) had skin infection that required surgical intervention post-baseline. The most commonly reported type of skin infection for subjects requiring surgical intervention in both treatment groups was simple abscess (26/59 [44%], trovafloxacin and 39/72 [54%], Vantin).

A summary of type of skin infection at baseline and number of subjects with a surgical drainage procedure is presented for clinical ITT subjects in Table 6b.3.

Table 6b.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT Subjects)		
	Trovafloxacin 100 mg (N=221)	Vantin 400 mg BID (N=225)
Type of Infection^a	Number and Percentage (%) of Subjects	
Simple Abscess	50 (23%)	56 (25%)
Impetiginous Lesion	15 (7%)	17 (8%)
Furuncle	22 (10%)	21 (9%)
Minor Wound Infection	52 (24%)	37 (16%)
Cellulitis with a Baseline Pathogen	32 (14%)	40 (18%)
Cellulitis without a Baseline Pathogen	25 (11%)	17 (8%)
Other	34 (15%)	52 (23%)
Subjects Requiring Surgical Intervention ^b	59 (26%)	72 (32%)
At Baseline	54 (24%)	68 (30%)
Post-Baseline ^c	4 (1%)	7 (3%)
Before the EOT Assessment	3 (1%)	6 (2%)
After the EOT Assessment	1 (<1%)	1 (<1%)

a A subject may have had more than one type of infection.
 b Two subjects in the trovafloxacin group (Subjects 5531-0463 and 5606-0359) and two subjects in the Vantin group (Subjects 5531-0340 and 5553-0426) had a surgical procedures done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report forms.
 c One subject (5017-0377) in the trovafloxacin group and five subjects (5013-0443, 5125-0283, 5177-0438, 5553-0511, and 5816-0286) in the Vantin group had surgical drainage procedures performed both prior to and post-baseline.

Reviewer's Note: There was some imbalance between treatment groups with regard to type of infection at baseline. More trovafloxacin patients had a diagnosis of minor wound infection (this difference was marginally significant; p=0.06 using the test of equal proportions based on the normal approximation to the binomial distribution), while fewer trovafloxacin patients had a diagnosis which fell under the "other" category (this difference was significant; p=0.04 using the test of equal proportions based on the normal approximation to the binomial distribution).

There were no marked differences between subjects in the trovafloxacin and Vantin groups with respect to medical history at baseline. The most common disease/syndrome reported at baseline for subjects in both treatment groups was diabetes mellitus (25/221 [11%], trovafloxacin; 40/225 [18%], Vantin).

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 6b.4. Trovafloxacin was considered therapeutically equivalent to Vantin at both EOT and EOS.

Table 6b.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 100 mg (N=211)	Vantin 400 mg BID (N=208)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment			
Number of Subjects Assessed	207 (100%)	207 (100%)	
Success (Cure + Improvement)	194 (94%)	192 (93%)	(-3.9, 5.8)
Distribution of Clinical Response:			
Cure	114 (55%)	100 (48%)	
Improvement	80 (39%)	92 (44%)	
Failure	13 (6%)	15 (7%)	
End of Study			
Number of Subjects Assessed	204 (100%)	194 (100%)	
Success (Cure + Improvement)	179 (88%)	168 (87%)	(-5.4, 7.7)
Distribution of Clinical Response:			
Cure	152 (75%)	137 (71%)	
Improvement	27 (13%)	31 (16%)	
Failure	13 (6%)	15 (8%)	
Relapse	12 (6%)	11 (6%)	

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 6b.5.

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Table 6b.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)

	Trovafloracin 100 mg (N=211)	Vantin 400 mg BID (N=208)	Trovafloracin 100 mg (N=204)	Vantin 400 mg BID (N=194)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>St. aureus</i>	71/76 (93%)	59/64 (92%)	63/73 (86%)	53/60 (88%)
<i>St. epidermidis</i>	30/34 (88%)	27/29 (93%)	30/35 (86%)	24/27 (89%)
<i>P. aeruginosa</i>	15/15 (100%)	8/8	15/15 (100%)	7/8
<i>E. faecalis</i>	13/13	13/13	12/13	10/13
<i>E. coli</i>	5/5	10/11	5/5	10/11
<i>Staphylococcus sp.</i>	10/10	2/2	9/10	2/2
<i>St. haemolyticus</i>	10/10	10/11	10/10	9/10
<i>St. hominis</i>	4/5	4/4	3/5	4/4
<i>St. simulans</i>	1/1	5/5	1/1	4/5
Coagulase Negative <i>Staphylococcus</i>	0/0	2/2	0/0	1/1
<i>Streptococcus sp.</i>	6/6	6/7	3/4	5/7
<i>Str. agalactiae</i>	8/9	10/13	8/10	9/12
<i>Str. aginosus</i>	2/2	0/0	2/2	0/0
<i>Str. mitis</i>	1/1	0/0	1/1	0/0
<i>Str. pyogenes</i>	9/9	6/6	9/9	5/5
<i>Str. sanguis I</i>	0/0	1/1	0/0	1/1
<i>Str. sanguis II</i>	1/1	2/2	1/1	1/2
Group G Beta <i>Streptococcus</i>	2/2	1/1	2/2	1/1
Alpha haemolytic <i>Streptococcus</i>	0/0	1/1	0/0	1/1

St. = *staphylococcus*; *Str.* = *Streptococcus*
 a ≥10 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

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When sponsor-defined clinical response was subset by type of baseline infection (simple abscess, impetiginous lesion, minor wound infection, cellulitis with and without a baseline pathogen, furuncle or other) in clinical ITT subjects, a trend towards a higher (≥10 percentage points) clinical success rate at EOT was observed among trovafloracin subjects with cellulitis and a baseline pathogen compared to Vantin subjects (trovafloracin: 31/32, 97%; Vantin: 34/40, 85%) and among trovafloracin subjects with furuncle compared to Vantin subjects (trovafloracin: 21/21, 100%; Vantin: 19/21, 90%). In addition, a trend towards a higher clinical success rate at EOS was observed among trovafloracin subjects with baseline infections classified as other compared with Vantin subjects (trovafloracin: 33/34, 97%; Vantin: 42/52, 81%).

Similar clinical success rates were observed between the two treatment groups among subjects with the other types of infection (simple abscess, impetiginous lesion, minor wound infection and cellulitis without a baseline pathogen) at both EOT and EOS, and similar clinical success rates were observed between the two treatment groups among subjects with cellulitis with a baseline pathogen and furuncle at EOS and subjects with other infections at EOT.

A summary of clinical success rates for clinical ITT subjects subset by type of infection at baseline at the end of treatment and at the end of study is presented by treatment group in Table 6b.6.

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Table 6b.6. Summary of Sponsor-Defined Clinical Success Rates Subset by Type of Baseline Infection (Clinical ITT Subjects)

	Trovafloracin 100 mg (N=221)		Vantin 400 mg BID (N=225)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection ^a	EOT		EOS	
Simple Abscess	46/49 (94%)	46/50 (92%)	50/56 (89%)	50/56 (89%)
Impetiginous Lesion	14/15 (93%)	12/15 (80%)	15/17 (88%)	12/17 (71%)
Minor Wound Infection	47/51 (92%)	45/52 (87%)	32/37 (86%)	32/37 (86%)
Cellulitis Without a Baseline Pathogen	20/25 (80%)	18/25 (72%)	14/17 (82%)	13/17 (76%)
Cellulitis With a Baseline Pathogen	31/32 (97%)	28/32 (88%)	34/40 (85%)	32/40 (80%)
Furuncle	21/21 (100%)	20/22 (91%)	19/21 (90%)	18/21 (86%)
Other ^b	32/33 (97%)	33/34 (97%)	45/51 (88%)	42/52 (81%)

a A subject may have had more than one type of infection at baseline.
 b Other infections included infected paronychia, ulcers, insect bites, cysts, hydradenitis, erysipelas, pyoderma, folliculitis, carbuncle, dermatitis, surgical wounds, boils and complex and perirectal abscesses

When sponsor-defined clinical response was subset by timing of surgical intervention in clinical ITT subjects, similar clinical success rates were observed between treatment groups at both EOT and EOS, for subjects with no surgical intervention and surgical intervention at baseline. Among subjects with surgical intervention before or after the end of treatment, subject subsets were too small for any definitive conclusions to be drawn.

A summary of clinical success rates for clinical ITT subjects subset by timing of surgical intervention at the end of treatment and at the end of study is presented by treatment group in Table 6b.7.

Table 6b.7. Summary of Sponsor-Defined Clinical Success Rates Subset by Timing of Surgical Intervention (Clinical ITT Subjects)

	Trovafloracin 100 mg (N=221)		Vantin 400 mg BID (N=225)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Timing of Surgical Intervention ^a	EOT ^b		EOS	
No Surgical Intervention	150/158 (95%)	143/162 (88%)	134/152 (88%)	125/153 (82%)
Surgical Intervention at Baseline	51/54 (94%)	50/54 (93%)	61/68 (90%)	61/68 (90%)
Surgical Intervention Post Baseline ^c				
Before the EOT Assessment	1/3 (33%)	1/3 (33%)	3/6 (50%)	3/6 (50%)
After the EOT Assessment	0/1	0/1	0/1	0/1

a Subjects may have had surgical intervention at more than one timepoint.
 b Four clinical intent-to-treat subjects in the trovafloxacin group and one subject in the Vantin group were not assessed for clinical response at the end of treatment.
 c Two subjects in the trovafloxacin group (Subjects 5531-0463 and 5606-0359) and two subjects in the Vantin group (Subjects 5531-0340 and 5553-0426) had a surgical procedures done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report forms.

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Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects were similar between the two treatment groups for the most frequently isolated pathogens at the end of treatment and the end of study as presented in Table 6b.8.

Table 6b.8. A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Trovafoxacin 100 mg (N=167)	Vantin 400 mg BID (N=162)	95% CI	Trovafoxacin 100 mg (N=161)	Vantin 400 mg BID (N=149)	95% CI
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>St. aureus</i>	68/76 (89%)	52/64 (81%)	-3.6, 20.0	59/73 (81%)	50/60 (83%)	-15.6, 10.5
<i>St. epidermidis</i>	32/33 (97%)	25/29 (86%)	-3.1, 24.6	31/34 (91%)	24/26 (92%)	-15.1, 12.9
<i>P. aeruginosa</i>	9/15 (60%)	4/8	ND	12/15 (80%)	4/7	ND
<i>E. faecalis</i>	13/13	12/13	ND	11/13	11/13	ND
<i>E. coli</i>	5/5	9/11	ND	4/5	10/11	ND
<i>Staphylococcus</i> sp.	10/10	2/2	ND	9/9	2/2	ND
<i>St. haemolyticus</i>	10/10	11/11	ND	10/10	10/10	ND
<i>St. hominis</i>	4/5	4/4	ND	4/5	4/4	ND
<i>St. simulans</i>	1/1	5/5	ND	1/1	4/5	ND
Coagulase Negative <i>Staphylococcus</i>	0/0	2/2	ND	0/0	1/1	ND
<i>Streptococcus</i> sp.	6/6	7/7	ND	3/4	6/6	ND
<i>Str. agalactiae</i>	8/9	11/13	ND	8/10	10/12	ND
<i>Str. anginosus</i>	2/2	0/0	ND	2/2	0/0	ND
<i>Str. mitis</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. pyogenes</i>	9/9	6/6	ND	9/9	5/5	ND
<i>Str. sanguis I</i>	0/0	1/1	ND	0/0	1/1	ND
<i>Str. sanguis II</i>	1/1	2/2	ND	1/1	2/2	ND
Group G Beta <i>Streptococcus</i>	2/2	1/1	ND	2/2	1/1	ND
Alpha haemolytic <i>Streptococcus</i>	0/0	1/1	ND	0/0	1/1	ND

ND = not done; *St.* = *staphylococcus*; *Str.* = *Streptococcus*
^a ≥10 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events, and clinically significant laboratory values is presented in Table 6b.9. Tables 6b.10 and 6b.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

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Table 6b.9. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 100 mg daily (N= 221)	Vantin 400 mg BID (N= 225)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	71/221 (32%)	86/225 (38%)
Treatment-Related Adverse Events	38/221 (17%)	48/225 (21%)
Discontinuations from Treatment Due to an Adverse Event ^a	8/221 (4%)	11/225 (5%)
Clinically Significant Laboratory Values	28/210 (13%)	26/208 (13%)

a Six subjects in each treatment group were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related.

Table 6b.10. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 100 mg (N=221)	Vantin 400 mg BID (N=225)
Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event	71 (32%)	86 (38%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM		
Dizziness	22 (10%)	23 (10%)
Headache	9 (4%)	6 (3%)
GASTROINTESTINAL SYSTEM		
Abdominal Pain	14 (6%)	15 (7%)
Diarrhea	22 (10%)	41 (18%)
Dyspepsia	5 (2%)	3 (1%)
Flatulence	10 (5%)	20 (9%)
Nausea	0 (0%)	4 (2%)
Vomiting	0 (0%)	5 (2%)
GENERAL		
Fatigue	7 (3%)	9 (4%)
OTHER		
Accidental Injury	3 (1%)	4 (2%)
SKIN/APPENDAGES		
Rash	11 (5%)	16 (7%)
	5 (2%)	4 (2%)
	4 (2%)	1 (<1%)
	4 (2%)	1 (<1%)
	13 (6%)	10 (4%)
	4 (2%)	2 (<1%)

a ≥2 % of subjects in any treatment group.
b Includes data up to 7 days after last dose of active study medication

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Reviewer's Note: A higher percentage of Vantin patients experienced gastrointestinal system adverse events (18% versus 10% for trovafloxacin; p=0.01 using the test of equal proportions based on the normal approximation to the binomial distribution).

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Table 6b.11. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)		
	Trovafloxacin 100 mg (N=221)	Vantin 400 mg BID (N=225)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	38 (17%)	48 (21%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	15 (7%)	10 (4%)
Dizziness	7 (3%)	5 (2%)
Headache	9 (4%)	3 (1%)
GASTROINTESTINAL SYSTEM	14 (6%)	34 (15%)
Diarrhea	7 (3%)	18 (8%)
Flatulence	0 (0%)	4 (2%)
Nausea	5 (2%)	7 (3%)
a ≥2 % of subjects in any treatment group.		
b Includes data up to 7 days after last dose of active study medication.		

Five (5) subjects in the trovafloxacin group and 7 subjects in the Vantin group had serious adverse events that were considered by the investigator to be unrelated to study drug.

One subject in the Vantin group had a serious adverse event (migraine headache) that was considered to be related to study drug.

One subject in the Vantin group died from congestive heart failure and coronary artery disease on Day 7. This death was not considered to be related to study drug.

Sponsor Summary and Conclusion: Trovafloxacin 100 mg once daily for 7-10 days and cefpodoxime proxetil (Vantin) 400 mg twice daily for 7-10 days were statistically equivalent for clinical success rates at the end of treatment and the end of study for both intent-to-treat and evaluable subjects with uncomplicated skin and skin structure infection. Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and the end of study for the most frequently isolated pathogens of (*S. aureus* and *S. epidermidis*).

The percentage of subjects discontinued from treatment due to adverse events was 4% in the trovafloxacin group and 5% in the Vantin group. Six (6) subjects in the trovafloxacin group and six subjects in the Vantin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all and treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the Vantin group (32% and 17% versus 38% and 21% respectively). The most commonly reported treatment-related adverse events in the trovafloxacin group were dizziness (3%) and headache (4%), and diarrhea (3%). The most commonly reported treatment-related adverse events in the Vantin group were diarrhea (8%) and nausea (3%).

Reviewer's Summary and Conclusions: Trovafloxacin 100 mg once daily for 7-10 days and cefpodoxime proxetil (Vantin) 400 mg twice daily for 7-10 days were therapeutically equivalent in terms of clinical success rates at both EOT and EOS for evaluable subjects with uncomplicated skin and skin structure infections.

The most common adverse events reported in the trovafloxacin group were headache (6%), diarrhea (5%), and dizziness (4%). In the Vantin group, the most commonly reported adverse events were diarrhea (9%), headache (7%), and nausea (4%). A higher percentage of Vantin patients experienced gastrointestinal system adverse events (18% versus 10% for trovafloxacin; $p=0.01$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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VII. COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS

The efficacy and safety of the IV-to-oral regimen in complicated skin infection was assessed in a double-blind, comparative trial versus IV piperacillin/tazobactam followed by oral cefpodoxime (154-131). The efficacy and safety of oral trovafloxacin in the treatment of complicated skin infections was assessed in one uncontrolled trial (diabetic foot; 154-132) and one open, comparative trial versus amoxicillin/clavulanate (154-139).

***Reviewer's Note:** The sponsor assessed whether efficacy differed in various subgroups in the complicated skin infection trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, race, and age.*

VII.A. Protocol 154-131

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A RANDOMIZED, MULTICENTER, INVESTIGATOR/SUBJECT-BLIND (DOUBLE-BLIND) TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN AND INTRAVENOUS PIPERACILLIN SODIUM/TAZOBACTAM SODIUM (ZOSYN™) FOLLOWED BY ORAL CEFPODOXIME PROXETIL (VANTIN™) FOR THE TREATMENT OF COMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE.

Study Dates: 27 June 1995 - 28 May 1996

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Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin with intravenous piperacillin sodium/tazobactam sodium (Zosyn™) followed by oral cefpodoxime proxetil (Vantin™) in the treatment of subjects with complicated infections of the skin and skin structure requiring initial inpatient intravenous therapy.

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Study Design: Study 154-131 was a randomized, double-blind, double-dummy, comparative, multicenter trial of intravenous alatrofloxacin (200 mg) administered once daily for 2 to 7 days followed by oral trovafloxacin (200 mg) administered once daily to complete a maximum total treatment duration of 10 or 14 days versus intravenous Zosyn (3.375 g) administered four-times daily for 2 to 7 days followed by oral Vantin™ (400 mg) administered twice daily to complete a maximum total treatment duration of 10 or 14 days for the treatment of complicated infections of the skin and skin structure [e.g., infected ischemic ulcers including diabetic foot ulcers without underlying osteomyelitis, infected burns, major abscesses, other skin structure infections requiring significant surgical intervention along with antimicrobial therapy, and infections of the deeper soft tissues].

Diagnoses and Criteria for Inclusion of Subjects: Men or women ≥ 18 years of age at the baseline assessment, with clinically documented complicated infection of the skin or skin structure.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical signs and symptoms of infection) and bacteriologic response (based on eradication of causative organisms isolated from culture specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11 or 15) and at the end of study (Visit 4; Day 30), or at the time of discontinuation from the study. A clinical evaluation to determine the length of treatment (10 or 14 days) was to be conducted at Visit 2 (Day 4). Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection, such as resolution of fever, disappearance or diminution in culturable exudate, the disappearance or reduction of erythema, tenderness, pain, induration, swelling or leukocytosis, and improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of the complicated skin or skin structure infection), improvement (incomplete resolution of signs and symptoms of complicated skin or skin structure infection and no requirement for additional antibiotics), or failure (lack of resolution of any of the signs and symptoms of complicated skin or skin structure infection and a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), Visit 3 (EOT; Day 11 or 15) and at Visit 4 (EOS; Day 30), or at the time of discontinuation from the study. Subject bacteriological response was to be classified by the sponsor as eradication, presumed eradication, persistence, presumed persistence or relapse; however, the protocol was amended to not include the analysis of subject bacteriological response. Instead, each pathogen was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection or colonization, and pathogen eradication rates were to be examined.

The primary efficacy endpoint was sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS.
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

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Reviewer's Note: *Since the EOT visit is only a day or so after treatment was discontinued, this reviewer will place more emphasis on the clinical response rates at EOS.*

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

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Analysis Groups

Table 7a.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Table 7a.1. Evaluation Groups

Evaluation Groups:	Alatrofloxacin (IV 200 mg/day) Trovafoxacin (200 mg/day)		Zosyn (IV 3.375g QID) Vantin™(400 mg BID)	
	Number and Percentage (%) of Subjects			
Randomized	145		142	
All Treated Subjects	144	(100%)	142	(100%)
Completed Treatment	94	(65%)	113	(80%)
Completed Study	117	(81%)	128	(90%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	143	(99%)	140	(99%)
Clinically Evaluable ^a	103	(71%)	123	(87%)
Bacteriological Intent-to-Treat	115	(79%)	103	(73%)
Bacteriologically Evaluable ^a	80	(55%)	89	(63%)
Assessed for Safety				
Adverse Events	144	(100%)	142	(100%)
Laboratory Tests	137	(95%)	139	(98%)

^a Based on End of Treatment assessment

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Reviewer's Note: A significantly lower proportion of alatrofloxacin/trovafoxacin patients completed treatment, completed the study, and were considered clinically evaluable ($p = 0.007, 0.03, \text{ and } 0.002$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution). Much of the difference in the percent of patients completing treatment can be accounted for by the significant difference in patients discontinuing treatment due to adverse events (regardless of relationship to study drug); 20 (14%) alatrofloxacin/trovafoxacin patients discontinued treatment due to an adverse event compared to 6 (4%) Zosyn/Vantin patients (see Table 7a.2), and this difference was highly statistically significant ($p = 0.004$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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Since a significantly lower proportion of alatrofloxacin/trovafoxacin patients were considered clinically evaluable, results will be presented below for the clinical intent-to-treat population, in addition to those given for the clinically evaluable population.

Of the 145 alatrofloxacin/trovafoxacin and 142 Zosyn/Vantin™ randomized subjects, one alatrofloxacin/trovafoxacin subject was randomized but not treated. Two alatrofloxacin/trovafoxacin subjects and two Zosyn/Vantin™ subjects had an inappropriate baseline diagnosis and were excluded from all intent-to-treat and evaluable analyses.

Of the 143 alatrofloxacin/trovafoxacin and 140 Zosyn/Vantin™ clinical ITT subjects, 40 in the alatrofloxacin/trovafoxacin group and 17 in the Zosyn/Vantin™ group were not clinically evaluable; therefore, 103 subjects in the alatrofloxacin/trovafoxacin group and 123 subjects in the Zosyn/Vantin™ group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy (20/145 [14%], alatrofloxacin/trovafoxacin and 11/142 [8%], Zosyn/Vantin™ subjects). Other reasons were concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical response in evaluable window, no post-baseline clinical assessment, prior antibiotic usage, and randomized, not treated.

Of the 143 alatrofloxacin/trovafloroxacin and 140 Zosyn/Vantin™ clinical ITT subjects, 28 subjects in the alatrofloxacin/trovafloroxacin group and 37 subjects in the Zosyn/Vantin™ group had negative baseline cultures; therefore, 115 subjects in the alatrofloxacin/trovafloroxacin group and 103 subjects in the Zosyn/Vantin™ group were included in the bacteriological ITT analysis.

Of the 103 alatrofloxacin/trovafloroxacin and 123 Zosyn/Vantin™ clinically evaluable subjects, 23 subjects in the alatrofloxacin/trovafloroxacin group and 34 subjects in the Zosyn/Vantin™ group were not included in the bacteriologically evaluable analyses; therefore, 80 subjects in the alatrofloxacin/trovafloroxacin group and 89 subjects in the Zosyn/Vantin™ group were bacteriologically evaluable. The more common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen 23/145 [16%], alatrofloxacin/trovafloroxacin and 34/142 [24%], Zosyn/Vantin™). The other reason was 'baseline culture outside window'.

Discontinuations

Of the 144 alatrofloxacin/trovafloroxacin and 142 Zosyn/Vantin™ treated subjects, 50 and 29 subjects, respectively, were prematurely discontinued from treatment as summarized in Table 7a.2.

Table 7a.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)				
	Alatrofloxacin ↓ Trovafloroxacin (N=144)		Zosyn ↓ Vantin™ (N=142)	
	Number and Percentage (%) of Subjects			
Total Discontinued	50	(35%)	29	(20%)
Discontinuations Related to Study Drug:	24	(17%)	12	(8%)
Adverse Event	12	(8%)	4	(3%)
Insufficient Response	11	(8%)	8	(6%)
Laboratory Abnormality	1	(<1%)	0	
Discontinuations Unrelated to Study Drug:	26	(18%)	17	(12%)
Adverse Event	8	(6%)	2	(1%)
Did Not Meet Randomization Criteria	0		1	(<1%)
Laboratory Abnormality	0		1	(<1%)
Lost to Follow-Up	1	(<1%)	2	(1%)
Other ^a	14	(10%)	7	(5%)
Protocol Violation	1	(<1%)	2	(1%)
Withdrawn Consent	2	(1%)	2	(1%)
a The most common "other" reason that led to discontinuation from treatment was the presence of methicillin-resistant <i>S. aureus</i> for subjects in the alatrofloxacin/trovafloroxacin (4 subjects) and Zosyn/Vantin™ (3 subjects) groups.				

Demographics

Eighty-seven (87) of the 144 treated alatrofloxacin/trovafloroxacin subjects (60%) were males and 57 were females (40%), and 85 of the 142 treated Zosyn/Vantin™ subjects (60%) were males and 57 were females (40%). The males and females in the alatrofloxacin/trovafloroxacin

and Zosyn/Vantin™ treatment groups were generally comparable with respect to age, race, and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The mean age of subjects in the alatrofloxacin/trovafloxacin and Zosyn/Vantin™ groups was 54.5 years and 54.8 years, respectively. Thirty-five percent (35%) of subjects in the alatrofloxacin/trovafloxacin group and 27% of subjects in the Zosyn/Vantin™ group were ≥65 years of age.

The primary diagnosis for clinical intent-to-treat subjects was complicated skin and skin structure infection. The median duration since onset of infection was 6.0 days for subjects in both treatment groups. Similar durations since onset of infection were observed for clinically evaluable subjects in both treatment groups. There were no marked differences between all treated subjects in the alatrofloxacin/trovafloxacin and Zosyn/Vantin™ treatment groups with respect to medical history at baseline. Sixty (60) subjects (42%) in the alatrofloxacin/trovafloxacin group and 71 subjects (50%) in the Zosyn/Vantin™ group had diabetes mellitus and 40 alatrofloxacin/trovafloxacin subjects (28%) and 45 Zosyn/Vantin™ subjects (32%) had peripheral vascular disease at baseline.

All types of infections were reported at similar rates in both treatment groups. The most commonly reported type of skin infection for subjects in both treatment groups was other deep soft tissue infections (post-operative surgical wound infections) (89/143 [62%], alatrofloxacin/trovafloxacin; and 82/140 [59%], Zosyn/Vantin™). For subjects in both treatment groups, the most commonly reported type of deep soft tissue infection was cellulitis (67/143 [47%], alatrofloxacin/trovafloxacin; and 61/140 [44%], Zosyn/Vantin™). Other types of deep soft tissue infections included post-operative surgical wound infections, abscesses, erysipelas, hydrantitis, and others [a gun shot wound, bursitis, infected stump, IV infection, traumatic injury, right pretibial hallux and posterior medial malleolus on right leg and infected laceration]).

The majority of clinical ITT subjects in both treatment groups (62%) required a surgical drainage procedure at baseline or during the study. Sixty-one (61) alatrofloxacin/trovafloxacin subjects (42%) and 47 Zosyn/Vantin™ subjects (33%) required surgical drainage at baseline, and 44 alatrofloxacin/trovafloxacin subjects (30%) and 53 Zosyn/Vantin™ subjects (37%) had surgical drainage done post-baseline.

A summary of type of skin infection at baseline and number of subjects with a surgical drainage procedure is presented for clinical ITT subjects in Table 7a.3.

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Table 7a.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT Subjects)

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	Alatrofloxacin ↓ Trovafoxacin (N=143)	Zosyn ↓ Vantin™ (N=140)
Type of Infection ^a	Number and Percentage (%) of Subjects	
Diabetic Foot Ulcer Without Osteomyelitis	23 (16%)	19 (14%)
Other Ischemic Ulcer	11 (8%)	14 (10%)
Infected Burn	0	2 (1%)
Major Abscess	22 (15%)	23 (16%)
Other Skin Structure Infection Requiring Significant Surgical Intervention	13 (9%)	19 (14%)
Cellulitis	6 (4%)	5 (4%)
Post-operative Surgical Wound Infection	0	1 (<1%)
Abscess	3 (2%)	5 (4%)
Ulcer	1 (<1%)	2 (1%)
Hydrantitis	0	1 (<1%)
Erysipelas	0	0
Other ^b	3 (2%)	5 (4%)
Other Deep Soft Tissue Infections (e.g., Post-Operative Surgical Wound Infection)	89 (62%)	82 (59%)
Cellulitis	67 (49%)	61 (44%)
Post-operative Surgical Wound Infection	13 (9%)	12 (9%)
Abscess	1 (<1%)	1 (<1%)
Ulcer	1 (<1%)	0
Hydrantitis	2 (1%)	1 (<1%)
Erysipelas	3 (2%)	2 (1%)
Other ^c	3 (2%)	5 (4%)
Subjects Requiring Surgical Drainage Procedure^d		
At Baseline	90 (62%)	88 (62%)
Post-Baseline		
Before the EOT Assessment	61 (42%)	47 (33%)
After the EOT Assessment	44 (30%)	53 (37%)
Before the EOT Assessment	36 (25%)	44 (31%)
After the EOT Assessment	18 (12%)	21 (15%)
a A subject may have had more than one type of infection. b Other types of skin structure infections requiring surgery pressure sores, flexor tenosynovitis, septic arthritis, necrotizing soft tissue infection, human bite, cat bite, right medial knee and bursae and embedded foreign object. c Other types of deep soft tissue infections included cellulitis, post-operative surgical wound infections, abscesses, erysipelas, hydrantitis, and others [a gun shot wound, bursitis, infected stump, IV infection, traumatic injury, right pretibial hallux and posterior medial malleolus on right leg and infected laceration]. One subject (5881-0081) in the alatrofloxacin/trovafoxacin group had both bursitis (classified as "other") and cellulitis listed as a deep soft tissue infection; neither was designated as the primary infection. d Subjects were counted in each timepoint that they had a surgical drainage procedure. Therefore, numbers do not add up to the total.		

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Clinical Response

A summary of clinical response rates for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 7a.4.

Alatrofloxacin/trovafloxacin was considered therapeutically equivalent to Zosyn/Vantin at both EOT and EOS.

Table 7a.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloxacin (N=103)		Zosyn ↓ Vantin™ (N=123)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	99	(100%)	117	(100%)	
Success (Cure + Improvement)	80	(81%)	99	(85%)	(-14.0%, 6.3%)
Distribution of Clinical Response:					
Cure	41	(41%)	41	(35%)	
Improvement	39	(39%)	58	(50%)	
Failure	19	(19%)	18	(15%)	
End of Study:					
Number of Subjects Assessed	85	(100%)	105	(100%)	
Success (Cure + Improvement)	62	(73%)	81	(77%)	(-16.6%, 8.2%)
Distribution of Clinical Response:					
Cure	55	(65%)	58	(55%)	
Improvement	7	(8%)	23	(22%)	
Failure	21	(25%)	18	(17%)	
Relapse	2	(2%)	6	(6%)	

A summary of clinical response rates for clinically ITT subjects at the end of treatment and at the end of study is presented by treatment group in Table 7a.5. Alatrofloxacin/trovafloxacin was considered therapeutically equivalent to Zosyn/Vantin at EOS, but not at EOT.

Reviewer's Note: EOS is considered the more important timepoint for consideration of efficacy by this reviewer, as stated above.

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Table 7a.5. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically ITT Subjects)					
	Trovafloracin ↓ Alatrofloxacin (N=143)		Zosyn ↓ Vantin™ (N=140)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	134	(100%)	133	(100%)	
Success (Cure + Improvement)	98	(73%)	106	(80%)	(-16.7%, 3.6%)
Distribution of Clinical Response:					
Cure	49	(37%)	45	(34%)	
Improvement	49	(37%)	61	(46%)	
Failure	36	(27%)	27	(20%)	
End of Study:					
Number of Subjects Assessed	143	(100%)	140	(100%)	
Success (Cure + Improvement)	102	(71%)	107	(76%)	(-15.3%, 5.1%)
Distribution of Clinical Response:					
Cure	83	(58%)	74	(53%)	
Improvement	19	(13%)	33	(24%)	
Failure	38	(27%)	27	(19%)	
Relapse	3	(2%)	6	(4%)	

A summary of clinical success rates at EOT and EOS for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 7a.6.

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Table 7a.6. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloracin (N=103)		Zosyn ↓ Vantin™ (N=123)		
	Number of Subjects				
Pathogen	End of Treatment		End of Study		
<i>St. aureus</i>	32/38	(84%)	31/37	(84%)	26/34 (76%) 26/33 (79%)
<i>St. epidermidis</i>	8/10	(80%)	10/15	(67%)	6/8 (75%) 11/16 (69%)
<i>Enterococcus faecalis</i>	9/11		9/13		7/10 7/11
<i>Str. agalactiae</i>	7/11		6/7		4/9 7/8

St. = *Staphylococcus*; *Str.* = *Streptococcus*
^a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15 at least once for a given pathogen.
 A subject could have had more than one pathogen isolated at baseline.

A summary of clinical success rates at EOT and EOS is presented by type of baseline infection and treatment group for clinical ITT subjects in Table 7a.7.

Table 7a.7. Summary of Sponsor-Defined Clinical Success Rates Subset by Type of Baseline Infection (Clinical ITT Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=143)		Zosyn ↓ Vantin™ (N=140)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection ^a	EOT	EOS	EOT	EOS
Diabetic Foot Ulcer Without Osteomyelitis	13/21 (62%)	15/23 (65%)	9/17 (53%)	11/19 (58%)
Other Ischemic Ulcer	7/10 (70%)	8/11 (73%)	11/14 (79%)	11/14 (79%)
Infected Burn	0/0	0/0	1/2 (50%)	0/2
Major Abscess	16/19 (84%)	17/22 (77%)	19/22 (86%)	20/23 (87%)
Other Skin-Structure Infection Requiring Significant Surgical Intervention	8/13 (62%)	7/13 (54%)	14/19 (74%)	13/19 (68%)
Other Deep Soft Tissue Infections (Post-Operative Surgical Wound Infections)	63/84 (75%)	64/89 (72%)	68/77 (88%)	69/82 (84%)

a A subject may have had more than one type of infection at baseline.

A summary of clinical success rates at EOT and EOS is presented by timing of surgical intervention and treatment group for clinical ITT subjects in Table 7a.8.

Table 7a.8. Summary of Sponsor-Defined Clinical Success Rates Subset by Timing of Surgical Intervention (Clinical ITT Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=143)		Zosyn ↓ Vantin™ (N=140)	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Timing of Surgical Intervention ^a	EOT	EOS	EOT	EOS
No Surgical Intervention	42/51 (82%)	43/53 (81%)	46/50 (92%)	46/52 (88%)
Surgical Intervention at Baseline	37/56 (66%)	40/61 (66%)	31/43 (72%)	34/47 (72%)
Surgical Intervention Post Baseline				
Before the EOT Assessment	20/32 (63%)	21/36 (58%)	28/41 (68%)	28/44 (64%)
After the EOT Assessment	7/16 (44%)	7/18 (39%)	11/20 (55%)	8/21 (38%)

a Subjects may have had surgical intervention at more than one timepoint.

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Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects were similar between the two treatment groups for the most frequently isolated pathogens at the end of treatment and the end of study as presented in Table 7a.9.

Table 7a.9. A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=80)	Zosyn ↓ Vantin™ (N=89)	95% CI	Alatrofloxacin ↓ Trovafoxacin (N=65)	Zosyn ↓ Vantin™ (N=77)	95% CI
Number of Pathogens						
Pathogen	End of Treatment			End of Study		
<i>St. aureus</i>	32/39 (82%)	26/37 (70%)	-7.2%, 30.8%	25/31 (81%)	23/33 (70%)	-10.0%, 31.9%
<i>St. epidermidis</i>	9/10 (90%)	14/15 (93%)	ND	7/8 (88%)	13/15 (87%)	ND
<i>Enterococcus faecalis</i>	10/11	9/13	ND	7/10	8/11	ND
<i>Str. agalactiae</i>	6/11	6/7	ND	5/8	7/8	ND

St. = *Staphylococcus*; *Str* = *Streptococcus*
^a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15 at least once for a given pathogen.
 A subject could have had more than one pathogen isolated at baseline.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuations from treatment due to adverse events, and clinically significant laboratory values are presented in Table 7a.10. Tables 7a.11 and 7a.12 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: A significantly higher proportion of alatrofloxacin/trovafoxacin patients discontinued treatment due to an adverse event ($p=0.0003$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 7a.10. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Alatrofloxacin ↓ Trovafoxacin	Zosyn ↓ Vantin™
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	101/144 (70%)	98/142 (69%)
Treatment-Related Adverse Events	39/144 (27%)	37/142 (26%)
Discontinuations from Treatment Due to an Adverse Event ^a	29/144 (20%)	8/142 (6%)
Clinically Significant Laboratory Values	61/137 (45%)	63/139 (45%)

^a Twelve (12) subjects in the alatrofloxacin/trovafoxacin group and four subjects in the Zosyn/Vantin™ group were discontinued due to adverse events that were considered by the investigator to be study drug-related.

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Reviewer's Note: *Alatrofloxacin/trovafloxacin patients experienced significantly more application/injection/incision/insertion site reaction and constipation than did Zosyn/Vantin patients (11/144=8% vs. 1/142 or <1%, p=0.005 using Fisher's exact test; and 22/144=15% vs. 7/142=5%, p=0.004 using the test of equal proportions based on the normal approximation to the binomial distribution, respectively). Zosyn/Vantin patients experienced significantly more diarrhea than did alatrofloxacin/trovafloxacin patients (17/142=12% vs. 7/144=5%, p=0.03 using the test of equal proportions based on the normal approximation to the binomial distribution). Of note, more alatrofloxacin/trovafloxacin patients experienced aggravated infection as an adverse event (this difference was marginally statistically significant: 9/144=6% vs. 2/142=1%, p=0.06 using Fisher's exact test).*

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Table 7a.11. A Summary of the Most Commonly Reported Adverse Events ^{a, b} by Body System - All Causalities (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=144)		Zosyn ↓ Vantin™ (N=142)	
Number and Percentage (%) of Subjects				
Number of Subjects With at Least One Adverse Event	101	(70%)	98	(69%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	17	(12%)	8	(6%)
Appl./Inj./Incision/Insertion Site Reaction	11	(8%)	1	(<1%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	29	(20%)	26	(18%)
Headache	17	(12%)	15	(11%)
GASTROINTESTINAL SYSTEM	49	(34%)	48	(34%)
Constipation	22	(15%)	7	(5%)
Diarrhea	7	(5%)	17	(12%)
Nausea	20	(14%)	23	(16%)
Vomiting	10	(7%)	11	(8%)
GENERAL	27	(19%)	26	(18%)
Infection (aggravated)	9	(6%)	2	(1%)
PSYCHIATRIC	15	(10%)	10	(7%)
Insomnia	4	(3%)	8	(6%)
REPRODUCTIVE SYSTEM	3	(2%)	8	(6%)
Vaginitis^c	3	(5%)	6	(11%)
SKIN/APPENDAGES	24	(17%)	15	(11%)
Pruritus	7	(5%)	6	(4%)
a ≥5% of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication. c Term is gender specific, and the percentages are based on the number of females.				

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Table 7a.12. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a, b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafoxacin (N=144)		Zosyn ↓ Vantin™ (N=142)	
Number and Percentage (%) of Subjects				
Number of Subjects With at Least One Adverse Event	39	(27%)	37	(26%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	9	(6%)	4	(3%)
Appl./Inj./Incision/Insertion Site Pain	4	(3%)	2	(1%)
Appl./Inj./Incision/Insertion Site Reaction	7	(5%)	0	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	11	(8%)	8	(6%)
Dizziness	4	(3%)	1	(<1%)
Headache	8	(6%)	7	(5%)
GASTROINTESTINAL SYSTEM	15	(10%)	19	(13%)
Diarrhea	5	(3%)	12	(8%)
Nausea	8	(6%)	5	(4%)
REPRODUCTIVE	3	(2%)	4	(3%)
Vaginitis ^c	3	(5%)	4	(7%)

a ≥3% of subjects in either treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Term is gender specific, and the percentages are based on the number of females.

Twenty-seven (27) subjects in the alatrofloxacin/trovafoxacin group and 38 subjects in the Zosyn/Vantin™ group had serious adverse events that were considered by the investigator to be unrelated to study drug.

One subject each in the alatrofloxacin/trovafoxacin group had presumed pseudomembranous colitis and allergic reaction and one subject in the Zosyn/Vantin™ group had *C. difficile* diarrhea, which were serious adverse events that were considered to be related to study drug.

Five subjects in the alatrofloxacin/trovafoxacin group and six subjects in the Zosyn/Vantin™ group died during this study. Two subjects in each group died within 30 days of the last dose of study drug. No death was considered to be treatment-related.

Sponsor Summary and Conclusions: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafoxacin (200 mg daily) for 10 or 14 days of total therapy and intravenous piperacillin sodium/tazobactam sodium (Zosyn™ - 3.375 g four times daily) followed by oral cefpodoxime proxetil (Vantin™ -400 mg twice daily) for 10 or 14 days of total therapy were equivalent for the sponsor-defined clinical success rate at the end of treatment and the end of study in clinically evaluable subjects with complicated skin and skin structure infection. Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and the end of study for the most frequently isolated pathogens of (*S. aureus* and *S. epidermidis*).

The percentage of subjects discontinued from treatment due to adverse events (all causality) was 20% in the alatrofloxacin/trovafoxacin group and 6% in the Zosyn/Vantin™ group. For subjects in the alatrofloxacin/trovafoxacin group, the most common treatment-related adverse events that led to discontinuation from treatment were insertion site reaction/pain, dizziness, flushing/hot flushes, headache, and nausea. For subjects in the Zosyn/Vantin™ group, the most common treatment-related adverse events that led to discontinuation from treatment were those associated with the gastrointestinal system (nausea and diarrhea). The overall percentage of all and treatment-related adverse events in the alatrofloxacin/trovafoxacin group was comparable to that of subjects in the Zosyn/Vantin™ group (70% and 27% versus 69% and 26%, respectively). The most commonly reported treatment-related adverse events were headache (6%), nausea (6%) and vaginitis (5%) in the alatrofloxacin/trovafoxacin group and diarrhea (8%), vaginitis (7%) and headache (5%) in the Zosyn/Vantin™ group.

Reviewer's Summary and Conclusions Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafoxacin (200 mg daily) for 10 or 14 days of total therapy was considered therapeutically equivalent to intravenous Zosyn™ (3.375 g four times daily) followed by oral Vantin™ (400 mg twice daily) for 10 or 14 days of total therapy at both EOT and EOS in clinically evaluable patients. In clinically ITT patients, alatrofloxacin/trovafoxacin and Zosyn/Vantin were considered therapeutically equivalent at EOS but not EOT. EOT was considered the test of cure visit by the sponsor. However, as the EOT visit was scheduled for only a day after the patient discontinued therapy, this reviewer places more emphasis on EOS results.

A significantly higher proportion of alatrofloxacin/trovafoxacin patients discontinued treatment due to an adverse event, experienced application/injection/incision/insertion site reaction, and developed constipation than did Zosyn/Vantin patients (29/144 = 20% vs. 8/142 = 6%, $p=0.0003$ using the test of equal proportions based on the normal approximation to the binomial distribution; 11/144 = 8% vs. 1/142 or < 1%, $p=0.005$ using Fisher's exact test; and 22/144 = 15% vs. 7/142 = 5%, $p=0.004$ using the test of equal proportions based on the normal approximation to the binomial distribution, respectively). Of note, more alatrofloxacin/trovafoxacin patients experienced aggravated infection as an adverse event (this difference was marginally statistically significant: 9/144 = 6% vs. 2/142 = 1%, $p=0.06$ using Fisher's exact test). Zosyn/Vantin patients experienced significantly more diarrhea than did alatrofloxacin/trovafoxacin patients (17/142 = 12% vs. 7/144 = 5%, $p=0.03$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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VII.B. Protocol 154-132

AN OPEN-LABEL, NON-COMPARATIVE, MULTICENTER TRIAL ON THE USE OF ORAL TROVAFLOXACIN FOR THE TREATMENT OF DIABETIC FOOT INFECTIONS.

Study Dates: 7 June 1995 - 16 May 1996

Study Objectives: The objective of this study was to evaluate the safety and efficacy of trovafloxacin in the treatment of subjects with diabetic foot infection requiring oral antibiotic therapy.

Study Design: Study 154-132 was an open-label, non-comparative, multicenter trial of trovafloxacin (200 mg once daily) administered orally for 10 or 14 days in the treatment of subjects with diabetic foot infection.

***Reviewer's Note:** Since this trial is uncontrolled, results should be interpreted with caution. This is especially true as clinical outcome is the primary efficacy variable, and may be judged somewhat subjectively by the investigator and/or the sponsor.*

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥ 18 years of age at the baseline visit with clinically documented diabetic foot infection (without underlying osteomyelitis) were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from culture specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11 or 15) and at the end of study (Visit 4; Day 30), or at the time of discontinuation from the study. A clinical evaluation to determine the length of treatment (10 or 14 days) was to be conducted at Visit 2 (Day 4). Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection such as resolution of fever, disappearance or diminution of culturable exudate, the disappearance or reduction of erythema, tenderness, pain, induration, swelling, or leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of all signs and symptoms of diabetic foot infection), improvement (incomplete resolution of signs and symptoms of diabetic foot infection and no requirement for additional antibiotics), or failure (lack of resolution of any of the signs and symptoms of diabetic foot infection and a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), Visit 3 (EOT; Day 11 or 15), and at Visit 4 (EOS; Day 30), or at the time of discontinuation from the study. Bacteriological response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence or relapse; each pathogen was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection or colonization.

The primary efficacy endpoint was sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS;
- Investigator-defined clinical response at EOT, in addition to sponsor-defined clinical response and investigator-defined clinical response at EOS.

Reviewer's Note: Since the EOT visit is only a day or so after treatment was discontinued, this reviewer will place more emphasis on the clinical response rates at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Efficacy Results:

Analysis Groups

Table 7b.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Table 7b.1. Evaluation Groups

Evaluation Groups:	Trovanoxacin 200 mg/day	
Enrolled Subjects	225	
All Treated Subjects	225	(100%)
Withdrawn from Treatment	15	(7%)
Completed Treatment	210	(93%)
Completed Study	217	(96%)
Completed Treatment and Study	209	(93%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	224	(>99%)
Clinically Evaluable	214	(95%)
Bacteriologically Intent-to-Treat	190	(84%)
Bacteriologically Evaluable	180	(80%)
Assessed for Safety		
Adverse Events	225	(100%)
Laboratory Tests	221	(98%)

Of the 225 enrolled subjects, one subject had an inappropriate baseline diagnosis (i.e., no clinical signs or symptoms of infected diabetic foot at baseline as defined by protocol) and was excluded from all intent-to-treat and evaluable analyses.

Of the 224 clinical ITT subjects, 10 subjects were not clinically evaluable; therefore, 214 subjects were clinically evaluable. The most common reasons for exclusion from the clinically evaluable efficacy analyses were no post-baseline clinical assessments and no post-baseline clinical response in evaluable window (each, 5/225, 2%). Other reasons were

insufficient therapy, prior antibiotic therapy, and concomitant antibiotic therapy. (Subjects may have had more than one reason for exclusion from analysis.)

Of the 224 clinical ITT subjects, 34 subjects had negative baseline cultures; therefore, 190 subjects were included in the bacteriological ITT analyses.

Of the 214 clinically evaluable subjects, 34 subjects were not included in the bacteriologically evaluable analyses; therefore, 180 subjects were bacteriologically evaluable. The only reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (34/225, 15%).

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Discontinuations

Of the 225 treated subjects, 15 were prematurely discontinued from treatment as summarized in Table 7b.2.

Table 7b.2. A Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Trovafloxacin 200 mg (N=225)	
	Number and Percentage (%) of Subjects	
Total Discontinued	15	(7%)
Discontinuations Related to Study Drug:	10	(4%)
Adverse Event	3	(1%)
Insufficient Response	7	(3%)
Discontinuations Unrelated to Study Drug:	5	(2%)
Lost to Follow-up	1	(<1%)
Withdrew Consent	4	(2%)

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Demographics

One hundred-sixteen (116) of the 225 treated subjects (52%) were males and 109 were females (48%). The males and females were generally comparable with respect to age, race, and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects. The mean age of subjects was 62.1 years. Forty-eight percent (48%) of subjects were ≥65 years of age.

The primary diagnosis for clinical ITT subjects was diabetic foot infection. The median duration since onset of infection was 11.5 days. Twenty-nine (29) subjects had a duration since onset of infection of >50 days. The maximum duration since onset of infection was 1118 days (Subject 5845-0007). Seventy-nine (79/224, 35%) clinical ITT subjects had Type I diabetes and 145/224 (65%) had Type II diabetes. Similar results were observed for clinically evaluable subjects.

The most commonly reported type of infection among clinical ITT subjects was foot ulcer (183/224, 82%). Of note, subjects may have had more than one type of infection at baseline. Other types of infections included cellulitis with and without a baseline pathogen and "other" infections (including abscess, paronychia, traumatic wound infection, ingrown or infected nail, leg, ankle, or toe ulcer, dehiscence at surgical site, leg or toe infection).

One hundred-thirteen (113) clinical ITT subjects (50%) did not require a surgical drainage procedure at baseline or during the study. Ninety-eight (98) clinical ITT subjects (43%) had skin infections that required surgical intervention at baseline and 73 (32%) had skin infection that required surgical intervention post-baseline. The most frequently performed type of surgical intervention post-baseline was surgical debridement (71/224, 32%). The most commonly reported type of skin infection for subjects requiring surgical intervention was foot ulcer (86/111, 77%).

A summary of type of skin infection at baseline and number of subjects with a surgical drainage procedure is presented for clinical intent-to-treat subjects in Table 7b.3.

Table 7b.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT Subjects)	
	Trovaflaxacin 200 mg (N=224)
Type of Infection^a	Number and Percentage (%) of Subjects
Cellulitis with a Baseline Pathogen	48 (21%)
Cellulitis without a Baseline Pathogen	13 (6%)
Foot Ulcer	183 (82%)
Other	21 (9%)
Subjects Requiring Surgical Intervention ^b	111 (49%)
At Baseline	98 (43%)
Post-Baseline ^c	73 (32%)
Before the EOT Assessment	65 (29%)
After the EOT Assessment	48 (21%)

a A subject may have had more than one type of infection.
 b Two of these subjects (Subjects 5190-0007 and 5842-0008) required surgical intervention, which occurred either outside of the end of study window (Subject 5842-0008; excision of the toe nail) or the surgical procedure and timing of the procedure was not specified on the case report form (Subject 5190-0007).
 c Sixty-two (62) subjects required surgical intervention both prior to and post-baseline (57 subjects had surgical drainage at baseline and before the end of treatment, and 43 subjects had surgical drainage at baseline and after the end of treatment). In addition, two subjects (Subjects 6027-0007 and 6447-0001) had surgical drainage procedures performed post-baseline both before and after the end of treatment.

Among all treated subjects, 97/225 (43%) had at least one disease/syndrome at baseline. The most common disease/syndrome reported at baseline was peripheral vascular disease (77/225, 34%).

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented in Table 7b.4.

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Table 7b.4. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
		Trovafloracin 200 mg (N=214)	
		Number and Percentage (%) of Subjects	
End of Treatment			
Number of Subjects Assessed		209	(100%)
Success (Cure + Improvement)		195	(93%)
Distribution of Clinical Response:			
Cure		93	(44%)
Improvement		102	(49%)
Failure		14	(7%)
End of Study			
Number of Subjects Assessed		206	(100%)
Success (Cure + Improvement)		179	(87%)
Distribution of Clinical Response:			
Cure		146	(71%)
Improvement		33	(16%)
Failure		16	(8%)
Relapse		11	(5%)

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented in Table 7b.5.

Table 7b.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)				
Pathogen	Trovafloracin 200 mg (N=180)		Trovafloracin 200 mg (N=174)	
	Number of Subjects			
	End of Treatment		End of Study	
<i>St. aureus</i>	53/59	(90%)	48/60	(80%)
<i>St. epidermidis</i>	27/27	(100%)	25/27	(93%)
<i>E. faecalis</i>	27/32	(84%)	23/32	(72%)
<i>St. haemolyticus</i>	16/16	(100%)	13/15	(87%)
<i>P. aeruginosa</i>	11/14		8/16	(50%)
<i>Corynebacterium sp.</i>	10/10		11/12	
<i>P. mirabilis</i>	10/11		10/11	
<i>E. coli</i>	11/14		11/14	
<i>Staphylococcus sp.</i>	7/7		6/7	
<i>St. simulans</i>	6/6		6/6	
<i>St. hominis</i>	6/6		5/6	
<i>Streptococcus sp.</i>	11/11		10/10	
<i>Str. agalactiae</i>	12/13		12/13	
<i>Peptostreptococcus sp.</i>	4/6		4/6	
<i>Peptostreptococcus magnus</i>	2/5		2/5	

St. = *Staphylococcus*; *Str.* = *streptococcus*
^a ≥10 isolates of a given pathogen at either timepoint and ≥5 isolates of any *staphylococcus* and *streptococcus* species; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

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A summary of clinical success rates for clinical intent-to-treat subjects subset by type of infection at baseline at the end of treatment and at the end of study is presented in Table 7b.6.

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Table 7b.6. Summary of Sponsor-Defined Clinical Success Rates Subset by Type of Baseline Infection (Clinical ITT Subjects)				
	Trovafloxacin 200 mg (N=224)			
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Type of Infection^a	EOT		EOS	
Foot Ulcers	161/179	(90%)	152/183	(83%)
Cellulitis Without a Baseline Pathogen	11/13	(85%)	11/13	(85%)
Cellulitis With a Baseline Pathogen	44/48	(92%)	43/48	(90%)
Other ^b	19/20	(95%)	20/21	(95%)

a A subject may have had more than one type of infection at baseline.
b Other infections included abscess, blister, paronychia, bulla, traumatic wound infection, ingrown or infected nail, leg, ankle, or toe ulcer, dehiscence at surgical site, leg or toe infection.

A summary of clinical success rates for clinical intent-to-treat subjects subset by timing of surgical intervention at the end of treatment and at the end of study is presented in Table 7b.7.

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Table 7b.7. Summary of Sponsor-Defined Clinical Success Rates Subset by Timing of Surgical Intervention (Clinical ITT Subjects)				
	Trovafloxacin 200 mg (N=224)			
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
Timing of Surgical Intervention^a	EOT^b		EOS	
No Surgical Intervention	103/112	(92%)	99/113	(88%)
Surgical Intervention at Baseline	84/94	(89%)	81/98	(83%)
Surgical Intervention Post Baseline ^c				
Before the EOT Assessment	57/63	(90%)	54/65	(83%)
After the EOT Assessment	41/46	(89%)	37/48	(77%)

a Subjects may have had surgical intervention at more than one timepoint.
b Five clinical intent-to-treat subjects were not assessed for clinical response at the end of treatment.
c Two subjects (Subjects 5190-0007 and 5842-0008) had surgical procedures performed, which occurred either outside of the end of study window (Subject 5842-0008; excision of the toe nail) or the surgical procedure and timing of the procedure was not specified on the case report form (Subject 5190-0007).

Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects for the most frequently isolated pathogens at the end of treatment and the end of study are presented in Table 7b.8.

Table 7b.8 A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Trovafloracin 200 mg (N=180)	Trovafloracin 200 mg (N=174)
	Number of Pathogens	
Pathogen	End of Treatment	End of Study
<i>St. aureus</i>	48/58 (83%)	49/60 (82%)
<i>St. epidermidis</i>	25/28 (89%)	24/27 (89%)
<i>E. faecalis</i>	25/33 (76%)	25/32 (78%)
<i>St. haemolyticus</i>	14/16 (88%)	12/15 (80%)
<i>P. aeruginosa</i>	9/15 (60%)	10/16 (63%)
<i>Corynebacterium</i> sp.	10/11	12/12
<i>E. coli</i>	13/14	13/14
<i>P. mirabilis</i>	11/11	11/11
<i>Staphylococcus</i> sp.	7/7	6/7
<i>St. hominis</i>	6/6	5/6
<i>St. simulans</i>	5/6	6/6
<i>Streptococcus</i> sp.	9/11	8/10
<i>Str. agalactiae</i>	11/13	12/13
<i>Peptostreptococcus</i> sp.	6/6	5/6
<i>Peptostreptococcus magnus</i>	4/5	3/5

St. = *staphylococcus*; *Str.* = *Streptococcus*
 a ≥10 isolates of a given pathogen at either timepoint and ≥5 isolates of any staphylococcus and streptococcus species; percents displayed only when denominator is ≥15.
 A subject could have had more than one pathogen isolated at baseline.

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Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events, and clinically significant laboratory values is presented in Table 7b.9. Tables 7b.10 and 7b.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 7b.9. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloracin 200 mg daily (N=225)
	Number and Percentage (%) of Subjects
Adverse Events: All Causalities	74/225 (33%)
Treatment-Related Adverse Events	37/225 (16%)
Discontinuations Due to an Adverse Event ^a	8/225 (4%)
Clinically Significant Laboratory Values	66/221 (30%)

a Three subjects were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related.

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Table 7b.10. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)	
Trovafloxacin 200 mg (N=225)	
Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	74 (33%)
BODY SYSTEM WHO Term	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	26 (12%)
Dizziness	20 (9%)
Headache	5 (2%)
GASTROINTESTINAL SYSTEM	25 (11%)
Dyspepsia	5 (2%)
Nausea	9 (4%)
GENERAL	14 (6%)
Fever	5 (2%)
SKIN AND APPENDAGES	14 (6%)
Pruritus	4 (2%)
a ≥2 % of subjects.	
b Includes data up to 7 days after last dose of active study medication.	

Table 7b.11. A Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)	
Trovafloxacin 200 mg (N=225)	
Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	37 (16%)
BODY SYSTEM WHO Term	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	22 (10%)
Dizziness	18 (8%)
Headache	5 (2%)
GASTROINTESTINAL SYSTEM	16 (7%)
Nausea	6 (3%)
a ≥2 % of subjects.	
b Includes data up to 7 days after last dose of active study medication.	

Two subjects died and both deaths occurred following completion of this study, as follows:

- Two subjects died >30 days after the last dose of study drug. Subject 5841-0024 died of cardiorespiratory arrest and Subject 6536-0010 died of acute myocardial infarction. Neither of these deaths was considered by the investigator to be related to study drug.

Seventeen (17) subjects had serious adverse events that occurred during or following completion of this study. None of the serious adverse events were considered by the investigator to be related to study drug; all serious adverse events were attributed to other illnesses, the disease under study, "other" reasons, or concomitant treatment.

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Sponsor Summary and Conclusions: Trovafloxacin 200 mg once daily for 10 or 14 days was clinically effective in the treatment of diabetic foot infection. In addition, trovafloxacin was bacteriologically effective in eradicating the most frequently isolated baseline pathogens including *S. aureus*, *S. epidermidis*, *E. faecalis*, *P. aeruginosa*, *E. coli*, and anaerobic streptococci.

The overall percentage of all and treatment-related adverse events was 33% and 16%, respectively. The most commonly reported treatment-related adverse event was dizziness (8%). The percentage of subjects discontinued from treatment due to adverse events was 4% (8 subjects), of whom three subjects were discontinued from treatment due to treatment-related adverse events.

Reviewer's Summary and Conclusions: *Clinical success rates for trovafloxacin 200 mg once daily for 10 or 14 days were 195/209 = 93% at EOT and 179/206 = 87% at EOS. Due to the nature of this trial (i.e., it is uncontrolled), however, it is difficult to know how these results should be interpreted.*

The most common adverse events experienced by patients in this trial were dizziness (9%) and nausea (4%).

VII.C. Protocol 154-139

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A RANDOMIZED, MULTICENTER, OPEN TRIAL COMPARING ORAL TROVAFLOXACIN (200 MG) AND AUGMENTIN FOR THE TREATMENT OF COMPLICATED INFECTIONS OF THE SKIN AND SKIN STRUCTURE.

Reviewer's Note: *"Open" is used here to indicate that the trial was unblinded.*

Study Dates: 23 September 1995 - 10 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin with Augmentin™ for the treatment of subjects with complicated infections of the skin and skin structure.

Study Design: Study 154-139 was a randomized, comparative, multicenter open trial of trovafloxacin (200 mg as a single dose in the morning) versus Augmentin (1.5 g daily in three equally divided doses of 500 mg), administered orally for 10 or 14 days for the treatment of complicated infections of the skin and skin structure [e.g., infected ischemic ulcers including diabetic foot ulcers without underlying osteomyelitis, infected burns, major abscesses, other skin structure infections requiring significant surgical intervention along with antimicrobial therapy, and infections of the deeper soft tissues].

Reviewer's Note: *Since the primary endpoint in this study is clinical outcome, it is of some concern that this study was not blinded. Results should be interpreted with caution.*

Diagnoses and Criteria for Inclusion of Subjects: Men or women ≥18 years of age at the baseline assessment, with clinically documented complicated infection of the skin or skin structure.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical signs and symptoms of infection) and bacteriologic response (based on eradication of causative organisms isolated from culture specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 11 or 15) and at the end of study (Visit 4; Day 30), or at the time of discontinuation from the study. A clinical evaluation to determine the length of treatment (10 or 14 days) was to be conducted at Visit 2 (Day 4). Clinical response was to be based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical signs of infection, such as resolution of fever, disappearance or diminution in culturable exudate, the disappearance or reduction of erythema, tenderness, pain, induration, swelling or leukocytosis, and improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of the complicated skin or skin structure infection), improvement (incomplete resolution of signs and symptoms of complicated skin or skin structure infection and no requirement for additional antibiotics), or failure (lack of resolution of any of the signs and symptoms of complicated skin or skin structure infection and a need for an additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), Visit 3 (EOT; Day 11 or 15) and at Visit 4 (EOS; Day 30), or at the time of discontinuation from the study. Bacteriological response was to be classified by the sponsor as eradication, presumed eradication, persistence, presumed persistence or relapse. Each pathogen was to be classified by the sponsor as eradication, presumed eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

The primary efficacy endpoint was sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS.
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

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Reviewer's Note: Since the EOT visit is only a day or so after treatment was discontinued, this reviewer will place more emphasis on the clinical response rates at EOS.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

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Efficacy Results:APPEARS THIS WAY
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Table 7c.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Table 7c.1. Evaluation Groups

Evaluation Groups:	Trovfloxacin		Augmentin	
	Number and Percentage (%) of Subjects			
Randomized	166		157	
All Treated Subjects	160	(96%)	156	(>99%)
Completed Treatment	145	(91%)	133	(85%)
Completed Study	150	(94%)	146	(94%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	165	(>99%)	156	(>99%)
Clinically Evaluable ^a	155	(93%)	146	(93%)
Bacteriological Intent-to-Treat	130	(78%)	114	(73%)
Bacteriologically Evaluable ^a	123	(74%)	108	(69%)
Assessed for Safety				
Adverse Events	160	(100%)	156	(100%)
Laboratory Tests	158	(99%)	149	(96%)

^a Based on End of Treatment assessment

One hundred sixty-six (166) subjects were randomized to trovafloxacin and 157 subjects were randomized to Augmentin treatment. Of the 166 randomized trovafloxacin subjects and 157 randomized Augmentin subjects, six trovafloxacin subjects and one Augmentin subject were not treated. Of the 160 trovafloxacin and 156 Augmentin-treated subjects, one subject (6134-0019) in the trovafloxacin group and one subject (6300-0378) in the Augmentin group were excluded from clinical intent-to-treat analysis due to incorrect administration of study drug.

Of the 165 trovafloxacin and 156 Augmentin clinical ITT subjects, 10 subjects in each group were not clinically evaluable; therefore, 155 trovafloxacin and 146 Augmentin subjects were clinically evaluable. The most common reasons for exclusion from the clinically evaluable efficacy analyses was randomized, not treated (trovfloxacin: 6/165, 4%; Augmentin: 1/156, ≤1%) in the trovafloxacin group and insufficient therapy (trovfloxacin: 3/165, 2%; Augmentin: 5/156, 3%) in the Augmentin group. Other reasons were no post-baseline clinical assessment, no post-baseline clinical assessment within the evaluable window, and concomitant antibiotic therapy for intercurrent illness.

Of the 165 trovafloxacin and 156 Augmentin clinical ITT subjects, 35 subjects in the trovafloxacin group and 42 subjects in the Augmentin group had negative baseline cultures; therefore, 130 subjects in the trovafloxacin group and 114 subjects in the Augmentin group were included in the bacteriological ITT analysis.

Of the 155 trovafloxacin and 146 Augmentin clinically evaluable subjects, 32 subjects in the trovafloxacin group and 38 subjects in the Augmentin group were not included in the bacteriologically evaluable analyses; therefore, 123 subjects in the trovafloxacin group and 108 subjects in the Augmentin group were bacteriologically evaluable. The more common

reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (32/165 [19%], trovafloxacin and 38/156 [24%], Augmentin). The other reason was baseline culture performed outside window. One subject (6417-0466) in the trovafloxacin group was not bacteriologically evaluable due to both no baseline culture and culture performed outside evaluable window.

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Discontinuations

Of the 160 trovafloxacin and 156 Augmentin treated subjects, 15 and 23 subjects, respectively, were prematurely discontinued from treatment as summarized in Table 7c.2.

Table 7c.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)		
	Trovafloxacin 200 mg (N=160)	Augmentin 500 mg TID (N=156)
	Number and Percentage (%) of Subjects	
Total Discontinued	15 (9%)	23 (15%)
Discontinuations Related to Study Drug:		
Adverse Event	5 (3%)	14 (9%)
Insufficient Response	4 (3%)	13 (8%)
	1 (<1%)	1 (<1%)
Discontinuations Unrelated to Study Drug:		
Adverse Event	10 (6%)	9 (6%)
Did Not Meet Randomization Criteria	4 (3%)	3 (2%)
Other	1 (<1%)	0
Protocol Violation	4 (3%)	5 (3%)
Withdrawn Consent	1 (<1%)	0
	0	1 (<1%)

Reviewer's Note: Significantly more Augmentin patients discontinued treatment due to treatment related causes (14/156=9% vs. 5/160=3%, p=0.03 using the test of equal proportions based on the normal approximation to the binomial distribution). Most of this difference was due to the higher percentage of Augmentin patients discontinuing due to treatment-related adverse events (13/156=8% vs. 4/160=3%, p=0.025 using Fisher's exact test).

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Demographics

Eighty-seven (87) of the 160 treated trovafloxacin subjects (54%) were males and 73 were females (46%), and 77 of the 156 treated Augmentin subjects (49%) were males and 79 were females (51%). The subjects in the trovafloxacin and Augmentin treatment groups were generally comparable with respect to age, race, and weight. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects. The mean age of subjects in the trovafloxacin and Augmentin groups was 55.2 years and 54.2 years, respectively. Thirty-nine percent (39%) of subjects in the trovafloxacin group and 37% of subjects in the Augmentin group were ≥65 years of age.

The primary diagnosis for clinical ITT subjects was complicated skin and skin structure infection. The median duration since onset of infection was 8.0 days for subjects in both treatment groups. Similar durations since onset of infection were observed for clinically evaluable subjects in both treatment groups.

There were no marked differences between all treated subjects in the trovafloxacin and Augmentin treatment groups with respect to medical history at baseline. The most commonly reported disease/syndromes at study entry were peripheral vascular disease (trovafloxacin: 47/160, 29%; Augmentin: 48/156, 31%) and diabetes mellitus (trovafloxacin: 40/160, 25%; Augmentin: 33/156, 21%).

All types of infections were reported at similar rates in both treatment groups. The most commonly reported type of skin infections for subjects in both treatment groups were other deep soft tissue infections (e.g., post-operative surgical wound infections) (62/165 [38%], trovafloxacin; and 55/156 [35%], Augmentin). The most commonly reported type of deep soft tissue infections were classified as "other" (these are listed in Table 7c.3) and reported for 21 of 165 trovafloxacin subjects (13%) and 17 of 156 Augmentin subjects (11%).

The majority of clinical ITT subjects in both treatment groups (76%) did not require a surgical drainage procedure at baseline or during the study. Thirty-three (33) trovafloxacin subjects (20%) and 30 Augmentin subjects (19%) required surgical drainage at baseline, and 16 subjects (10%) in each treatment group had surgical drainage done post-baseline.

A summary of type of skin infection at baseline and number of subjects with a surgical drainage procedure is presented for clinical ITT subjects in Table 7c.3.

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Table 7c.3. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure (Clinical ITT Subjects)

	Trovafloxacin 200 mg (N=165)	Augmentin 500 mg TID (N=156)
Type of Infection^a	Number and Percentage (%) of Subjects	
Diabetic Foot Ulcer without Osteomyelitis	24 (15%)	26 (17%)
Other Ischemic Ulcer	36 (22%)	38 (24%)
Infected Burn	8 (5%)	7 (4%)
Major Abscess	26 (16%)	26 (17%)
Other Skin Structure Infection Requiring Surgery	9 (5%)	5 (3%)
Ulcers	1 (<1%)	1 (<1%)
Cysts	3 (2%)	0
Hydrantitis	1 (<1%)	1 (<1%)
Post-operative surgical wound infection	1 (<1%)	0
Other ^b	3 (2%)	3 (2%)
Other Deep Soft Tissue Infections (Post-Operative)	62 (38%)	55 (35%)
Abscess	0	1 (<1%)
Ulcers	3 (2%)	4 (3%)
Cellulitis	17 (11%)	13 (8%)
Erysipelas	2 (1%)	2 (1%)
Hydrantitis	1 (<1%)	1 (<1%)
Post-operative surgical wound infection	16 (10%)	16 (10%)
Cysts	1 (<1%)	1 (<1%)
Other ^c	21 (13%)	17 (11%)
Subjects Requiring Surgical Drainage Procedure^d	39 (24%)	37 (24%)
At Baseline	33 (20%)	30 (19%)
Post-Baseline	16 (10%)	16 (10%)
Before the EOT Assessment	12 (7%)	12 (8%)
After the EOT Assessment	8 (5%)	10 (6%)

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a A subject may have had more than one type of infection.
 b Other types of skin structure infections requiring surgery included a laceration, infected hematoma, pimple, abrasion, toe infection, and whitlow.
 c Other types of deep soft tissue infections included chronic infections, pyogenic granule, wound infections, sequelae of osteomyelitis, chronic edema, paronychia, furuncle, fistula, bursitis, eczema, infected insect bites, vasculitis, impetiginous lesion, thrombophlebitis, whitlow, pyoderma, and blister infected dermatitis.
 d Subjects were counted in each timepoint that they had a surgical drainage procedure. Therefore, numbers do not add up to the total.

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Clinical Response

A summary of clinical response rates for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 7c.4. Trovafloxacin was considered therapeutically equivalent to Augmentin at both EOT and EOS.

Table 7c.4. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)			
	Trovafloxacin 200 mg (N=155)	Augmentin 500 mg TID (N=146)	95% CI
Number and Percentage (%) of Subjects			
End of Treatment:			
Number of Subjects Assessed	154 (100%)	140 (100%)	
Success (Cure + Improvement)	143 (93%)	130 (93%)	(-5.9, 5.9)
Distribution of Clinical Response:			
Cure	49 (32%)	45 (32%)	
Improvement	94 (61%)	85 (61%)	
Failure	11 (7%)	10 (7%)	
End of Study:			
Number of Subjects Assessed	139 (100%)	141 (100%)	
Success (Cure + Improvement)	119 (86%)	121 (86%)	(-8.4, 8.0)
Distribution of Clinical Response:			
Cure	86 (62%)	81 (57%)	
Improvement	33 (24%)	40 (28%)	
Failure	11 (8%)	11 (8%)	
Relapse	9 (6%)	9 (6%)	

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A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 7c.5.

Table 7c.5. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)

	Trovafloracin 200 mg (N=155)	Augmentin 500 mg TID (N=146)	Trovafloracin 200 mg (N=155)	Augmentin 500 mg TID (N=146)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>St. aureus</i>	56/59 (95%)	52/58 (90%)	48/54 (89%)	48/56 (86%)
<i>P. aeruginosa</i>	21/21 (100%)	14/15 (93%)	18/20 (90%)	12/15 (80%)
<i>E. faecalis</i>	15/16 (94%)	11/11 (100%)	13/14 (93%)	13/13 (100%)
<i>P. mirabilis</i>	14/15 (93%)	5/5 (100%)	12/13 (92%)	6/6 (100%)
<i>St. epidermidis</i>	6/8	8/10	4/6	8/10
<i>E. coli</i>	8/9	5/5	7/9	5/5
<i>K. oxytoca</i>	7/7	5/5	5/6	5/5
<i>Staphylococcus sp.</i>	4/5	4/4	3/4	4/4
<i>St. haemolyticus</i>	0/1	1/1	0/1	1/1
<i>St. hominis</i>	1/1	3/3	1/1	3/3
<i>St. saprophyticus</i>	0/0	1/1	0/0	1/1
Coagulase Negative <i>Staphylococcus</i>	0/0	1/1	0/0	1/1
<i>Streptococcus sp.</i>	0/1	2/4	0/1	2/4
Anaerobic <i>Streptococcus</i>	1/1	0/0	1/1	0/0
<i>Str. agalactiae</i>	7/8	5/5	5/8	4/5
<i>Str. anginosus</i>	1/1	0/0	1/1	0/0
<i>Str. equisimilis</i>	5/5	3/3	2/2	3/3
<i>Str. oralis</i>	1/1	0/0	1/1	0/0
<i>Str. pyogenes</i>	4/4	6/6	2/2	6/6
Group A Beta <i>Streptococcus</i>	0/0	2/2	0/0	2/2
Group B Beta <i>Streptococcus</i>	0/0	1/1	0/0	0/1
Group G Beta <i>Streptococcus</i>	4/4	0/0	1/2	0/0
Beta hemolytic <i>Streptococcus</i>	0/0	1/1	0/0	1/1
<i>Peptostreptococcus sp.</i>	0/0	2/2	0/0	2/2
<i>P. prevotti</i>	0/1	2/2	0/1	2/2
<i>P. magnus</i>	0/0	2/2	0/0	2/2

St. = *Staphylococcus*; Str. = *Streptococcus*

a ≥5 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15 at least once for a given pathogen in either treatment group.

A subject could have had more than one pathogen isolated at baseline.

A summary of clinical success rates for clinical intent-to-treat subjects subset by type of infection at baseline at the end of treatment and at the end of study is presented by treatment group in Table 7c.6.

Type of Infection ^a	EOT		EOS	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
	Trovafloxacin 200mg (N=165)	Augmentin 500 mg TID (N=156)	Trovafloxacin 200mg (N=165)	Augmentin 500 mg TID (N=156)
Diabetic Foot Ulcer Without Osteomyelitis	21/24 (88%)	21/23 (91%)	19/24 (79%)	20/26 (77%)
Other Ischemic Ulcer	34/35 (97%)	33/37 (89%)	33/36 (92%)	31/38 (82%)
Infected Burn	7/8 (88%)	7/7 (100%)	7/8 (88%)	7/7 (100%)
Major Abscess	21/26 (81%)	22/25 (88%)	20/26 (77%)	22/26 (85%)
Other Skin Structure Infection Requiring Significant Surgical Interventions	8/9 (89%)	4/5 (80%)	8/9 (89%)	4/5 (80%)
Other Deep Soft Tissue Infections (Post-Operative)	53/62 (85%)	48/53 (91%)	49/62 (79%)	48/55 (87%)

^a A subject may have had more than one type of infection at baseline.

A summary of clinical success rates for clinical ITT subjects subset by timing of surgical intervention at the end of treatment and at the end of study is presented by treatment group in Table 7c.7. Comparable clinical success rates were observed between treatment groups at both EOT and EOS for subjects with no surgical intervention and subjects with surgical intervention at baseline. Among subjects with post-baseline surgical intervention before or after the end of treatment, subject subsets were too small for definitive conclusions to be drawn.

Timing of Surgical Intervention ^a	EOT		EOS	
	Number of Clinical Successes/Number of Subjects in a Subset and Percentage (%) of Subjects			
	Trovafloxacin 200 mg (N=165)	Augmentin 500 mg TID (N=156)	Trovafloxacin 200 mg (N=165)	Augmentin 500 mg TID (N=156)
No Surgical Intervention	111/125 (89%)	106/115 (92%)	104/126 (83%)	102/119 (86%)
Surgical Intervention at Baseline	27/33 (82%)	24/28 (86%)	26/33 (79%)	24/30 (80%)
Surgical Intervention Post Baseline				
Before the EOT Assessment	10/12 (83%)	8/11 (73%)	10/12 (83%)	8/12 (67%)
After the EOT Assessment	6/8 (75%)	6/9 (67%)	5/8 (63%)	6/10 (60%)

^a Subjects may have had surgical intervention at more than one timepoint.

Bacteriologic Response

Sponsor-defined pathogen eradication rates among bacteriologically evaluable subjects were comparable between the two treatment groups for *S. aureus*, *P. aeruginosa* and *E. faecalis* at the end of treatment and the end of study as presented in Table 7c.8.

Table 7c.8. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Trovafoxacin (N=123)	Augmentin (N=108)	95% CI	Trovafoxacin (N=110)	Augmentin (N=104)	95% CI
Number of Pathogens						
Pathogen	End of Treatment			End of Study		
<i>St. aureus</i>	46/59 (78%)	47/58 (81%)	-17.7, 11.5	43/54 (80%)	41/56 (73%)	-9.4, 22.2
<i>P. aeruginosa</i>	13/21 (62%)	6/15 (40%)	-10.4, 54.2	14/20 (70%)	9/15 (60%)	-21.9, 41.9
<i>E. faecalis</i>	14/16 (88%)	10/12 (83%)	ND	13/14 (93%)	11/13 (85%)	ND
<i>P. mirabilis</i>	9/15 (60%)	2/5 (40%)	ND	8/13 (62%)	5/6 (83%)	ND
<i>St. epidermidis</i>	4/7	9/11	ND	4/5	8/10	ND
<i>E. coli</i>	8/9	3/5	ND	8/9	3/5	ND
<i>K. oxytoca</i>	7/7	3/5	ND	5/6	3/5	ND
<i>Staphylococcus sp.</i>	5/5	4/4	ND	4/4	4/4	ND
<i>St. haemolyticus</i>	0/0	1/1	ND	0/1	1/1	ND
<i>St. hominis</i>	1/1	3/3	ND	1/1	3/3	ND
<i>St. saprophyticus</i>	0/0	1/1	ND	0/0	1/1	ND
Coagulase Negative <i>Staphylococcus</i>	0/0	1/1	ND	0/0	1/1	ND
<i>Streptococcus sp.</i>	0/1	4/4	ND	0/1	3/4	ND
Anaerobic <i>Streptococcus</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. agalactiae</i>	5/8	5/5	ND	5/8	4/5	ND
<i>Str. anginosus</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. equisimilis</i>	2/5	1/3	ND	1/2	1/3	ND
<i>Str. oralis</i>	1/1	0/0	ND	1/1	0/0	ND
<i>Str. pyogenes</i>	4/4	6/6	ND	2/2	6/6	ND
Group A Beta <i>Streptococcus</i>	0/0	2/2	ND	0/0	2/2	ND
Group B Beta <i>Streptococcus</i>	0/0	1/1	ND	0/0	0/1	ND
Group G Beta <i>Streptococcus</i>	2/4	0/0	ND	1/2	0/0	ND
Beta hemolytic <i>Streptococcus</i>	0/0	1/1	ND	0/0	1/1	ND
<i>Peptostreptococcus sp.</i>	0/0	2/2	ND	0/0	2/2	ND
<i>P. prevoti</i>	1/1	2/2	ND	1/1	2/2	ND
<i>P. magnus</i>	0/0	2/2	ND	0/0	2/2	ND

ND = not done; *St.* = *Staphylococcus*; *Str.* = *Streptococcus*

a ≥5 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15 at least once for a given pathogen in either treatment group.

A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events, and clinically significant laboratory values are presented in Table 7c.9. Tables 7c.10 and 7c.11 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 7c.9. Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Trovafloxacin (N=160)	Augmentin (N=156)
Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	54/160 (34%)	53/156 (34%)
Treatment-Related Adverse Events	25/160 (16%)	36/156 (23%)
Discontinuations From Treatment Due to an Adverse Event^a	9/160 (6%)	16/156 (10%)
Clinically Significant Laboratory Values	50/158 (32%)	48/149 (32%)
a Four (4) subjects in the trovafloxacin group and 13 subjects in the Augmentin group were discontinued due to adverse events that were considered by the investigator to be study drug-related.		

Reviewer's Note: As can be seen in Table 7c.10, significantly more trovafloxacin patients experienced dizziness (12/160=8% vs. 1/156 which is <1%, p=0.003 using Fisher's exact test), while significantly more Augmentin patients experienced diarrhea (23/156=15% vs. 2/160=1%, p<0.001 using Fisher's exact test).

Table 7c.10. Summary of the Most Commonly Reported Adverse Events ^{a, b} by Body System - All Causalities (All Treated Subjects)				
	Trovafloxacin 200 mg (N=160)		Augmentin 500 mg TID (N=156)	
Number and Percentage (%) of Subjects				
Number of Subjects With at Least One Adverse Event	54	(34%)	53	(34%)
BODY SYSTEM				
WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	19	(12%)	4	(3%)
Dizziness	12	(8%)	1	(<1%)
Headache	5	(3%)	2	(1%)
GASTROINTESTINAL SYSTEM	19	(12%)	35	(22%)
Abdominal Pain	3	(2%)	8	(5%)
Constipation	5	(3%)	1	(<1%)
Diarrhea	2	(1%)	23	(15%)
Nausea	5	(3%)	9	(6%)
Vomiting	3	(2%)	4	(3%)
GENERAL	9	(6%)	6	(4%)
Fever	4	(3%)	0	
a ≥3% of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				

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Table 7c.11. Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a, b} by Body System (All Treated Subjects)		
	Trovafloxacin 200 mg (N=160)	Augmentin 500 mg TID (N=156)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	25 (16%)	36 (23%)
BODY SYSTEM		
WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	14 (9%)	1 (<1%)
Dizziness	8 (5%)	1 (<1%)
Headache	4 (3%)	0
GASTROINTESTINAL SYSTEM	11 (7%)	31 (20%)
Abdominal Pain	2 (1%)	8 (5%)
Constipation	3 (2%)	0
Diarrhea	1 (<1%)	22 (14%)
Nausea	4 (3%)	7 (4%)
Vomiting	2 (1%)	4 (3%)
a ≥2% of subjects in either treatment group. b Includes data up to 7 days after last dose of active study medication.		

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Twelve (12/160, 8%) subjects in the trovafloxacin group and seven (7/156, 4%) subjects in the Augmentin group had serious adverse events during this study, none of which were considered by the investigators to be related to the study drugs.

One subject in each treatment died during this study, both within 30 days of the last treatment dose. Neither of these deaths was considered to be treatment-related.

Sponsor Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 10 or 14 days of total therapy and Augmentin (1.5 g in three equally divided doses of 500 mg daily) administered orally for 10 or 14 days of total therapy were comparable for the sponsor-defined clinical success rate at the end of treatment and the end of study in the subjects with complicated skin and skin structure infection. Sponsor-defined pathogen eradication rates were comparable between the two treatment groups at the end of treatment and the end of study for the most frequently isolated pathogens (*S. aureus*, *P. aeruginosa* and *E. faecalis*).

The percentage of subjects discontinued from treatment due to adverse events was 6% in the trovafloxacin group and 10% in the Augmentin group. The overall percentage of all causality and treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the Augmentin group (34% and 16% versus 34% and 23%, respectively). The most commonly reported treatment-related adverse events in the trovafloxacin group were dizziness (5%), headache (3%) and nausea (3%). The most commonly reported treatment-related adverse events in the Augmentin group were diarrhea (14%), abdominal pain (5%) and nausea (4%).

Reviewer's Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 10 or 14 days of total therapy and Augmentin (1.5 g in three equally divided doses of 500 mg daily) administered orally for 10 or 14 days of total therapy were shown to be therapeutically equivalent in terms of sponsor-defined clinical success rate at both the end of treatment and the end of study in subjects with complicated skin and skin structure infection. These results should be interpreted with some caution, however, due to the fact that this study was not blinded.

In this study significantly more trovafloxacin patients experienced dizziness (12/160 = 8% vs. 1/156 which is < 1%, $p = 0.003$ using Fisher's exact test), while significantly more Augmentin patients experienced diarrhea (23/156 = 15% vs. 2/160 = 1%, $p < 0.001$ using Fisher's exact test).

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VIII. CONCLUSIONS (Which May be Conveyed to the Sponsor)

1. Nosocomial Pneumonia

Overall, efficacy and safety appear acceptable for alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment in the treatment of nosocomial pneumonia.

The alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, thus if approved it will need to be labeled accordingly. In addition, it is of note that a significantly higher proportion of alatrofloxacin/trovafloxacin patients experienced adverse events and discontinued treatment due to adverse events compared to the control arm in both studies.

Conclusions from the individual protocols follow.

*Protocol 154-113: Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ciprofloxacin at both EOT and EOS in terms of clinical success rate for clinically evaluable patients for both the sponsor and the MO analysis. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional aztreonam or vancomycin to treat documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, respectively, if approved it will need to be labeled this way.*

A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced adverse events, 95% versus 81% for ciprofloxacin patients, and discontinued treatment due to adverse events, 15% versus 7% for ciprofloxacin patients ($p < 0.001$ and $p = 0.047$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

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*Protocol 154-137: Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ceftazidime/ciprofloxacin at both EOT and EOS in terms of the clinical success rate for clinically evaluable patients for both the sponsor and the MO analysis. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional gentamycin or vancomycin to treat documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, respectively, if approved it will need to be labeled this way.*

A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced treatment-related adverse events, 12% versus 4% for ceftazidime/ciprofloxacin patients, discontinued treatment due to an adverse event, 12% versus 4% for ceftazidime/ciprofloxacin patients, and discontinued treatment due to a treatment-related adverse event, 5% versus $< 1\%$ for ceftazidime/ciprofloxacin patients ($p = 0.01$, 0.02 and 0.03 , respectively, using the test of equal proportions based on the normal approximation to the binomial distribution for the first two comparisons and Fisher's exact test for the third comparison).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment for the treatment of nosocomial pneumonia. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, if approved it should be labeled accordingly.

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2. Community-Acquired Pneumonia

Overall, efficacy and safety appear acceptable for both (1) trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and (2) alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy in the treatment of community-acquired pneumonia.

Conclusions from the individual protocols follow.

Protocol 154-102: This was an exploratory study to examine the efficacy and safety of two different trovafloxacin doses. Clinical response rates for trovafloxacin 200 mg, trovafloxacin 300 mg, and cefaclor appeared similar at both EOT and EOS. However, sample sizes were too small to allow for any definitive conclusions about equivalence.

A significantly higher proportion of trovafloxacin 300 mg patients experienced adverse events, both all causality and treatment-related ($p=0.01$ and $p<0.001$, respectively, using the Chi-square test). A higher proportion of trovafloxacin 300 mg patients also discontinued treatment due to an adverse event (this was marginally significant; $p=0.07$ using Fisher's exact test).

Protocol 154-110: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy was considered therapeutically equivalent to intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy at both EOT and EOS.

The most common adverse events in the alatrofloxacin/trovafloxacin arm were headache (16%), insomnia (11%), constipation (9%), and nausea (9%). The most common adverse events in the ciprofloxacin/ampicillin/amoxicillin arm were insomnia (12%), headache (11%), constipation (10%), and nausea (10%).

Protocol 154-111: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.

Alatrofloxacin/trovafloxacin patients experienced a significantly higher percentage of the following adverse events than did ceftriaxone/cefepodoxime patients: central and peripheral nervous system events (overall), dizziness, headache, and constipation ($p < 0.001$, $p < 0.001$, $p = 0.046$, and $p = 0.01$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Protocol 154-112: Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxicillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were considered therapeutically equivalent in terms of clinical response in clinically evaluable patients at both EOT and EOS.

The proportion of trovafloxacin patients experiencing central and peripheral nervous system events (all causalities) was marginally significantly higher than that in the amoxicillin group ($p = 0.07$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Protocol 154-134: Trovafloxacin 200 mg once daily for 7 or 10 days and clarithromycin 500 mg BID for 7 or 10 days were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.

Overall, a higher proportion of clarithromycin patients experienced adverse events ($p = 0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution). In terms of individual adverse events, a higher proportion of trovafloxacin patients experienced dizziness ($p = 0.003$ using the test of equal proportions based on the normal approximation to the binomial distribution), while a higher proportion of clarithromycin patients experienced diarrhea and taste perversion ($p = 0.01$ and $p < 0.001$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of both (1) trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and (2) alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy for the treatment of community-acquired pneumonia.

3. Acute Exacerbation of Chronic Bronchitis

Overall, efficacy and safety appear acceptable for trovafloxacin 100 mg given once daily for 7 days in the treatment of acute bacterial exacerbation of chronic bronchitis.

Conclusions from the individual protocols follow.

Protocol 154-101: This was a Phase II study to examine the efficacy and safety of two different trovafloxacin doses. Clinical response rates for trovafloxacin 100 mg, trovafloxacin 300 mg, and ofloxacin appeared similar at both EOT and EOS (perhaps more

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similar at EOT), but sample sizes were too small to allow for any definitive conclusions about equivalence.

The percent of patients experiencing adverse events regardless of relationship to study drug, treatment-related adverse events, and discontinuations due to an adverse event were all significantly different across treatment groups (rates were higher in the trovafloxacin 300 mg arm; p-values <0.0001, <0.0001, and =0.001, respectively, using the chi-square test). In addition, the rate of dizziness in the trovafloxacin 300 mg arm was rather high (40% of patients experienced dizziness; 37% of patients experienced dizziness that was considered treatment related).

Protocol 154-109: Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to clarithromycin 500 mg twice daily for 7 days in terms of clinical-success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.

There was a higher incidence of both adverse events, regardless of relationship to study drug, and treatment-related adverse events in the clarithromycin arm ($p=0.04$ and $p<0.0001$, respectively). The most commonly reported adverse events in the trovafloxacin group were headache (10%), dizziness (6%), and nausea (6%) and the most commonly reported adverse events in the clarithromycin group were taste perversion (16%), nausea (10%), diarrhea (7%), and insomnia (7%).

Protocol 154-141: Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to ciprofloxacin 500 mg twice daily for 7 days in terms of clinical success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.

The most commonly reported adverse events in the trovafloxacin group were nausea (8%), dizziness (4%), headache (4%), and insomnia (4%) and the most commonly reported adverse events in the ciprofloxacin group were nausea (10%), dizziness (6%), diarrhea (5%), and insomnia (4%).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of trovafloxacin 100 mg given once daily for 7 days in the treatment of acute bacterial exacerbation of chronic bronchitis.

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4. Acute Sinusitis

Overall, efficacy and safety appear acceptable for trovafloxacin 200 mg given once daily for 10 days in the treatment of acute sinusitis. There is some concern about the high rate of dizziness (and patients discontinuing treatment due to dizziness), however this can probably be taken care of with appropriate labeling.

Conclusions from the individual protocols follow.

Protocol 154-114: Trovafloxacin 200 mg once daily for 10 days appears to have been effective in the treatment of acute sinusitis in this trial. Caution should be taken in interpreting results, however, due to the fact that this was an uncontrolled trial. Eighteen percent of trovafloxacin patients reported dizziness that was considered treatment related. Eleven percent of trovafloxacin patients reported nausea that was considered treatment related.

One of the investigators involved in this trial, Dr. Fiddes, has plead guilty to violations of FDA regulations. Results are fairly robust when patients from Dr. Fiddes' center are excluded. The number of evaluable patients with *M. catarrhalis* drops to 11 (slightly below the number of 15 recommended in the Division of Anti-Infective Drug Products 1992 "Points to Consider" document), however eradication rates still appear acceptable (10/11 = 91% patients are eradicated at EOT; 9/11 = 82% patients are eradicated at EOS).

Protocol 154-115: A greater number of patients in the trovafloxacin arm were excluded from the evaluable efficacy analysis ($p=0.025$), due largely to the greater number of patients who discontinued treatment due to an adverse event in the trovafloxacin arm ($p=0.002$). However, clinical response for trovafloxacin 200 mg once daily for 10 days was therapeutically equivalent to clarithromycin 500 mg BID for 14 days at both EOT and EOS for both the clinically evaluable and ITT patient group.

Central and peripheral nervous system adverse events were the most frequently occurring adverse events that led to discontinuation from treatment with trovafloxacin. Twenty-six trovafloxacin subjects (26/203, 13%) were discontinued due to dizziness, headache, vertigo, paresthesia, and/or hypoesthesia, compared to only four clarithromycin subjects (4/214, 2%) who discontinued due to headache, dizziness, paresthesia and/or hypertonia ($p<0.0001$).

Protocol 154-138: Trovafloxacin 200 mg once daily for 10 days was therapeutically equivalent to amoxicillin/clavulanate 500/125 mg three times daily for 10 days in terms of clinical-success rates at both EOT (the primary efficacy endpoint) and EOS. This was true for both the evaluable and ITT patient group (recall that a significantly higher number of trovafloxacin patients were excluded from the evaluable efficacy analysis, $p=0.025$).

Safety appears acceptable, although dizziness was noted in a number of patients (17%, regardless of relationship to treatment).

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The data provided by the sponsor in this submission support the approval of trovafloxacin 200 mg given once daily for 10 days in the treatment of acute sinusitis. There is some concern about the high rate of dizziness observed in the three sinusitis trials for patients on the trovafloxacin regimen (rates were 17% in study 154-138, 20% in study 154-114, and 34% in study 154-115). Thus, if approved it might be useful to include this information in the label.

5. Uncomplicated Skin and Skin Structure Infections

Overall, efficacy and safety appear acceptable for trovafloxacin 100 mg given once daily for 7-10 days in the treatment of uncomplicated skin and skin structure infections.

Conclusions from the individual protocols follow.

Protocol 154-129: Trovafloxacin 100 mg once daily for 7 days demonstrated therapeutic equivalence to flucloxacillin 500 mg every six hours for 7 days for clinical success rates at both EOT and EOS. Of note, although the numbers are small, trovafloxacin did not appear very effective against leg ulcers (only 1/8 = 13% patients was considered a clinical success at EOS).

A significantly higher proportion of trovafloxacin patients discontinued treatment due to an adverse event (12/140 = 9% trovafloxacin patients versus 3/138 = 2% flucloxacillin patients; $p=0.03$ using Fisher's exact test). Higher proportions of flucloxacillin patients experienced dyspepsia and urinary tract infections; the difference in dyspepsia rates was statistically significant (< 1% trovafloxacin patients vs. 5% flucloxacillin patients; $p=0.04$ using Fisher's exact test), the difference in urinary tract infection rates was marginally statistically significant (0% trovafloxacin vs. 3% flucloxacillin; $p=0.06$ using Fisher's exact test).

Protocol 154-130: Trovafloxacin 100 mg once daily for 7-10 days and cefpodoxime proxetil (Vantin) 400 mg twice daily for 7-10 days were therapeutically equivalent in terms of clinical success rates at both EOT and EOS for evaluable subjects with uncomplicated skin and skin structure infections.

The most common adverse events reported in the trovafloxacin group were headache (6%), diarrhea (5%), and dizziness (4%). In the Vantin group, the most commonly reported adverse events were diarrhea (9%), headache (7%), and nausea (4%). A higher percentage of Vantin patients experienced gastrointestinal system adverse events (18% versus 10% for trovafloxacin; $p=0.01$ using the test of equal proportions based on the normal approximation to the binomial distribution).

RECOMMENDED REGULATORY ACTION:

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The data provided by the sponsor in this submission support the approval of trovafloxacin 100 mg given once daily for 7-10 days in the treatment of uncomplicated skin and skin structure infections.

6. Complicated Skin and Skin Structure Infections

Overall, efficacy and safety appear acceptable for alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg daily) for 10 or 14 days of total therapy in the treatment of complicated skin and skin structure infections. This conclusion is based on results from study 154-131.

It is harder to come to a conclusion regarding the regimen of trovafloxacin 200 mg once daily for 10 or 14 days in the treatment of complicated skin and skin structure infections. Two studies, 154-132 and 154-139, were conducted using this regimen. Results regarding efficacy and safety appear acceptable in these two studies, however study 154-132 was uncontrolled and study 154-139, while controlled, was unblinded. Since the primary outcome in both studies was clinical success (not an entirely objective outcome measure), caution needs to be exercised in interpreting results from both studies.

Conclusions from the individual protocols follow.

Protocol 154-131: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg daily) for 10 or 14 days of total therapy was considered therapeutically equivalent to intravenous Zosyn™ (3.375 g four times daily) followed by oral Vantin™ (400 mg twice daily) for 10 or 14 days of total therapy at both EOT and EOS in clinically evaluable patients. In clinically ITT patients, alatrofloxacin/trovafloxacin and Zosyn/Vantin were considered therapeutically equivalent at EOS but not EOT. EOT was considered the test of cure visit by the sponsor. However, as the EOT visit was scheduled for only a day after the patient discontinued therapy, this reviewer places more emphasis on EOS results.

A significantly higher proportion of alatrofloxacin/trovafloxacin patients discontinued treatment due to an adverse event, experienced application/injection/incision/insertion site reaction, and developed constipation than did Zosyn/Vantin patients (29/144=20% vs. 8/142=6%, $p=0.0003$ using the test of equal proportions based on the normal approximation to the binomial distribution; 11/144=8% vs. 1/142 or <1%, $p=0.005$ using Fisher's exact test; and 22/144=15% vs. 7/142=5%, $p=0.004$ using the test of equal proportions based on the normal approximation to the binomial distribution, respectively). Of note, more alatrofloxacin/trovafloxacin patients experienced aggravated infection as an adverse event (this difference was marginally statistically significant: 9/144=6% vs. 2/142=1%, $p=0.06$ using Fisher's exact test). Zosyn/Vantin patients experienced significantly more diarrhea than did alatrofloxacin/trovafloxacin patients (17/142=12% vs. 7/144=5%, $p=0.03$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Protocol 154-132: Clinical success rates for trovafloxacin 200 mg once daily for 10 or 14 days were 195/209=93% at EOT and 179/206=87% at EOS. However, since this trial had no control group it is difficult to know how to interpret these results.

The most common adverse events experienced by patients in this trial were dizziness (9%) and nausea (4%).

Protocol 154-139: Trovafloxacin (200 mg once daily) administered orally for 10 or 14 days of total therapy and Augmentin (1.5 g in three equally divided doses of 500 mg daily) administered orally for 10 or 14 days of total therapy were shown to be therapeutically equivalent in terms of sponsor-defined clinical success rate at both the end of treatment and the end of study in subjects with complicated skin and skin structure infection. These results should be interpreted with some caution, however, due to the fact that this study was not blinded.

In this study significantly more trovafloxacin patients experienced dizziness (12/160 = 8% vs. 1/156 which is < 1%, $p = 0.003$ using Fisher's exact test), while significantly more Augmentin patients experienced diarrhea (23/156 = 15% vs. 2/160 = 1%, $p < 0.001$ using Fisher's exact test).

RECOMMENDED REGULATORY ACTION:

The data provided by the sponsor in this submission support the approval of alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg daily) for 10 or 14 days of total therapy for the treatment of complicated skin and skin structure infections.

It is harder to come to a conclusion regarding the regimen of trovafloxacin 200 mg once daily for 10 or 14 days in the treatment of complicated skin and skin structure infections. Two studies, 154-132 and 154-139, were conducted using this regimen. Results regarding efficacy and safety appear acceptable in these two studies, however study 154-132 was uncontrolled and study 154-139, while controlled, was unblinded. Since the primary outcome in both studies was clinical success (not an entirely objective outcome measure), the reviewing medical officer will have to determine whether results from these two trials are reasonable.

/S/

11/18/97

Nancy Paul Silliman, Ph.D.
Mathematical Statistician, Division of Biometrics IV

/S/

11/29/97

Concur: Mohammad Huque, Ph.D.
Acting Director, Division of Biometrics IV

cc:
Orig. NDA #20-759
Orig. NDA #20-760
HFD-590
HFD-590/Dr. Goldberger
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HFD-725/Dr. Jiang
HFD-725/Dr. Lin
HFD-725/Ms. Shores
HFD-344/Dr. Thomas
This review contains 197 pages.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020759/020760

MICROBIOLOGY REVIEW(S)

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520

Division of Anti-Infective Drug Products
Clinical Microbiological Review

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DRUG PRODUCT NAME

Proprietary:

Trovan

Nonproprietary/USAN:

Trovan I.V.

Code Names/#'s:

Trovafloracin Mesylate tablets

Therapeutic Class:

Alatrofloracin Mesylate I.V.

CP-116,517-27; CP 99,219;

1 S

PHARMACOLOGICAL CATEGORY:

Fluoroquinolone

DOSAGE FORM:

Tablets

STRENGTHS:

Aqueous concentrate injection

100 and 200 mg/tablet

5 µg/mL, solution

ROUTE OF ADMINISTRATION:

Oral

Intravenous infusion

DISPENSED:

X Rx OTC

RELATED DOCUMENTS (if applicable):

INDs.

REMARKS/COMMENTS:

This application is for a fluoroquinolone, trovafloxacin. The application is for the treatment of patients with nosocomial pneumonia; community acquired pneumonia; acute bacterial exacerbation of chronic bronchitis; acute sinusitis; complicated intra-abdominal infections, including post-surgical infections; gynecologic and pelvic infections, including post-surgical infections; surgical prophylaxis; skin and skin structure infections; uncomplicated urinary tract infections; uncomplicated urethral, cervical pharyngeal and rectal gonorrhea; nongonococcal urethritis and cervicitis; pelvic inflammatory disease

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY section of the package insert. The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 126-137.

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I. INTRODUCTION

Trovafloracin is a new fluoronaphthyridone antimicrobial structurally related to the fluoroquinolones, and containing a novel 6-amino-3-azabicyclo-hexane side chain at position 7. Trovafloracin compared with ciprofloracin is somewhat more active against Gram-positive organisms. Against *Streptococcus pneumoniae* the median MIC₉₀ of trovafloracin for 1,867 strains is 0.125 µg/mL. It is equally active against penicillin-susceptible and -resistant pneumococci. Trovafloracin is somewhat more active than ciprofloracin, ofloxacin, and sparfloracin against staphylococci. Like other fluoroquinolones trovafloracin is also active against fastidious organisms that are associated with respiratory tract infections including *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. It is as active as ciprofloracin against ciprofloracin-susceptible *Neisseria* spp. Trovafloracin is also active against ciprofloracin -resistant gonococci. Trovafloracin is less active than ciprofloracin against the *Enterobacteriaceae*, being fourfold less active against many species and as active against others. Trovafloracin is about twofold less potent than ciprofloracin against *Pseudomonas aeruginosa*. Trovafloracin is bactericidal against facultative and aerobic organisms, with minimum bactericidal values being fourfold above the MIC. Trovafloracin's *in vitro* activity against anaerobes such as *Bacteroides* and *Prevotella* spp. and distinguishes it from other fluoroquinolones. The MIC₉₀ of trovafloracin for 1,404 *B. fragilis* strains ranged

Trovafloracin is rapidly absorbed after oral dosing, possesses extensive tissue distribution and an elimination half-life of 10-12 h, allowing once-daily dosing. Trovafloracin is 70-88% bound to plasma proteins and is concentrated up to 28-fold in PMNs and macrophages. Elimination appears to be primarily by the biliary route. Trovafloracin appears to have low potential for phototoxicity and it does not antagonize the metabolism of theophylline. A highly soluble L-ala-L-ala prodrug, alatrofloracin, has been designed for intravenous administration. *In vivo*, alatrofloracin is rapidly and completely hydrolyzed to trovafloracin. Intact alatrofloracin has poor antimicrobial activity, with MICs of ≥50 µg/mL against many clinical isolates of bacteria.

The clinical indications for trovafloracin/alatrofloracin are: sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, nosocomial pneumonia, complicated and uncomplicated skin and skin structure infections, uncomplicated (b)(4) urinary tract infections, prostatitis, gonorrhea, pelvic inflammatory disease, nongonococcal urethritis and cervicitis, acute pelvic infections, complicated intraabdominal infections, epidemic meningococcal meningitis and surgical prophylaxis.

II. PRECLINICAL EFFICACY (IN VITRO)

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A. Mechanism of Action

1. Primary Mechanism of Action

Biochemical and genetic evidence indicates that both DNA gyrase (a type II topoisomerase) and topoisomerase IV are antibacterial targets for trovafloxacin. Topoisomerases are enzymes found in all cells which alter the topological state of DNA. To date, four topoisomerases have been identified in *E. coli* and other species of bacteria(1,2). Studies using purified enzymes have indicated that fluoroquinolones are not potent inhibitors of two of these enzymes, topoisomerases I and III. The type II topoisomerase, DNA gyrase, is the sole enzyme in the bacterial cell capable of introducing negative supercoils into DNA. This enzyme, in concert with topoisomerase I, functions to maintain the appropriate superhelicity of DNA in the cell, which is critical for many cellular processes such as replication and transcription. Extensive studies with drug-resistant mutants and cell-free gyrases have provided evidence that fluoroquinolones elicit their bactericidal action by interacting with DNA gyrase(3). Work from several laboratories has described a second type II enzyme in bacterial cells, topoisomerase IV that appears to play a key role in the partitioning of chromosomal DNA during cell division (6,7).

E. coli DNA gyrase consists of two subunits A and B with molecular weights of 97 and 90 kDa, respectively (3). Functional DNA gyrase consists of an A₂B₂ complex. Mechanistically, gyrase makes a double strand break in one strand of DNA, leading to an intermediate characterized by covalent bonds between the 5' phosphates of the broken DNA strands and the tyrosine 122 hydroxyl groups of each gyrase A subunit. This "cleavable complex" allows a second double strand of DNA to pass through the broken sequence. Following strand passage, gyrase reseals the double strand cut, completing the strand-passage reaction (4). The A subunits of gyrase, as mentioned above, are responsible for catalyzing the double strand breakage and reunion of DNA, the energy for which is supplied by hydrolysis of ATP. The B subunits carry out the ATP hydrolysis reaction.

The role of fluoroquinolones as inhibitors of the DNA strand passage reaction has been elucidated through experiments employing sodium dodecyl sulfate to disrupt a ternary complex created by gyrase, DNA, and bound quinolone (3). The available data indicate that fluoroquinolones exert their inhibitory effect on gyrase by binding to a complex created by gyrase and DNA. A partially unwound region of DNA undoubtedly exists in this complex, allowing the drug to enter a "binding pocket" consisting of conserved amino acid residues from the A subunit of gyrase, and single stranded DNA (3).

Productive drug binding and "freezing" of the cleavable complex by the fluoroquinolone creates a cellular poison that is responsible for the bactericidal activity of these agents. It has been found that formation of the drug-gyrase-DNA complex prevents passage of polymerases necessary for DNA and cellular replication (5). This mechanism of cell death would also explain why the wild type *gyrA* allele is dominant over mutant *gyrA* in a merodiploid bacterial cell containing copies of both genes. In such a cell, the chromosomally encoded mutant gyrase would be refractory to the action of the quinolone. However, the presence of normal gyrase enzyme (encoded on a plasmid) would restore the drug's capability to form a lethal complex in the cell. This poison hypothesis is important in understanding the lethal action of quinolones against bacteria.

Topoisomerase IV, on the other hand cannot supercoil DNA. This enzyme can relax DNA *in vitro* but its preferred catalytic activity is decatenation, a reaction that is favored over relaxation by a margin of up to 10 to 1 when specific activities are compared *in vitro* (6-8). Studies with

temperature-sensitive mutants of *E. coli* first revealed the important role of topoisomerase IV in cell division (8). DNA gyrase can only partially compensate for topoisomerase IV in such temperature-sensitive cells, indicating that topoisomerase IV is essential for proper cell growth. Topoisomerase IV is thought to be a membrane-bound enzyme, consistent with its key role in chromosome partitioning (6).

Reports from several investigators have indicated that nalidixic acid and the fluoroquinolones are 3- to 30-fold less potent against *E. coli* topoisomerase IV than they are against DNA-gyrase, as judged by inhibition of enzyme activity (6,8). This, coupled with initial failure to obtain quinolone-resistant mutants in *E. coli* that mapped to topoisomerase IV, led investigators to conclude that this enzyme was not a primary target for fluoroquinolones. Evidence suggests, however, that this relationship may be different in *S. aureus* and other Gram-positive organisms. Ferrero *et al.* (9) used the polymerase chain reaction (PCR) to amplify the quinolone resistance determining region (QRDR) of *gyrA* and *grlA* (the topoisomerase IV homolog) in clinical isolates of *S. aureus* showing varying levels of resistance to fluoroquinolones. Isolates with ciprofloxacin minimum inhibitory concentrations (MICs) between 2 and 16 $\mu\text{g}/\text{mL}$ had changes only in *grlA*, which led to substitution of Phe or Tyr for Ser 80 in the GrlA subunit. Strains with MICs >32 $\mu\text{g}/\text{mL}$ (and one with an MIC of 16 $\mu\text{g}/\text{mL}$) had changes in both the GrlA and GyrA subunits (9).

A second study from this group used step-wise laboratory selection to assess the changes that conferred ciprofloxacin resistance in *S. aureus* (10). In agreement with their first study, these investigators found that first-step mutants (MIC to ciprofloxacin of 2 $\mu\text{g}/\text{mL}$) had a substitution of Ser 80 by Tyr or Glu 84 by Lys in the GrlA subunit. Mutants with higher levels of resistance to ciprofloxacin (MIC 128 $\mu\text{g}/\text{mL}$) all exhibited changes in GyrA in addition to a GrlA mutation. The conclusion derived from these studies was that, at least in *S. aureus*, topoisomerase IV appears to be a primary target for fluoroquinolones (9,10). Enzyme inhibition studies using purified topoisomerase IV from *S. aureus* have not yet been reported. This new information regarding topoisomerase IV may be relevant in explaining the improved potency of some new fluoroquinolones such as trovafloxacin against Gram-positive organisms.

The inhibitory activity of trovafloxacin against purified DNA gyrase of *E. coli* has been studied (11). The lowest amount of trovafloxacin which stimulated gyrase-mediated DNA cleavage *in vitro* was 0.78 $\mu\text{g}/\text{mL}$ (1.9 μM), compared with 0.26 and 0.14 $\mu\text{g}/\text{mL}$ for ciprofloxacin and sparfloxacin, respectively (11). In the same study, the MIC_{90s} against 40 clinical isolates of *E. coli* were 0.125, 0.062, and 0.062 $\mu\text{g}/\text{mL}$ for trovafloxacin, ciprofloxacin, and sparfloxacin, respectively. As observed previously, the amount of fluoroquinolone required to inhibit the activity of purified gyrase *in vitro* is higher than that required to inhibit cell growth. In another report (12) trovafloxacin was ten-fold less potent at inhibiting the relaxation activity of *E. coli* topoisomerase IV (IC₅₀ of 8.5 μM) than it was against the supercoiling activity of DNA gyrase (IC₅₀ of 0.8 μM). Genetic evidence suggests that topoisomerase IV is a primary target for trovafloxacin in the Gram-positive organism *Streptococcus pneumoniae* (13).

2. Additional Mechanisms of Action

While the principal mechanism of action for fluoroquinolones is thought to involve inhibition of bacterial DNA gyrase and topoisomerase IV, other mechanisms are thought to be involved as well.

Many quinolones have been included in a series of studies aimed at characterizing their bactericidal mechanism of action (14). It has been shown that the quinolones possess four bactericidal mechanisms of action, designated as mechanisms A, B, B₁ and C. Mechanism A, the basic quinolone mechanism, is the sole mechanism of action shown by older quinolones such as nalidixic acid. This mechanism requires bacteria to be undergoing multiplication and protein or RNA synthesis (14). Mechanism B is an additional mechanism possessed by several modern quinolones (15). This bactericidal mechanism is active against non-dividing bacteria and does not require active protein or RNA synthesis. A related bactericidal mechanism, B₁, has also been identified, but only with clinafloxacin; this mechanism does not require protein or RNA synthesis but does require dividing bacteria (16). Mechanism C, on the other hand, does not require bacterial multiplication, but does require active protein or RNA synthesis. This mechanism has been found with norfloxacin and enoxacin (17) only.

It has been suggested that the failure of ciprofloxacin to eradicate some staphylococcal infections may be due to a lack of an additional bactericidal mechanism B, B₁ or C (18). A study examining trovafloxacin for these properties (18) found it to have a typical quinolone biphasic (U-shaped) dose response curve for killing of *E. coli*, *S. aureus*, and *S. pneumoniae*. It was noted that the optimum bactericidal concentration (OBC) for trovafloxacin against *S. pneumoniae* C3LN4 was 1.5 µg/mL compared with 5.0, 5.0, and 15.0 µg/mL for ciprofloxacin, levofloxacin, and ofloxacin, respectively. Trovafloxacin remained bactericidal against strains of *E. coli*, *S. aureus*, and *S. pneumoniae* that were exposed to growth inhibitory levels of chloramphenicol, a protein synthesis inhibitor. In contrast, chloramphenicol markedly antagonized the bactericidal activity of trovafloxacin against three isolates of *Enterococcus faecalis* (18). These results suggest that like ofloxacin, trovafloxacin exhibits the additional mechanism B in its bactericidal action against certain microorganisms.

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B. Antimicrobial Spectrum of Activity

The data presented in this section summarizes all of the preclinical microbiology results available for trovafloxacin. The data is compiled from over 40 publications, abstracts, or project reports sent to the sponsor from independent investigators. The susceptibility data in Tables 1-6 are presented for each species in terms of the Minimum Inhibitory Concentration (MIC) range, MIC₉₀ range, and median MIC₉₀ for all available studies. The sponsor has defined the MIC as the lowest concentration of drug that inhibits the visible growth of an organism in tests run under National Committee for Clinical Laboratory Standards (NCCLS) conditions (31,32)

For comparative purposes, the susceptibility values for trovafloxacin is presented along with those for ciprofloxacin, ofloxacin, and sparfloxacin. The *in vitro* data for 15,648 clinical isolates were obtained from widely diverse locations including the United States, Europe, South Africa, and the Middle East. The susceptibility data presented in Tables 1 through 6, are organized according to the clinical indications that are proposed for trovafloxacin and the most common organisms that can be associated with these indications. The antimicrobial activity of trovafloxacin against multiply resistant organisms such as penicillin-resistant *S. pneumoniae*, enterococci, *S. aureus*, *P. aeruginosa*, and mycobacteria is given in Table 28.

The overall conclusions in this susceptibility section point to the broad spectrum of trovafloxacin including gram-positive and gram-negative aerobic, fastidious, and anaerobic organisms.

Trovafloracin has good activity against gram-positive species and anaerobes as compared to other fluoroquinolones. Trovafloracin is less active than ciprofloracin or sparfloracin against members of the *Enterobacteriaceae*. Trovafloracin is more active than ciprofloracin and as active as sparfloracin against some species such as *Staphylococcus aureus* and *Neisseria gonorrhoeae* that show reduced susceptibility to ciprofloracin. Against other isolates with reduced susceptibility to ciprofloracin such as *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia*, trovafloracin appears to have no potency advantage over ciprofloracin. Against multi-resistant enterococci, trovafloracin like other fluoroquinolones examined, has no activity.

1. Antimicrobial Activity of Trovafloracin Against Organisms Associated with Respiratory Infections

a. Upper Respiratory Tract

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i. Sinusitis

The *in vitro* activity of trovafloracin against four bacterial species that are often associated with sinusitis are compared with that of ciprofloracin, ofloxacin, and sparfloracin in Table 1. The MIC range observed with trovafloracin against 1,867 penicillin-susceptible isolates of *Streptococcus pneumoniae* was [redacted]. The upper range observed in this group for ciprofloracin, ofloxacin, and sparfloracin was 8 µg/mL, indicating that strains exist in nature which are resistant to these agents. The MIC₉₀ range for trovafloracin was [redacted] for these isolates of pneumococci reported from nineteen separate studies. According to the median MIC₉₀ values for Penicillin-susceptible *Streptococcus pneumoniae* (Table 1), trovafloracin is 16, 32, and 4-fold more potent than ciprofloracin, ofloxacin, and sparfloracin, respectively.

This degree of potency for trovafloracin is maintained against 498 strains of penicillin-resistant *Streptococcus pneumoniae* reported from five separate studies. The MIC₉₀ range for trovafloracin against penicillin-resistant *Streptococcus pneumoniae* was [redacted] and the most resistant isolates in this group had MIC of 0.25 µg/mL. The median MIC₉₀ for trovafloracin against penicillin-resistant *Streptococcus pneumoniae* was 16, 32, and 10-fold lower than that observed for ciprofloracin, ofloxacin, and sparfloracin, respectively.

Trovafloracin is also very active *in vitro* against clinical isolates of *Moraxella catarrhalis* and *Haemophilus influenzae*. The MIC₉₀ range for trovafloracin against 403 isolates of *H. influenzae*, reported from ten separate studies, was [redacted]. The median MIC₉₀s for trovafloracin and the other fluoroquinolones tested were similar at [redacted]. This degree of potency was also demonstrated against 304 strains of *M. catarrhalis*, reported from nine separate studies, where the MIC₉₀ range and median MIC₉₀ values for trovafloracin were [redacted] and 0.03 µg/mL, respectively. At the median MIC₉₀, the potency of trovafloracin is similar to that of sparfloracin, ciprofloracin, and ofloxacin.

Strains of methicillin-resistant (MRSA) or susceptible (MSSA) *Staphylococcus aureus* can also cause sinusitis. The data in Table 1 show that trovafoxacin is active against MSSA, with an MIC₉₀ range of _____ and a median MIC₉₀ of 0.06 µg/mL for 666 isolates reported from thirteen studies. The MIC₉₀ range of ciprofloxacin was _____ and the median MIC₉₀ was 0.75 µg/mL, indicating that trovafoxacin is about tenfold more potent than ciprofloxacin against this group. In considering the full MIC ranges reported in these studies, it is clear that some isolates of MSSA exist which appear resistant (MIC ≥4 µg/mL) to trovafoxacin, ciprofloxacin, ofloxacin, or sparfoxacin.

All four fluoroquinolones were less active *in vitro* against MRSA. The MIC range of trovafoxacin was _____ for 487 isolates of MRSA reported from sixteen separate studies. The upper MIC range for the other three fluoroquinolones were from _____

The median MIC₉₀s were 2.0, >16, 16, and 8 µg/mL for trovafoxacin, ciprofloxacin, ofloxacin, and sparfoxacin, respectively. Trovafoxacin like the other fluoroquinolones, has marginal activity against MRSA. The relative activity of trovafoxacin against laboratory strains of *S. aureus* with characterized mutations conferring quinolone resistance will be described in section II.H. (Table 12).

b. Lower Respiratory Tract

i. Acute Bacterial Exacerbation of Chronic Bronchitis

The organisms associated with acute bacterial exacerbation of chronic bronchitis are the same as the ones associated with sinusitis, including *S. pneumoniae* (both penicillin-susceptible and penicillin-resistant strains), *H. influenzae*, *M. catarrhalis*, and *S. aureus*. Trovafoxacin is active against the same spectrum of susceptible microorganisms as those associated with sinusitis. Data on the antimicrobial activity of trovafoxacin and other fluoroquinolones against these organisms is shown in Table 1. The description for the relative potency of trovafoxacin is the same as that given in the previous section on sinusitis.

ii. Community Acquired Pneumonia

The *in vitro* activity of trovafoxacin against 5,492 bacteria that can be associated with community acquired pneumonia has been compared with that of ciprofloxacin, ofloxacin, and sparfoxacin. Data for the isolates of *S. pneumoniae* (including penicillin-susceptible and resistant strains), *H. influenzae*, *M. catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *S. aureus*, and *Legionella pneumophila* obtained from several studies are found in Table 1. The comparative MIC₉₀ results for trovafoxacin and the other fluoroquinolones for *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. aureus* have been described in section II.B.1.a.i. for sinusitis.

The activity of trovafoxacin against 50 isolates of *M. pneumoniae* has been described in two studies. The data in Table 1 indicate that the MIC range for trovafoxacin against these isolates is _____

The MIC₉₀ range for trovafoxacin was _____ compared with values of 1.0, 1.0, and 0.25 µg/mL for ciprofloxacin, ofloxacin, and sparfoxacin, respectively.

This indicates that trovafoxacin is as active as sparfoxacin and about fourfold more active than either ciprofloxacin or ofloxacin against *M. pneumoniae*.

The activity of trovafoxacin against *C. pneumoniae* is described in one study. In this report, the activity of trovafoxacin against 13 isolates was equivalent to that of ofloxacin, with an MIC₉₀ of 1.0 µg/mL. Despite the small size of the study one may conclude that trovafoxacin has a borderline questionable activity against *C. pneumoniae*.

Table 1. Antimicrobial Activity of Trovafoxacin and Other Fluoroquinolones Against Organisms Associated with Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis, and Community Acquired Pneumonia.

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Streptococcus pneumoniae</i> pen-S ^a	1,867	Trovafoxacin			0.125	11,33-50
	1,847	Ciprofoxacin			2.0	11,34-50
	1,427	Ofloxacin			4.0	11,36,38,39,43,45,46,48-50
	541	Sparfoxacin			0.5	11,34,36,37,39,42-45,47-50
<i>Streptococcus pneumoniae</i> pen-R ^b	498	Trovafoxacin			0.125	11,43,44,46,49
	498	Ciprofoxacin			2.0	11,43,44,46,49
	343	Ofloxacin			4.0	43,46,49
	306	Sparfoxacin			1.25	43,44
<i>Haemophilus influenzae</i>	403	Trovafoxacin			0.015	11,35-42,47
	403	Ciprofoxacin			0.015	11,35-42,47
	67	Ofloxacin			0.023	38,51
	150	Sparfoxacin			0.015	11,37,39,42,47
<i>Moraxella catarrhalis</i>	304	Trovafoxacin			0.03	11,35,37-40,42,47,51
	304	Ciprofoxacin			0.06	11,35,37-40,42,47,51
	53	Ofloxacin			0.075	38,51
	131	Sparfoxacin			0.031	11,37,39,42,47
<i>Staphylococcus aureus</i> MSSA ^c	666	Trovafoxacin			0.06	11,33-41,51-53,98
	646	Ciprofoxacin			0.75	11,34-41,51-53,98
	194	Ofloxacin			0.5	35,36,38,51,53
	130	Sparfoxacin			0.125	11,34,36,37,39
<i>Staphylococcus aureus</i> MRSA ^d CRSA ^e	487	Trovafoxacin			2.0	33-42,47,51-54,98
	452	Ciprofoxacin			>16	34,40,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfoxacin			8	34,36-37,39,42
<i>Chlamydia pneumoniae</i>	13	Trovafoxacin			1.0	57
	13	Ofloxacin			1.0	57
<i>Mycoplasma pneumoniae</i>	50	Trovafoxacin			0.185	38,55
	10	Ciprofoxacin			1.0	38
	50	Ofloxacin			1.0	38,55
	40	Sparfoxacin			0.25	55
<i>Legionella pneumophila</i>	148	Trovafoxacin			0.008	35,38,56
	133	Ciprofoxacin			0.038	35,38
	148	Ofloxacin			0.032	35,38,56

^a Penicillin-susceptible, MIC < 0.05 µg/mL.

^b Penicillin-resistant, MIC > 0.5 µg/mL.

^c Methicillin-susceptible *S. aureus*.

^d Methicillin-resistant *S. aureus*.

^e Ciprofoxacin-resistant *S. aureus*.

Trovafloracin's activity against 148 isolates of *L. pneumophila* was determined in three separate studies (Table 1). The MIC₉₀ ranges for trovafloracin, ciprofloracin and ofloxacin were . The median MIC₉₀ values for trovafloracin, ciprofloracin and ofloxacin were 0.008, 0.038, and 0.032 µg/mL, respectively. These data indicate that Trovafloracin is as active as ciprofloracin or ofloxacin against *L. pneumophila*.

iii. Nosocomial Pneumonia

The *in vitro* antibacterial activity of trovafloracin has been compared with that of ciprofloracin, ofloxacin, and sparfloracin in studies with 6,198 bacterial isolates that can be associated with nosocomial pneumonia. Comparative susceptibility data with *S. pneumoniae*, *S. aureus* (MRSA and MSSA) and *H. influenzae* were discussed in section II.B.1.a.i. when describing sinusitis. In addition to these organisms, data for *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Serratia marcescens*, *Morganella morganii*, and *Stenotrophomonas maltophilia* are shown in Table 2.

The antimicrobial activity of trovafloracin was evaluated against 476 isolates of *E. coli* in eleven separate studies. The MIC range for trovafloracin was somewhat inferior to that for ciprofloracin, ofloxacin, and sparfloracin. The MIC₉₀ range for trovafloracin was for ciprofloracin, ofloxacin, and sparfloracin respectively. The upper range for trovafloracin was higher than that observed for ciprofloracin, ofloxacin, and sparfloracin. The median MIC₉₀s were similar for all four fluoroquinolones. The data from 331 *K. pneumoniae* gathered from eight separate studies indicates that trovafloracin is slightly more active than ciprofloracin and ofloxacin, but less active than sparfloracin. Here, the MIC₉₀ range for trovafloracin was 0.06-1.0 µg/mL, with a median of 0.125 µg/mL. Corresponding values for ciprofloracin, ofloxacin, and sparfloracin were and 0.06 µg/mL; 1.0 µg/mL; 0.125 µg/mL respectively. Against 242 strains of *E. cloacae* from eight separate studies, the MIC₉₀ range for trovafloracin was compared with values of ciprofloracin, ofloxacin, and sparfloracin, respectively. The relative order of potency as judged by median MIC₉₀ values was sparfloracin (0.085 µg/mL), ciprofloracin (0.312 µg/mL), trovafloracin (1.6 µg/mL), and ofloxacin (2.12 µg/mL). For 298 strains of *P. mirabilis* in ten studies, the MIC₉₀ ranged for trovafloracin. Against *P. mirabilis*, ciprofloracin with an MIC₉₀ range and ofloxacin with an MIC₉₀ range of were about four- and sixteen-fold more potent than trovafloracin respectively. The median MIC₉₀s for trovafloracin, ciprofloracin, ofloxacin, and sparfloracin were 0.5, 0.06, 0.125, and 0.5 µg/mL, respectively. Trovafloracin was as active as ciprofloracin, ofloxacin, and sparfloracin against 195 *M. morganii* isolates, with an MIC₉₀ range of 0.125 to 2.0 µg/mL and a median MIC₉₀ of 0.5 µg/mL. Corresponding values for ciprofloracin, ofloxacin, and sparfloracin were respectively.

All of the fluoroquinolones studied were inactive against *P. aeruginosa*. The MIC ranges were broad for all four compounds, with a range for trovafloracin. The MIC₉₀ ranges were also similar for all four compounds with a range reported for trovafloracin when a total of 566 isolates were tested in eleven studies. The median MIC₉₀

values for trovafloracin, ciprofloracin, ofloxacin, and sparfloracin were 2.0, 2.0, >8.0, and 2.0 $\mu\text{g/mL}$, respectively.

This inactivity was also observed with strains of *S. marcescens* and *S. maltophilia*. In tests with 211 isolates of *S. marcescens* from 9 studies, the MIC range for trovafloracin was and the MIC₉₀ values ranged from which was similar to that observed for ofloxacin. The relative order of potency as judged by median MIC₉₀ values was sparfloracin (0.5 $\mu\text{g/mL}$), ciprofloracin (1.0 $\mu\text{g/mL}$), ofloxacin (2.25 $\mu\text{g/mL}$), and trovafloracin (2.5 $\mu\text{g/mL}$). All four fluoroquinolones were also inactive against 227 strains of *S. maltophilia* reported in seven studies. The MIC₉₀ of trovafloracin ranged between 0.5 and >8 $\mu\text{g/mL}$, while the median MIC₉₀ was 2.0 $\mu\text{g/mL}$. Corresponding values for ciprofloracin, ofloxacin, and sparfloracin were $\mu\text{g/mL}$; and >8 $\mu\text{g/mL}$; >8.0 $\mu\text{g/mL}$; respectively. Sparfloracin seems to be more active than the other three fluoroquinolones.

With 574 Vancomycin-susceptible *E. faecalis* isolates reported from sixteen studies, trovafloracin had an MIC₉₀ range of This was compared with MIC₉₀ ranges of for ciprofloracin, ofloxacin, and sparfloracin, respectively. The median MIC₉₀s for trovafloracin, ciprofloracin, ofloxacin, and sparfloracin were 2.0, 2.0, 4.0, and 1.0 $\mu\text{g/mL}$, respectively. Sparfloracin is twice as active as trovafloracin against Van-S *E. faecalis*.

In general, trovafloracin has moderately greater *in vitro* activity than ciprofloracin, ofloxacin, and sparfloracin against some Gram-positive organisms that can be associated with nosocomial pneumonia such as penicillin-susceptible and penicillin-resistant *S. pneumoniae*, methicillin susceptible *S. aureus*, and vancomycin-susceptible *Enterococcus faecalis*. Trovafloracin is almost comparable in potency to ciprofloracin against commonly isolated *Enterobacteriaceae* (*E. coli*, *P. mirabilis*, *K. pneumoniae*, and *M. morgani*) and MIC₉₀ studies suggest that the majority of these strains will be in the susceptible range for trovafloracin ($\leq 1 \mu\text{g/mL}$). Like ciprofloracin, ofloxacin, and sparfloracin, trovafloracin is inactive against *P. aeruginosa*, *S. marcescens*, and *S. maltophilia*. This suggests that combination chemotherapy with a fluoroquinolone and another agent would be required in treating nosocomial pneumonia with these organisms.

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Table 2. Antimicrobial Activity of Trovafloracin and Other Fluoroquinolones Against Organisms Associated with Nosocomial Pneumonia

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Escherichia coli</i>	476	Trovafloracin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloracin			0.062	11,35-39,41-42,47,51,53
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloracin			0.062	11,36-37,39,42
<i>Klebsiella pneumoniae</i>	331	Trovafloracin			0.125	11,35-36,39,41-42,47,53
	331	Ciprofloracin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
	141	Sparfloracin			0.125	11,36,39,42
<i>Enterobacter cloacae</i>	242	Trovafloracin			1.6	11,35-36,39,41-42,51,53
	242	Ciprofloracin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
	135	Sparfloracin			0.085	11,36,39,42
<i>Proteus mirabilis</i>	298	Trovafloracin			0.5	11,35-37,39,41-42,47,51,53
	298	Ciprofloracin			0.06	11,35-37,39,41-42,47,51,53
	80	Ofloxacin			0.125	35,36,51,53
	166	Sparfloracin			0.5	11,36-37,39,42
<i>Pseudomonas aeruginosa</i>	566	Trovafloracin			2.0	11,35-39,41,51,53,58-59
	566	Ciprofloracin			2.0	11,35-39,41,51,53,58-59
	357	Ofloxacin			>8	35-36,38,51,53,58-59
	256	Sparfloracin			2.0	11,36-37,39,58
<i>Haemophilus influenzae</i>	403	Trovafloracin			0.015	11,35-42,47
	403	Ciprofloracin			0.015	11,35-42,47
	67	Ofloxacin			0.023	38,51
	150	Sparfloracin			0.015	11,37,39,42,47
<i>Staphylococcus aureus</i>	487	Trovafloracin			2.0	33-42,47,51-54,98
	452	Ciprofloracin			>16	34-42,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfloracin			8	34,36-37,39,42
<i>Streptococcus pneumoniae</i> Pen-S ^a	1,867	Trovafloracin			0.125	11,33-50
	1,847	Ciprofloracin			2.0	11,34-50
	1,427	Ofloxacin			4.0	11,36,38,43,45,46,48-50
	541	Sparfloracin			0.5	11,34,36,37,39,42-45,47,50
<i>Streptococcus pneumoniae</i> Pen-R ^b	498	Trovafloracin			0.125	11,43,44,46,49
	498	Ciprofloracin			2.0	11,43,44,46,49
	343	Ofloxacin			4.0	43,46,49
	306	Sparfloracin			1.25	43,44
<i>Enterococcus faecalis</i> Van-S ^c	574	Trovafloracin			2.0	11,33-41,47,51-53,59,107
	537	Ciprofloracin			2.0	11,34-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloracin			1.0	11,34,36,37,39

Organism	No. Isolates	Compound	MIC Range ($\mu\text{g/mL}$)	MIC ₉₀ Range ($\mu\text{g/mL}$)	Median MIC ₉₀ ($\mu\text{g/mL}$)	References
<i>Serratia marcescens</i>	211	Trovafloracin			2.5	11,35-36,39,41,47,51,53
	211	Ciprofloracin			1.0	11,35-36,39,41,47,51,53
	100	Ofloxacin			2.25	35-36,51,53
	91	Sparfloracin			0.5	11,36,39
<i>Morganella morganii</i>	195	Trovafloracin			0.5	11,35-37,39,41,47,51,53
	195	Ciprofloracin			0.125	11,35-37,39,41,47,51,53
	46	Ofloxacin			0.19	35-36,51,53
	93	Sparfloracin			1.0	11,36,37,39,53
<i>Stenotrophomonas maltophilia</i>	227	Trovafloracin			2.0	35-37,39,53,58, 59
	227	Ciprofloracin			>8	35-37,39,53,58
	197	Ofloxacin			>8	35,36,53,58-59
	142	Sparfloracin			2.0	36,37,39,58

- ^a Penicillin-susceptible, MIC $\leq$ 0.05 $\mu\text{g/mL}$.
- ^b Penicillin-resistant, MIC $\geq$ 0.5 $\mu\text{g/mL}$.
- ^c Methicillin-susceptible *S. aureus*.
- ^d Methicillin-resistant *S. aureus*.
- ^e Ciprofloracin-resistant *S. aureus*.
- ^f Vancomycin-susceptible *E. faecalis*.

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2. Antimicrobial Activity of Trovafloracin Against Organisms Associated with Complicated and Uncomplicated Skin and Skin Structure Infections

a. Uncomplicated Skin and Skin Structure Infections

The *in vitro* activity of trovafloracin against organisms associated with uncomplicated skin and skin structure infections is summarized in Table 3. The comparative activity of trovafloracin against *S. aureus* (both MRSA and MSSA) was discussed in section II.B.1.a.i. under sinusitis. The activity of trovafloracin against 118 isolates of methicillin-resistant *S. epidermidis* (MRSE) isolated in four different studies is depicted in Table 3. The MIC₉₀ range with trovafloracin for MRSE was _____, while that for ciprofloracin, ofloxacin, and sparfloracin was _____.

The median MIC₉₀s for trovafloracin, ciprofloracin, ofloxacin, and sparfloracin were 2.5, >16, >16, and 8 $\mu\text{g/mL}$, respectively. This data indicate that all four fluoroquinolones are equally ineffective against MRSE isolated.

Trovafloracin was slightly more active than the other three fluoroquinolones tested against 242 strains of *S. pyogenes* in ten different studies. The MIC₉₀ range for trovafloracin was 0.06-0.5 $\mu\text{g/mL}$ against *S. pyogenes*. The MIC₉₀ range for ciprofloracin, ofloxacin, and sparfloracin was _____.

Against 246 strains of viridans streptococci tested in 8 separate studies, trovafloracin was moderately more active than the other three fluoroquinolones. The median MIC₉₀ for trovafloracin, sparfloracin, ciprofloracin, and ofloxacin were 0.25, 1.0, 4.0, and 6.0, respectively against viridans streptococci.

b. Complicated Skin and Skin Structure Infections

In addition to the Gram-positive organisms mentioned for uncomplicated skin and skin structure infections, several members of the *Enterobacteriaceae*, nonfermenter, and anaerobe groups can be associated with this disease. The comparative antimicrobial activity of trovafloracin against *E. coli*, *E. cloacae*, *K. pneumoniae*, *M. morgani*, *P. mirabilis*, *Pseudomonas aeruginosa*, and *Serratia marcescens* was discussed in section II.B.1.b.iii. under nosocomial pneumonia. Other organisms in Table 3 of this section include *Providencia stuartii*, *Proteus vulgaris*, *K. oxytoca*, *Acinetobacter baumannii*, *C. freundii*, *Bacteroides fragilis*, and peptostreptococci.

Against 40 strains of *P. stuartii* in three studies, the MIC₉₀ range for trovafloracin, ciprofloracin, ofloracin, and sparfloracin are The median MIC₉₀s for trovafloracin, ciprofloracin, ofloracin, and sparfloracin are 2.0, 0.25, 5.0, and 1.0 µg/mL. Trovafloracin while more active than ofloracin, it was less active than ciprofloracin and sparfloracin against *P. stuartii*. The MIC₉₀ for trovafloracin against 89 strains of *P. vulgaris* in six studies ranged , compared with for ciprofloracin; for ofloracin; and 0.5 µg/mL for sparfloracin. As judged by median MIC₉₀s, trovafloracin while less active than ciprofloracin and ofloracin, it was as active as sparfloracin against *P. vulgaris*.

None of the three fluoroquinolones studied were active against the 30 strains of *A. baumannii* used in a single study, giving median MIC₉₀ values >8 µg/mL for each.

Trovafloracin was as active as the other three fluoroquinolones against *K. oxytoca*, and *Citrobacter freundii* with median MIC₉₀ of 0.155 and 0.375 µg/mL respectively.

Table 3. Antimicrobial Activity of Trovafloracin and Other Fluoroquinolones Against Organisms Associated with Complicated and Uncomplicated Skin and Skin Structure, Uncomplicated and Complicated Urinary Tract Infections, and Prostatitis.

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Staphylococcus aureus</i> (MRSA) ^f and (MSSA) ^p	487	Trovafloracin			2.0	33-42,47-51,54-98
	452	Ciprofloracin			>16	34-42,47,51-54,98
	134	Ofloracin			16	35-36,38,51,53
	102	Sparfloracin			8	34,36-37,39,42
<i>Staphylococcus epidermidis</i> (MRSE) ^f	118	Trovafloracin			2.5	35-36,53,98
	118	Ciprofloracin			>16	35-36,53,98
	55	Ofloracin			>16	35-36,53
	10	Sparfloracin			8	36
<i>Streptococcus pyogenes</i>	242	Trovafloracin			0.125	11,34-37,39-41,51-52
	90	Sparfloracin			0.5	11,34,36,37,39
	242	Ciprofloracin			0.75	11,34-37,39-41,51-52
	35	Ofloracin			1.5	36,51
<i>viridans</i>	246	Trovafloracin			0.25	33-34,36,38-40,47,52

Organism	No. Isolates	Compound	MIC Range ($\mu\text{g/mL}$)	MIC ₉₀ Range ($\mu\text{g/mL}$)	Median MIC ₉₀ ($\mu\text{g/mL}$)	References
streptococci	226	Ciprofloxacin			4.0	34,36,38-40,47,52
	55	Ofloxacin			6.0	36,38
	56	Sparfloxacin			1.0	34,36,39
<i>Escherichia coli</i>	476	Trovafloracin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloxacin			0.062	11,35-39,41-42,47,51,53
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloxacin			0.062	11,36-37,39,42
<i>Enterobacter cloacae</i>	242	Trovafloracin			1.6	11,35-36,39,41-
	135	Sparfloxacin			0.085	42,51,53,11,36,39,42
	242	Ciprofloxacin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
<i>Klebsiella oxytoca</i>	94	Trovafloracin			0.155	11,35-36,39
	94	Ciprofloxacin			0.06	11,35-36,39
	36	Ofloxacin			0.185	35-36
	83	Sparfloxacin			0.25	11,36,39
<i>Citrobacter freundii</i>	123	Trovafloracin			0.375	11,35-36,39,51,53
	123	Ciprofloxacin			0.125	11,35-36,39,51,53
	75	Ofloxacin			1.0	35-36,51,53
	63	Sparfloxacin			0.25	11,36,39
<i>Proteus mirabilis</i>	298	Trovafloracin			0.5	11,35-37,39,41-42,47,51,53
	298	Ciprofloxacin			0.06	11,35-37,39,41-42,47,51,53
	80	Ofloxacin			0.125	35,36,51,53
	166	Sparfloxacin			0.5	11,36-37,39,42
<i>Pseudomonas aeruginosa</i>	566	Trovafloracin			2.0	11,35-39,41,51,53,58-59
	256	Sparfloxacin			2.0	11,36-37,39,58
	566	Ciprofloxacin			2.0	11,35-39,41,51,53,58-59
	357	Ofloxacin			>8	35-36,38,51,53,58-59
<i>Klebsiella pneumoniae</i>	331	Trovafloracin			0.125	11,35-36,39,41-42,47,53
	141	Sparfloxacin			0.125	11,36,39,42
	331	Ciprofloxacin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
<i>Morganella morganii</i>	195	Trovafloracin			0.5	11,35-37,39,41,47,51,53
	93	Sparfloxacin			1.0	11,36,37,39,53
	195	Ciprofloxacin			0.125	11,35-37,39,41,47,51,53
	46	Ofloxacin			0.19	35-36,51,53
<i>Serratia marcescens</i>	211	Trovafloracin			2.5	11,35-36,39,41,47,51,53
	91	Sparfloxacin			0.5	11,36,39
	211	Ciprofloxacin			1.0	11,35-36,39,41,47,51,53
	100	Ofloxacin			2.25	35-36,51,53
<i>Providencia stuartii</i>	40	Trovafloracin			2.0	35,39,51
	40	Ciprofloxacin			0.25	35,39,51
	20	Ofloxacin			5.0	35,51
	20	Sparfloxacin			1.0	39

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Proteus vulgaris</i>	89	Trovafloracin			0.5	35,37,39,47,51,53
	38	Sparfloracin			0.5	37,39
	89	Ciprofloracin			0.03	35,37,39,47,51,53
	30	Ofloxacin			0.125	35,51,53
<i>Acinetobacter baumannii</i>	30	Trovafloracin			>8	30
	30	Ciprofloracin			>8	30
	30	Ofloxacin			>8	30
<i>Bacteroides fragilis</i>	1,404	Trovafloracin			0.5	11,37-39,60-67
	515	Metronidazole			1.28	11,60-62,64,66
	1,339	Ciprofloracin			16.0	11,37,39,60-64,66-67
	874	Ofloxacin			16.0	38,62-63,66
<i>Peptostreptococci</i>	156	Trovafloracin			1.0	38,60-61,66
	156	Ciprofloracin			4.0	38,60-61,66
	55	Ofloxacin			12.0	38,66
	123	Metronidazole			1.0	60-61
<i>Streptococcus agalactiae</i>	120	Trovafloracin			0.25	34-37,39,41,51
	120	Ciprofloracin			2.0	34-37,39,41,51
	40	Ofloxacin			2.0	36-51
	56	Sparfloracin			0.75	34,36,37,39
<i>Enterococcus faecalis</i> Van-S ^d	574	Trovafloracin			2.0	11,33-41,47,51-53,59,107
	537	Ciprofloracin			2.0	11,33-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloracin			1.0	11,34,36,37,39

^a Methicillin-susceptible *S. aureus*.
^b Methicillin-resistant *S. aureus*.
^c Methicillin-resistant *S. epidermidis*.
^d Vancomycin-susceptible *E. faecalis*.

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Trovfloxacin has improved activity over the other fluoroquinolones studied against 1,404 isolates of *B. fragilis* in 12 separate studies. The MIC₉₀ range for trovfloxacin was compared with _____ for ciprofloxacin and _____ for ofloxacin. The median MIC₉₀s for trovfloxacin, ciprofloxacin, and ofloxacin were 0.5, 16.0, and 16.0 µg/mL, respectively. Trovfloxacin was also active against 156 isolates of peptostreptococci in four studies, with an MIC range _____. Trovfloxacin was 4 to 8-fold more active than ciprofloxacin against this group when the MIC₉₀ ranges and median MIC₉₀s are considered. Trovfloxacin was as active as metronidazole against *B. fragilis* and peptostreptococci as judged by median MIC₉₀s.

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3. Antimicrobial Activity of Trovfloxacin Against Organisms Associated with Uncomplicated Urinary Tract Infections

Uncomplicated urinary tract infection (cystitis) can be associated with infection by *E. coli*, *Klebsiella* spp., other Enterobacteriaceae, *S. saprophyticus*, *P. mirabilis*, *P. aeruginosa*, enterococci, *Acinetobacter* spp., *Alcaligenes* spp., *Citrobacter* spp., *Gardnerella vaginalis*, beta-hemolytic streptococci, and *Neisseria gonorrhoeae*.

The antimicrobial activity of trovfloxacin compared with ciprofloxacin, ofloxacin, and sparfloxacin against organisms that can be associated with these infections is given in Table 3. The relative antimicrobial activity of trovfloxacin against most of these organisms has been discussed in sections II.B.1. and II.B.2. nosocomial pneumonia and skin/skin structure infections. In addition, the activity of trovfloxacin against isolates of *S. agalactiae* is shown in Table 3. Trovfloxacin had an MIC₉₀ range of _____ against 120 isolates of this species reported from seven studies. Trovfloxacin was as active as sparfloxacin and eightfold more active than ciprofloxacin and ofloxacin at the median MIC₉₀.

The median MIC₉₀ values of trovfloxacin would not support its use in urinary tract infections due to *P. aeruginosa* or *E. cloacae*.

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4. Antimicrobial Activity of Trovfloxacin Against Organisms Associated with Prostatitis

Development of prostatitis has been associated with infection of the prostate by *E. coli*. The antimicrobial activity of trovfloxacin against isolates of *E. coli* is shown in Table 3 and the comparative activity was discussed in Section II.B.1.b.iii. nosocomial pneumonia.

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5. Antimicrobial Activity of Trovfloxacin Against Organisms Associated with Acute, Uncomplicated Urethral, Cervical and Pharyngeal Gonorrhea

The antimicrobial activity of trovfloxacin compared with that of ciprofloxacin, ofloxacin, and sparfloxacin against *Neisseria gonorrhoeae* is shown in Table 4. In studies with 509 clinical isolates from six different investigators, the MIC range for trovfloxacin was _____. The MIC₉₀ range was _____ and the median MIC₉₀ was 0.006 µg/mL. Trovfloxacin was comparable in potency to ciprofloxacin and ofloxacin and less potent than sparfloxacin against *N.*

gonorrhoeae. The median MIC₉₀ for ofloxacin was 0.03 µg/mL and that for sparfloracin was 0.0028 µg/mL.

Table 4. Antimicrobial Activity of Trovafloracin and Other Fluoroquinolones Against *Neisseria gonorrhoeae*

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Neisseria gonorrhoeae</i>	509	Trovafloracin			0.006	11,35,37-38,68-69
	509	Ciprofloracin			0.008	11,35,37-38,68-69
	295	Ofloxacin			0.03	38,68
	70	Sparfloracin			0.0028	11,37

6. Antimicrobial Activity of Trovafloracin Against Organisms Associated with Pelvic Inflammatory Disease

Pelvic inflammatory disease is a serious illness that can be associated with infection by *N. gonorrhoeae* and *Chlamydia trachomatis*. The comparative antimicrobial activity of trovafloracin against gonococci is given in Table 4 and discussed in section II.B.5. on acute, uncomplicated gonorrhea. *Chlamydia trachomatis* is discussed below.

7. Antimicrobial Activity of Trovafloracin Against Organisms Associated with Nongonococcal Urethritis and Cervicitis

Nongonococcal urethritis and cervicitis can be associated with infection by *Chlamydia trachomatis*. The activity of trovafloracin and ofloxacin were evaluated in one study with 19 organisms (70). The MIC ranges were respectively. The MIC₉₀ for trovafloracin was 0.05 µg/mL compared to 1.0 µg/mL for ofloxacin.

8. Antimicrobial Activity of Trovafloracin Against Organisms Associated with Acute Pelvic Infections

Acute pelvic infections in adult females can be associated with a mixed etiology of microorganisms. *E. coli*, *E. cloacae*, *K. pneumoniae*, *E. faecalis*, *S. agalactiae*, *Peptostreptococcus*, *Prevotella* spp., and *Staphylococcus* spp. can be associated with these infections. The antimicrobial activity of trovafloracin against these organisms is shown in Table 5. This group of organisms is contained within those that cause complicated skin and skin structure infections, complicated intraabdominal or urinary tract infections, and are discussed in sections (II.B.2., II.B.3. and II.B.8.).

Table 5. Antimicrobial Activity of Trovafoxacin and Other Fluoroquinolones Against Organisms Associated with Acute Pelvic Infections

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC Range (µg/mL)	Median MIC ₅₀ (µg/mL)	References
<i>Escherichia coli</i>	476	Trovafoxacin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloxacin			0.062	11,35-39,41-42,47,51,52
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloxacin			0.062	11,36-37,39,42
<i>Klebsiella pneumoniae</i>	331	Trovafoxacin			0.125	11,35-36,39,41-42,47,53
	141	Sparfloxacin			0.125	11,36,39,42
	331	Ciprofloxacin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
<i>Enterobacter cloacae</i>	242	Trovafoxacin			1.6	11,35-36,39,41-42,51,53
	135	Sparfloxacin			0.085	11,36,39,42
	242	Ciprofloxacin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
<i>Pseudomonas aeruginosa</i>	566	Trovafoxacin			2.0	11,35-39,41,51,53,58-59
	256	Sparfloxacin			2.0	11,36-37,39,58
	566	Ciprofloxacin			2.0	11,35-39,41,51,53,58-59
	357	Ofloxacin			>8	35-36,38,51,53,58-59
<i>Staphylococcus aureus</i> (MRSA)	487	Trovafoxacin			2.0	33-42,47,51-54,98
	102	Sparfloxacin			8	34,36-37,39,42
	452	Ciprofloxacin			>16	34-42,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
<i>E. faecalis</i> (Van-S)	574	Trovafoxacin			2.0	11,33-41,47,51-53,59, 107
	537	Ciprofloxacin			2.0	11,34-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloxacin			1.0	11,34,36,37,39
<i>Streptococcus agalactiae</i>	120	Trovafoxacin			0.25	34-37,39,41,51
	120	Ciprofloxacin			2.0	34-37,39,41,51
	40	Ofloxacin			2.0	36-51
	56	Sparfloxacin			0.75	34,36,37,39
<i>Prevotella bivia</i>	118	Trovafoxacin			1.5	60,65,66
	101	Ciprofloxacin			32	60,66
	50	Ofloxacin			16	66
	101	Metronidazole			2.5	60,66
<i>Peptostreptococci</i>	156	Trovafoxacin			1.0	38,60-61,66
	156	Ciprofloxacin			4.0	38,60-61,66
	55	Ofloxacin			12.0	38,66
	123	Metronidazole			1.0	60-61
<i>Prevotella intermedia</i>	27	Trovafoxacin			1.0	60,62
	27	Ciprofloxacin			8.25	60,62
	13	Ofloxacin			0.5	62
	27	Metronidazole			2.25	60,62

9. Antimicrobial Activity of Trovafloracin Against Organisms Associated with Complicated Intraabdominal Infections

Intraabdominal infections, like complicated skin structure or acute pelvic infections, can have a mixed etiology. Such infections are often the result of surgery and other trauma. Thus, these infections can involve a mixture of aerobic Gram-positive organisms, *Enterobacteriaceae*, nonfermenters, and a diverse group of anaerobes. The antimicrobial activity of trovafloracin against many of these organisms (*E. coli*, *Enterobacter cloacae*, *K. pneumoniae*, viridans streptococci, enterococci, and *S. aureus*) is given in Table 6. The comparative activity of trovafloracin against this group of bacteria is discussed in section II.B.2. complicated skin and skin structure infections. In addition, a more extensive list of enterococci is given in Table 6. In fifteen studies with *E. faecalis*, trovafloracin had an MIC₉₀ range of _____ against 574 vancomycin-susceptible isolates. This was compared with MIC₉₀ ranges of _____ for ciprofloracin, ofloxacin, and sparfloracin, respectively. The median MIC₉₀s for trovafloracin, ciprofloracin, ofloxacin, and sparfloracin were 2.0, 2.0, 4.0, and 1.0 µg/mL, respectively. MICs for vancomycin resistant *E. faecalis* were considerably higher for all of the fluoroquinolones. This trend was also evident when data was compared from vancomycin-susceptible and -resistant isolates of *E. faecium* (Table 6). The median MIC₉₀ for 285 vancomycin-resistant *E. faecium* was 8.0 µg/mL for trovafloracin and >16 µg/mL for ciprofloracin.

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Table 6. Antimicrobial Activity of Trovafloracin and Other Agents Against Organisms That can be Associated with Intraabdominal Infections

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Escherichia coli</i>	476	Trovafloracin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloracin			0.062	11,35-39,41-42,47, 51,53
	193	Ofloxacin			0.125	35-36,38,51,53
	188	Sparfloracin			0.062	11,36-37,39,42
<i>Enterobacter cloacae</i>	242	Trovafloracin			1.6	11,35-36,39,41-42,51,53
	242	Ciprofloracin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
	135	Sparfloracin			0.085	11,36,39,42
<i>Klebsiella pneumoniae</i>	331	Trovafloracin			0.125	11,35-36,39,41-42,47,53
	331	Ciprofloracin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
	141	Sparfloracin			0.125	11,36,39,42
<i>Staphylococcus aureus</i> (MSSA) ^a and (MRSA) ^b	487	Trovafloracin			2.0	33-42,47,51 54,98
	452	Ciprofloracin			>16	34-42,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfloracin			8	34,36-37,39,42
Viridans streptococci	246	Trovafloracin			0.25	33-34,36,38-40,47,52
	226	Ciprofloracin			4.0	34,36,38-40,47,52
	55	Ofloxacin			6.0	36,38
	56	Sparfloracin			1.0	34,36,39
<i>E. faecalis</i> (Van-S) ^f	574	Trovafloracin			2.0	11,33-41,47,51-53,59,107
	537	Ciprofloracin			2.0	11,34-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloracin			1.0	11,34,36,37,39
<i>E. faecalis</i> (Van-R) ^d	33	Trovafloracin			8	33,67,97,107
	19	Ciprofloracin			16	67,97
	12	Ofloxacin			>8	67
	19	Sparfloracin			>16	67,97
<i>E. faecium</i> (Van-S)	130	Trovafloracin			2.0	33,35,37,39,40,51,52,107
	110	Ciprofloracin			4.0	35,37,39,40,51,52
	20	Ofloxacin			6.0	35,51
	23	Sparfloracin			1.0	37,39
<i>E. faecium</i> (Van-R)	285	Trovafloracin			8.0	33,34,36,52,53,67,97,107
	231	Ciprofloracin			>16	34,36,52,53,67,97
	150	Ofloxacin			>16	36,53,67
	195	Sparfloracin			>10	34,36,67,97

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Bacteroides fragilis</i>	1,404	Trovafoxacin			0.5	11,37-39,60-67
	1,339	Ciprofloxacin			16.0	11,37,39,60-64,66-67
	874	Ofloxacin			16.0	38,62-63,66
	515	Metronidazole			1.28	11,60-62,64,66
<i>Bacteroides thetaiotaomicron</i>	361	Trovafoxacin			1.0	60,62-64,66
	361	Ciprofloxacin			32	60,62-64,66
	238	Ofloxacin			64	62-63,66
	159	Metronidazole			1.25	60,62,64,66
<i>B. ovatus</i>	218	Trovafoxacin			2.0	60,62-64,66
	218	Ciprofloxacin			64	60,62-64,66
	135	Ofloxacin			64	62-63,66
	100	Metronidazole			1.25	60,62,64,66
<i>B. distasonis</i>	245	Trovafoxacin			1.0	60,62-64,66
	245	Ciprofloxacin			32.0	60,62-64,66
	173	Ofloxacin			16.0	62,63,66
	127	Metronidazole			1.5	60,62,64,66
<i>B. vulgatus</i>	150	Trovafoxacin			4.0	60,62-64,66
	150	Ciprofloxacin			64	60,62-64,66
	105	Ofloxacin			64	62,63,66
	95	Metronidazole			1.0	60,62,64,66
<i>B. uniformis</i>	74	Trovafoxacin			4.0	62-64,66
	74	Ciprofloxacin			40	62-64,66
	58	Ofloxacin			64	62-63,66
	54	Metronidazole			1.0	62,64,66
<i>B. fragilis</i> Group	2,018	Trovafoxacin			1.0	60-61,63-65
	723	Ciprofloxacin			32.0	60-61,64
	723	Metronidazole			2.0	60-61,64
<i>Clostridium perfringens</i>	179	Trovafoxacin			0.25	38,60-62,65-66
	161	Ciprofloxacin			0.5	38,60-62
	121	Ofloxacin			0.5	38,62,66
	109	Metronidazole			1.5	60-62,66
<i>C. difficile</i>	71	Trovafoxacin			1.0	38,60-62
	71	Ciprofloxacin			8.0	38,60-62
	44	Ofloxacin			8.0	38,62
	41	Metronidazole			0.25	60-62
<i>Prevotella bivia</i>	118	Trovafoxacin			1.0	60,65,66
	101	Ciprofloxacin			32.0	60,66
	50	Ofloxacin			16.0	66
	101	Metronidazole			2.5	60,66

Organism	No. Isolates	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>P. intermedia</i>	27	Trovafoxacin			1.0	60,62
	27	Ciprofoxacin			8.25	60,62
	13	Ofloxacin			0.5	62
	27	Metronidazole			2.25	60,62
<i>Prevotella melaninogenica</i>	21	Trovafoxacin			1.5	60,66
	21	Ciprofoxacin			16.0	60
	10	Ofloxacin			64.0	66
	21	Metronidazole			2.25	60,66
<i>Prevotella sp.</i>	126	Trovafoxacin			1.0	38,61-62,66
	126	Ciprofoxacin			12.0	38,61-62,66
	77	Ofloxacin			16.0	38,62,66
	101	Metronidazole			1.0	61-62,66
<i>Fusobacterium nucleatum</i>	68	Trovafoxacin			0.375	60-62,66
	68	Ciprofoxacin			2.0	60-62,66
	29	Ofloxacin			3.0	62,66
	68	Metronidazole			0.25	60-62,66
<i>Peptostreptococci</i>	156	Trovafoxacin			1.0	38,60-61,66
	156	Ciprofoxacin			4.0	38,60-61,66
	55	Ofloxacin			12.0	38,66
	123	Metronidazole			1.0	60-61,66

- a Methicillin-susceptible *S. aureus*.
- b Methicillin-resistant *S. aureus*.
- c Vancomycin-susceptible.
- d Vancomycin-resistant.

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The activity of trovafoxacin against an extensive list of anaerobic pathogens is also given in Table 6. Unlike ciprofoxacin and ofloxacin, trovafoxacin inhibits the majority of anaerobe species with a median MIC₉₀ ≤ 1.0 µg/mL. A total of 1,404 isolates of *Bacteroides fragilis* were tested in twelve separate studies. The MIC₉₀ range for trovafoxacin was compared with MIC₉₀ ranges for ciprofoxacin, ofloxacin, and metronidazole of µg/mL, respectively. When considering the median MIC₉₀, trovafoxacin was as active as metronidazole and 32-fold more active than ciprofoxacin and ofloxacin. When considering median MIC₉₀s, trovafoxacin was also as active as metronidazole and more active than ciprofoxacin and ofloxacin against isolates of *B. thetaiotaomicron*, and *B. distasonsis* (Table 6). The median MIC₉₀s for trovafoxacin against these species in the order given are 1.0, and 1.0 µg/mL. Trovafoxacin was also tested against 2,018 strains classified in five studies as *B. fragilis* group. The trovafoxacin MIC₉₀ range for these organisms was compared with for ciprofoxacin. The median MIC₉₀s for trovafoxacin, ciprofoxacin, and metronidazole were 1.0, 32.0, and 2.0 µg/mL, respectively. As judged by the median MIC₉₀s, trovafoxacin was not active against *B. ovatus*, *B. vulgatus*, and *B. uniformis*. The median

MIC₉₀s for trovafoxacin against these species in the order given are 2.0, 4.0, and 4.0 µg/mL as compared to metronidazole's median MIC₉₀s of 1.25, 1.0, and 1.0 µg/mL, respectively.

Trovafoxacin is as active as ciprofloxacin, ofloxacin, and metronidazole against *Clostridium perfringens*. The MIC₉₀ range against 179 isolates of *C. perfringens* tested in 6 separate studies was with a median of 0.25 µg/mL. This is compared to median MIC₉₀ values for ciprofloxacin, ofloxacin, and metronidazole of 0.5, 0.5, and 1.5 µg/mL, respectively. The median MIC₉₀ of trovafoxacin against *C. difficile* was 1.0 µg/mL.

This median value is three dilutions lower than that obtained with ciprofloxacin and ofloxacin. However, metronidazole is four folds more active against *C. difficile* than trovafoxacin. The median MIC₉₀ for metronidazole against *C. difficile* is 0.25 µg/mL.

In general trovafoxacin is as active as metronidazole and more active than ciprofloxacin and ofloxacin against *Prevotella* spp. Against 126 isolates classified as *Prevotella* spp. in four separate studies, the MIC₉₀ range for trovafoxacin was compared with values of for metronidazole, ciprofloxacin and ofloxacin, respectively. The median MIC₉₀s for trovafoxacin, metronidazole, ciprofloxacin and ofloxacin, against these species are 1.0, 1.0, 12.0, and 16.0 µg/mL.

Trovafoxacin was also as active as metronidazole and slightly more active than ciprofloxacin or ofloxacin against *Fusobacterium nucleatum*. The median MIC₉₀ for 68 isolates reported in four separate studies was 0.375, 2.0, 3.0, and 0.25 µg/mL for trovafoxacin, ciprofloxacin, ofloxacin, and metronidazole, respectively.

Trovafoxacin was as active as metronidazole and moderately more active than ciprofloxacin or ofloxacin against 156 isolates of peptostreptococci tested in four different studies. The median MIC₉₀ was 1.0, 4.0, 12.0, and 1.0 µg/mL for trovafoxacin, ciprofloxacin, ofloxacin, and metronidazole, respectively.

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10. Antimicrobial Activity of Trovafoxacin Against Organisms Associated with Meningitis

Bacterial meningitis in children and adults is most commonly caused by *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*. The *in vitro* activity of trovafoxacin against *S. pneumoniae* (penicillin-susceptible and -resistant isolates) and *H. influenzae* has been discussed in detail in section II.B.1.a.i., sinusitis. Trovafoxacin is also highly potent against isolates of *N. meningitidis*. Against 71 isolates of *N. meningitidis* tested in two studies, the MIC range for trovafoxacin was and the median MIC₉₀ was 0.005 µg/mL. These values are comparable to those obtained for ciprofloxacin, ofloxacin, and sparfoxacin (see Table 7).

11. In Vitro susceptibility profile of Trovafoxacin

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Trovafoxacin has been tested for *in vitro* activity against a variety of microorganisms derived from infections throughout the world. Data derived from these studies are summarized in Table 7. These studies were conducted using standardized and controlled *in vitro* susceptibility test methods. Minimum inhibitory concentrations (MICs) were determined by a dilution method,

most commonly using Mueller-Hinton (MH) broth for aerobes, supplemented as required for support of fastidious organisms and Wilkins-Chalgren (WC) agar for anaerobes. For investigators using broth microdilution methods an inoculum of about 10^5 CFU per milliliter was used in most studies. For investigators using agar dilution an inoculum of about 10^4 CFU per spot for aerobes and 10^5 CFU per spot for anaerobes was used in most studies. Tests for aerobes were read after overnight incubation at 35-37° C, but some anaerobes required up to 48 hours incubation. These agar and inocula are those recommended by the National Committee for Clinical Laboratory Standards (NCCLS).

The NDA holders letter of January 1993 suggested that at least 100 isolates from each species should be tested. Therefore, only species with around 100 isolates will be considered for inclusion in the *in vitro* section (second list) of the package insert. The NDA holders letter also states that in order to be included in the label (second list) a microorganism should be a significant (not anecdotal) pathogen at the body site(s) or in the infection(s) for which clinical effectiveness for other pathogens has been established. Since the sponsor is requesting nosocomial pneumonia; community acquired pneumonia; acute bacterial exacerbation of chronic bronchitis; acute sinusitis; complicated intra-abdominal infections, including post-surgical infections; gynecologic and pelvic infections, including post-surgical infections; surgical prophylaxis; skin and skin structure infections; uncomplicated urinary tract infections; complicated urinary tract infections; bacterial prostatitis; acute, uncomplicated urethral, cervical pharyngeal and rectal gonorrhea; nongonococcal urethritis and cervicitis; pelvic inflammatory disease; and epidemic meningococcal meningitis in children, only potential pathogenic microorganisms usually found at these sites will be included in the second list of the label. The susceptibility breakpoint for trovafloxacin is 1.0 $\mu\text{g/mL}$ (2.0 $\mu\text{g/mL}$ for anaerobes), therefore, in order to be allowed in the *in vitro* list in the label the MIC_{90} value for an organism must be $\leq 1.0 \mu\text{g/mL}$ ($\leq 2.0 \mu\text{g/mL}$ for anaerobes).

The labeling submitted by the sponsor includes the following organisms in the *in vitro* activity (second) list:

Aerobic gram-positive microorganisms:

Bacillus cereus
Corynebacterium jeikeium
Enterococcus faecium (including vancomycin-sensitive and vancomycin-resistant strains)
Staphylococcus saprophyticus

Aerobic gram-negative microorganisms:

Acinetobacter baumannii
Alcaligenes faecalis
Alcaligenes xylosoxidans spp. *denitrificans*
Alcaligenes xylosoxidans spp. *xylosoxidans*
Bordetella bronchiseptica
Brevundimonas diminuta

Burkholderia cepacia
Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Neisseria meningitidis
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens putida
Pseudomonas stutzeri
Salmonella enteritidis
Salmonella typhi
Salmonella spp.
Serratia marcescens
Shigella spp.
Stenotrophomonas maltophilia
Vibrio cholerae
Yersinia enterocolitica

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Anaerobic microorganisms:

Bacteroides distasonis
Bacteroides ovatus
Bacteroides uniformis
Clostridium difficile
Clostridium perfringens
Clostridium ramosum
Fusobacterium mortiferum
Fusobacterium nucleatum
Prevotella bivia
Prevotella intermedia
Prevotella melaninogenica

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Other microorganisms:

Legionella dumoffii
Legionella micdadei
Legionella longbeacheae
Legionella maltophilia??
Mycoplasma hominis
Toxoplasma gondii
Ureaplasma urealyticum

Table 7. Summary Table of All Preclinical Susceptibility Data

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Acinetobacter baumannii</i>	30	Trovafoxacin			>8	59
	30	Ciprofloxacin			>8	59
	30	Ofloxacin			>8	59
<i>Alcaligenes faecalis</i>	25	Trovafoxacin			>8	59
	25	Ciprofloxacin			>8	59
	25	Ofloxacin			>8	59
<i>Alcaligenes xylosoxidans</i> ssp. <i>denitrificans</i>	11	Trovafoxacin			4.0	59
	11	Ciprofloxacin			2.0	59
	11	Ofloxacin			4.0	59
<i>Alcaligenes xylosoxidans</i> ssp. <i>xylosoxidans</i>	24	Trovafoxacin			>8.0	59
	24	Ciprofloxacin			>8.0	59
	24	Ofloxacin			>8.0	59
<i>Bacillus cereus</i>	25	Trovafoxacin			0.06	35-36
	25	Ciprofloxacin			0.125	35-36
	25	Ofloxacin			0.25	35-36
	15	Sparfloxacin			0.125	36
<i>Bacteroides distasonsis</i>	245	Trovafoxacin			1.0	60,62-64,66
	245	Ciprofloxacin			32	60,62-64,66
	173	Ofloxacin			16	62,63,66
	127	Metronidazole			1.5	60,62,64
<i>Bacteroides fragilis</i>	1,404	Trovafoxacin			0.5	11,37-39,60-67
	1,339	Ciprofloxacin			16.0	11,37,39,60-64,66-67
	874	Ofloxacin			16.0	38,62-63,66
	515	Metronidazole			1.28	11,60-62,64,66
<i>B. fragilis</i> Group	2,018	Trovafoxacin			1.0	60-61,63-65
	723	Ciprofloxacin			32.0	60-61,64
	723	Metronidazole			2.0	60-61,64
<i>B. ovatus</i>	218	Trovafoxacin			2.0	60,62-64,66
	218	Ciprofloxacin			64	60,62-64,66
	135	Ofloxacin			64	62-63,66
	100	Metronidazole			1.25	60,62,64,66
<i>B. thetaiotaomicron</i>	361	Trovafoxacin			1.0	60,62-64,66
	361	Ciprofloxacin			32	60,62-64,66
	238	Ofloxacin			64	62-63,66
	159	Metronidazole			1.25	60,62,64,66
<i>B. uniformis</i>	74	Trovafoxacin			4.0	62-64,66

Organism	No. Isolate	Compound	MIC Range ($\mu\text{g/mL}$)	MIC ₉₀ Range ($\mu\text{g/mL}$)	Median MIC ₉₀ ($\mu\text{g/mL}$)	References
	74	Ciprofloxacin			40	62-64,66
	58	Ofloxacin			64	62-63,66
	54	Metronidazole			1.0	62,64,66
<i>B. vulgatus</i>	150	Trovafoxacin			4.0	60,62-64,66
	150	Ciprofloxacin			64	60,62-64,66
	105	Ofloxacin			64	62,63,66
	95	Metronidazole			1.0	60,62,64,66
<i>Bordetella bronchiseptica</i>	12	Trovafoxacin			1.0	59
	12	Ciprofloxacin			1.0	59
	12	Ofloxacin			1.0	59
<i>Brevundimonas diminuta</i>	11	Trovafoxacin			8.0	59
	11	Ciprofloxacin			8.0	59
	11	Ofloxacin			>8.0	59
<i>Burkholderia cepacia</i>	16	Trovafoxacin			4.0	59
	16	Ciprofloxacin			>8	59
	16	Ofloxacin			>8	59
<i>Chlamydia pneumoniae</i>	13	Trovafoxacin			1.0	57
	13	Ofloxacin			1.0	57
<i>Chlamydia trachomatis</i>	19	Trovafoxacin			0.05	70
	19	Ofloxacin			0.35	70
<i>Citrobacter freundii</i>	123	Trovafoxacin			0.375	11,35-36,39,51, 53
	123	Ciprofloxacin			0.125	11,35-36,39,51, 53
	75	Ofloxacin			1.0	35-36,51-53
	63	Sparfloxacin			0.25	11,36,39
<i>Citrobacter diversus</i>	77	Trovafoxacin			0.06	11,35-36,39,51, 53
	77	Ciprofloxacin			0.015	11,35-36,39,51, 53
	50	Ofloxacin			0.125	35,36,51,53
	37	Sparfloxacin			0.25	11,36,39
<i>Clostridium perfringens</i>	179	Trovafoxacin			0.25	38,60-62,65-66
	161	Ciprofloxacin			0.5	38,60-62
	121	Ofloxacin			0.5	38,62,66
	109	Metronidazole			1.5	60-62,66
<i>C. difficile</i>	71	Trovafoxacin			1.0	38,60-62
	71	Ciprofloxacin			8.0	38,60-62
	44	Ofloxacin			8.0	38,62
	41	Metronidazole			0.25	60-62
<i>C. ramosum</i>	15	Trovafoxacin			0.5	61
	15	Ciprofloxacin			8.0	61

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
	15	Metronidazole			1.0	61
<i>Corynebacterium jeikeium</i>	37	Trovafloxacin			2.0	35,51
	37	Ciprofloxacin			16	38,51
	37	Ofloxacin			4	38,51
<i>Enterobacter aerogenes</i>	165	Trovafloxacin			0.125	11,35-36,39,41, 51,53
	165	Ciprofloxacin			0.125	11,35-36,39,41,51,53
	70	Ofloxacin			0.5	35,36,53
	83	Sparfloxacin			0.25	11,36,39
<i>E. agglomerans</i>	45	Trovafloxacin			0.06	35,36,39,53
	45	Ciprofloxacin			0.03	35,36,39,53
	35	Ofloxacin			0.1	35,36,53
	27	sparfloxacin			0.09	36,39
<i>Enterobacter cloacae</i>	242	Trovafloxacin			1.6	11,35-36,39,41-42,51,53
	242	Ciprofloxacin			0.312	11,35-36,39,41-42,51,53
	90	Ofloxacin			2.12	35-36,51,53
	135	Sparfloxacin			0.085	11,36,39,42
<i>Enterobacter</i> spp.	93	Trovafloxacin			0.125	37,38,47
	93	Ciprofloxacin			0.06	37,38,47
	61	Ofloxacin			1.0	38
	10	Sparfloxacin			0.125	37
<i>Enterococcus faecalis</i> (Van-S)	574	Trovafloxacin			2.0	11,33-41,47,51-53,59,107
	537	Ciprofloxacin			2.0	11,34-41,47,51-53
	188	Ofloxacin			4.0	35-36,38,51,53
	89	Sparfloxacin			1.0	11,34,36,37,39
<i>E. faecalis</i> (Van-R)	33	Trovafloxacin			8	33,67,97,107
	19	Ciprofloxacin			16	67,97
	12	Ofloxacin			>8	67
	19	Sparfloxacin			>16	67,97
<i>E. faecium</i> (Van-S)	130	Trovafloxacin			2.0	33,35,37,39,40,51,52,107
	110	Ciprofloxacin			4.0	35,37,39,40,51,52
	20	Ofloxacin			6.0	35,51
	23	Sparfloxacin			1.0	37,39
<i>E. faecium</i> (Van-R)	285	Trovafloxacin			8.0	33,34,36,52,53,67,97,107
	231	Ciprofloxacin			>16	34,36,52,53,67,97
	150	Ofloxacin			>16	36,53,67
	195	Sparfloxacin			>10	34,36,67,97
<i>Escherichia coli</i>	476	Trovafloxacin			0.06	11,35-39,41-42,47,51,53
	476	Ciprofloxacin			0.062	11,35-39,41-42,47,51,52
	193	Ofloxacin			0.125	35-36,38,51,53

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
	188	Sparfloxacin			0.062	11,36-37,39,42
<i>Fusobacterium nucleatum</i>	68	Trovafoxacin			0.375	60-62,66
	68	Ciprofloxacin			2.0	60-62,66
	29	Ofloxacin			3.0	62,66
	68	Metronidazole			0.25	60-62,66
<i>Fusobacterium</i> spp.	101	Trovafoxacin			1.0	38,60,61,66
	101	Ciprofloxacin			3.0	38,60,61,66
	37	Ofloxacin			4.0	38,66
	76	Metronidazole			0.5	60,61,66
<i>Gardnerella vaginalis</i>	23	Trovafoxacin			2.0	38
	23	Ciprofloxacin			2.0	38
	23	Ofloxacin			2.0	38
<i>Haemophilus influenzae</i>	403	Trovafoxacin			0.015	11,35-42,47
	403	Ciprofloxacin			0.015	11,35-42,47
	67	Ofloxacin			0.023	38,51
	150	Sparfloxacin			0.015	11,37,39,42,47
<i>Klebsiella pneumoniae</i>	331	Trovafoxacin			0.125	11,35-36,39,41-42,47,53
	331	Ciprofloxacin			0.06	11,35-36,39,41-42,47,53
	95	Ofloxacin			1.0	36,39,53
	141	Sparfloxacin			0.125	11,36,39,42
<i>Klebsiella oxytoca</i>	94	Trovafoxacin			0.155	11,35-36,39
	94	Ciprofloxacin			0.06	11,35-36,39
	36	Ofloxacin			0.185	35-36
	83	Sparfloxacin			0.25	11,36,39
<i>Klebsiella</i> spp.	113	Trovafoxacin			1.0	37,38,51
	113	Ciprofloxacin			0.25	37,38,51
	63	Ofloxacin			4.5	38,51
	50	Sparfloxacin			0.5	37
<i>Legionella pneumophila</i>	155	Trovafoxacin			0.008	35,38,56
	133	Ciprofloxacin			0.038	35,38
	155	Ofloxacin			0.032	35,38,56
<i>Listeria monocytogenes</i>	61	Trovafoxacin			0.25	38,39
	61	Ciprofloxacin			1.5	38,39
	43	Ofloxacin			4.0	38
	18	Sparfloxacin			1.0	39
<i>Moraxella catarrhalis</i>	304	Trovafoxacin			0.03	11,35,37-40,42,47,51
	304	Ciprofloxacin			0.06	11,35,37-40,42,47,51

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
	53	Ofloxacin			0.075	38,51
	131	Sparfloxacin			0.031	11,37,39,42,47
<i>Morganella morganii</i>	195	Trovafoxacin			0.5	11,35-37,39,41,47,51,53
	195	Ciprofloxacin			0.125	11,35-37,39,41,47,51,53
	46	Ofloxacin			0.19	35-36,51,53
	93	Sparfloxacin			1.0	11,36,37,39,53
<i>Mycoplasma pneumoniae</i>	50	Trovafoxacin			0.185	38,55
	10	Ciprofloxacin			1.0	38
	50	Ofloxacin			1.0	38,55
	40	Sparfloxacin			0.25	55
<i>Mycoplasma hominis</i>	121	Trovafoxacin			0.03	38,55,104
	79	Ciprofloxacin			0.75	38,104
	121	Ofloxacin			1.0	38,55,104
	42	Sparfloxacin			0.03	55
<i>Neisseria gonorrhoeae</i> (Cip-S)	509	Trovafoxacin			0.006	11,35,37-38,68-69
	509	Ciprofloxacin			0.008	11,35,37-38,68-69
	295	Ofloxacin			0.03	38,68
	70	Sparfloxacin			0.0028	11,37
<i>Neisseria gonorrhoeae</i> (Cip-R) ^a	30	Trovafoxacin			0.06	68
	30	Ciprofloxacin			0.5	68
	30	Ofloxacin			0.5	68
<i>Neisseria meningitidis</i>	71	Trovafoxacin			0.005	37,38
	71	ciprofloxacin			0.005	37,38
	61	Ofloxacin			0.03	38
	10	Sparfloxacin			0.002	37
<i>Peptostreptococci</i>	156	Trovafoxacin			1.0	38,60-61,66
	156	Ciprofloxacin			4.0	38,60-61,66
	55	Ofloxacin			12.0	38,66
	123	Metronidazole			1.0	60-61
<i>Prevotella bivia</i>	118	Trovafoxacin			1.5	60,65,66
	101	Ciprofloxacin			32	60,66
	50	Ofloxacin			16	66
	101	Metronidazole			2.5	60,66
<i>Prevotella intermedia</i>	27	Trovafoxacin			1.0	60,62
	27	Ciprofloxacin			8.25	60,62
	13	Ofloxacin			0.5	62
	27	Metronidazole			2.25	60,62
<i>P. melaninogenica</i>	21	Trovafoxacin			1.5	60,66

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
	21	Ciprofloxacine			16.0	60
	10	Ofloxacine			64.0	66
	21	Metronidazole			2.25	60,66
<i>Prevotella</i> spp.	126	Trovafloracin			1.0	38,61-62,66
	126	Ciprofloxacine			12.0	38,61-62,66
	77	Ofloxacine			16.0	38,62,66
	101	Metronidazole			1.0	61-62,66
<i>Proteus mirabilis</i>	298	Trovafloracin			0.5	11,35-37,39,41-42,47,51,53
	298	Ciprofloxacine			0.06	11,35-37,39,41-42,47,51,53
	80	Ofloxacine			0.125	35,36,51,53
	166	Sparfloxacine			0.5	11,36-37,39,42
<i>Proteus vulgaris</i>	89	Trovafloracin			0.5	35,37,39,47,51,53
	89	Ciprofloxacine			0.03	35,37,39,47,51,53
	30	Ofloxacine			0.125	35,51,53
	38	Sparfloxacine			0.5	37,39
<i>Providencia rettgeri</i>	30	Trovafloracin			0.5	35,39,51
	30	Ciprofloxacine			0.5	35,39,51
	20	Ofloxacine			1.5	35,51
	10	Sparfloxacine			0.5	39
<i>Providencia stuartii</i>	40	Trovafloracin			2.0	35,39,51
	40	Ciprofloxacine			0.25	35,39,51
	20	Ofloxacine			5.0	35,51
	20	Sparfloxacine			1.0	39
<i>Pseudomonas aeruginosa</i>	566	Trovafloracin			2.0	11,35-39,41,51,53,58-59
	566	Ciprofloxacine			2.0	11,35-39,41,51,53,58-59
	357	Ofloxacine			>8	35-36,38,51,53,58-59
	256	Sparfloxacine			2.0	11,36-37,39,58
<i>P. fluorescens putida</i>	15	Trovafloracin			1.0	59
	15	Ciprofloxacine			0.25	59
	15	Ofloxacine			2.0	59
<i>P. stutzeri</i>	23	Trovafloracin			0.25	59
	23	Ciprofloxacine			0.125	59
	23	Ofloxacine			0.25	59
<i>Salmonella typhi</i>	34	Trovafloracin			0.03	38,39
	34	Ciprofloxacine			0.03	38,39
	30	Ofloxacine			0.06	38

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
<i>Salmonella enteritidis</i>	15	Trovafoxacin			0.075	35,37
	15	Ciprofloxacin			0.045	35,37
	10	Ofloxacin			0.125	35
<i>Salmonella</i> spp.	127	Trovafoxacin			0.09	11,36,38,39
	127	Ciprofloxacin			0.06	11,36,38,39
	79	Ofloxacin			0.25	36,38
	55	Sparfloxacin			0.06	11,36,39
<i>Serratia marcescens</i>	211	Trovafoxacin			2.5	11,35-36,39,41,47,51,53
	211	Ciprofloxacin			1.0	11,35-36,39,41,47,51,53
	100	Ofloxacin			2.25	35-36,51,53
	91	Sparfloxacin			0.5	11,36,39
<i>Shigella</i> spp.	111	Trovafoxacin			0.03	11,35,38,39,42
	111	Ciprofloxacin			0.02	11,35,38,39,42
	58	Ofloxacin			0.09	35,38
	53	Sparfloxacin			0.03	11,39,42
<i>S. aureus</i> MSSA	666	Trovafoxacin			0.06	11,33-41,51,53,98
	646	Ciprofloxacin			0.75	11,34-41,51-53,98
	194	Ofloxacin			0.5	35,36,38,51,53
	130	Sparfloxacin			0.125	11,34,36,37,39
<i>Staphylococcus aureus</i> MRSA CIP-R	487	Trovafoxacin			2.0	33-42,47,51-54,98
	452	Ciprofloxacin			>16	34-42,47,51-54,98
	134	Ofloxacin			16	35-36,38,51,53
	102	Sparfloxacin			8	34,36-37,39,42
<i>S. aureus</i> MRSA CIP-Sus	28	Trovafoxacin			0.06	11,34
	28	Ciprofloxacin			2.25	11,34
	28	Sparfloxacin			0.31	11,34
<i>S. epidermidis</i> Meth-Cip-R	118	Trovafoxacin			2.5	35,36,53,98
	118	Ciprofloxacin			>16	35,36,53,98
	55	Ofloxacin			>16	35,36,53
Staphylococci coagulase-negative Meth-Cip-S	187	Trovafoxacin			0.06	33-35,37,39,51, 52
	167	Ciprofloxacin			0.5	33-35,37,39,51, 52
	160	Sparfloxacin			0.25	34,37,39
Staphylococci coagulase-negative Meth-R Cip-S	260	Trovafoxacin			0.125	37,40,41
	260	Ciprofloxacin			0.5	37,40,41

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
Staphylococcus haemolyticus	20	Trovafloracin			2.0	35,36
	20	Ciprofloracin			8.0	35,36
	20	Ofloxacin			8.0	35,36
	10	Sparfloracin			8.0	36
Staphylococcus saprophyticus	35	Trovafloracin			0.06	34,36,51
	29	Ciprofloracin			0.5	34,51
	9	Ofloxacin			0.03	51
	26	Sparfloracin			0.25	34,36
Stenotrophomonas (Xanthomonas) maltophilia	227	Trovafloracin			2.0	35-37,39,53,58, 59
	227	Ciprofloracin			>8	35-37,39,53,58
	197	Ofloxacin			>8	35,36,53,58-59
	142	Sparfloracin			2.0	36,37,39,58
Streptococcus agalactiae (group B)	120	Trovafloracin			0.25	34-37,39,41,51
	120	Ciprofloracin			2.0	34-37,39,41,51
	40	Ofloxacin			2.0	36-51
	56	Sparfloracin			0.75	34,36,37,39
Streptococcus pneumoniae pen-S	1,867	Trovafloracin			0.125	11,33-50
	1,847	Ciprofloracin			2.0	11,34-50
	1,427	Ofloxacin			4.0	11,36,38,43,45,46,48-50
	541	Sparfloracin			0.5	11,34,36,37,39,42-45,47,50
Streptococcus pneumoniae pen-R	498	Trovafloracin			0.125	11,43,44,46,49
	498	Ciprofloracin			2.0	11,43,44,46,49
	343	Ofloxacin			4.0	43,46,49
	306	Sparfloracin			1.25	43,44
Streptococcus pyogenes	242	Trovafloracin			0.125	11,34-37,39-41,51-52
	242	Ciprofloracin			0.75	11,34-37,39-41,51-52
	35	Ofloxacin			1.5	36,51
	90	Sparfloracin			0.5	11,34,36,37,39
viridans streptococci	246	Trovafloracin			0.25	33-34,36,38-40,47,52
	226	Ciprofloracin			4.0	34,36,38-40,47, 52
	55	Ofloxacin			6.0	36,38
	56	Sparfloracin			1.0	34,36,39
Ureaplasma urealyticum	157	Trovafloracin			0.5	38,55,104
	111	Ciprofloracin			4.0	38,104
	57	Ofloxacin			3.0	38,55
	46	Sparfloracin			1.0	55
Vibrio	15	Trovafloracin			0.03	38

Organism	No. Isolate	Compound	MIC Range (µg/mL)	MIC ₉₀ Range (µg/mL)	Median MIC ₉₀ (µg/mL)	References
cholerae	15	Ciprofloxacin			0.004	38
	15	Ofloxacin			0.015	38
Yersinia enterocolitica	45	Trovafoxacin			0.06	35,38
	45	Ciprofloxacin			0.03	35,38
	45	Ofloxacin			0.185	35,38

Each of microorganisms in the in vitro activity list will be discussed below along with the reasons for inclusion in or exclusion from the label.

a. Activity Against Gram-positive Aerobes

Bacillus cereus: Two studies, 25 isolates, MIC range: _____ MIC₉₀ range: _____
median MIC₉₀: 0.06 µg/mL.

In addition to food poisoning, based on many reports and frequent and regular occurrence *Bacillus cereus* is now accepted to be associated with mild to severe, necrotic or gangrenous infected wounds. Even though the median MIC₉₀ is acceptable the number of the organisms tested are very few. This organism will not be allowed in the label.

Corynebacterium jeikeium Two studies, 37 isolates, MIC range: _____ MIC₉₀ range: _____
, median MIC₉₀: 2.0 µg/mL.

Corynebacterium jeikeium is the most common corynebacterial pathogen isolated in the clinical laboratory. It is associated with septicemia, endocarditis skin and soft tissue infections, and occasionally, meningitis, peritonitis, and pneumonia, particularly in the compromised and previously treated host. The number of the isolates and the MIC₉₀ of 2.0 µg/mL is not acceptable. This organisms will not be allowed in the label.

Enterococcus faecium (Van-S) Eight studies, 130 isolates, MIC range _____ MIC₉₀ range: _____
, median MIC₉₀: 2.0 µg/mL.

Enterococcus faecium (Van-R) Eight studies, 285 isolates, MIC range: _____ MIC₉₀ range: _____
median MIC₉₀: 8.0 µg/mL.

Enterococci are involved most commonly in urinary tract infections and are implicated in 10% of all such infections. Intra abdominal or pelvic wound infections are the next commonly encountered infections. However, these wound cultures are frequently polymicrobial, and the role of enterococci in this setting remains controversial. Bacteremia is the third most common type of infection, and enterococci are the third leading cause of nosocomial bacteremia. Endocarditis is less common than bacteremia and enterococci is estimated to be the causative agent _____ of bacterial endocarditis cases. *E. faecalis* is the most commonly encountered species in this setting, but various other species also have been implicated as causes of endocarditis. The MIC₉₀ is above the susceptible breakpoint for both Van-R and Van-S *E. faecium*. This organism will not be

allowed in the label

Staphylococcus saprophyticus Three studies, 35 isolates, MIC range: _____, MIC₉₀ _____
range: _____, median MIC₉₀: 0.06 µg/mL.

--One study had 20 isolates collected between 1990 and 1991 at Massachusetts General Hospital. MIC range was _____
MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.125 µg/mL.

--One study had 9 U. S. isolates which according to the authors were neither recent clinical isolates nor typical of a consecutive clinical isolate distribution. They had known quinolone resistance. Neither MIC range nor MIC₉₀ was given. The MIC₅₀ was 0.03 µg/mL.

--One U.S. study had 6 isolates collected from cancer patients admitted to The University of Texas M. D. Anderson Cancer Center at Houston during the past 5 years. The MIC range was _____. The MIC₉₀ and MIC₅₀ was not given.

Staphylococcus saprophyticus is an important opportunistic pathogen in human urinary tract infections, especially in young, sexually active females. It has been proposed as an agent of nongonococcal urethritis in males and prostatitis. Although the median MIC₉₀ was 0.06 µg/mL, the number of the isolates are not sufficient to justify inclusion in the label. *Staphylococcus saprophyticus* will not be allowed in the label.

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b. Activity Against Gram-negative Aerobes

Acinetobacter baumannii One study, 30 isolates, MIC range: _____, MIC₅₀: ≤0.06 µg/mL, MIC₉₀: >8.0 µg/mL.

--The study was performed in the U.S., 85% of the isolates were collected between 1994-1995 at the Ohio State University Medical Center and 15%, all representing uncommon species, were isolated from 1978-1995 in the same hospital.

There are few isolates and the MIC₉₀ is >8.0 µg/mL. *Acinetobacter baumannii* will not be allowed in the label.

Alcaligenes faecalis One study, 25 isolates, MIC range: _____, MIC₅₀: _____
4.0 µg/mL, MIC₉₀: >8.0 µg/mL.

--The study was performed in the U.S., 85% of the isolates were collected between 1994-1995 at the Ohio State University Medical Center and 15%, all representing uncommon species, were isolated from 1978-1995 in the same hospital

There is few isolates and the MIC₉₀ is >8.0 µg/mL. *Alcaligenes faecalis* will not be allowed in the

label

Alcaligenes xylosoxidans
subsp. *denitrificans*

One study, 11 isolates, MIC range
2.0 µg/mL, MIC₉₀: 4.0 µg/mL.

MIC₅₀:

--The study was performed in the U.S., 85% of the isolates were collected between 1994-1995 at the Ohio State University Medical Center and 15%, all representing uncommon species, were isolated from 1978-1995 in the same hospital

There are few isolates and the MIC₉₀ is 4.0 µg/mL. *Alcaligenes xylosoxidans* subsp. *denitrificans* will not be allowed in the label

Alcaligenes xylosoxidans
subsp. *xylosoxidans*

One study, 24 isolates, MIC range
>8.0 µg/mL, MIC₉₀: >8.0 µg/mL.

MIC₅₀:

--The study was performed in the U.S., 85% of the isolates were collected between 1994-1995 at the Ohio State University Medical Center and 15%, all representing uncommon species, were isolated from 1978-1995 in the same hospital

There is few isolates and the MIC₉₀ is >8.0 µg/mL. *Alcaligenes xylosoxidans* subsp. *xylosoxidans* will not be allowed in the label

Bordetella bronchiseptica

One study, 12 isolates, MIC range
0.5 µg/mL, MIC₉₀: 1.0 µg/mL.

MIC₅₀:

--The study was performed in the U.S., 85% of the isolates were collected between 1994-1995 at the Ohio State University Medical Center and 15%, all representing uncommon species, were isolated from 1978-1995 in the same hospital

There are data on very few isolates and the MIC₉₀ is 1.0 µg/mL. *Bordetella bronchiseptica* will not be allowed in the label

Brevundimonas diminuta

One study, 11 isolates, MIC range
µg/mL, MIC₉₀: 8.0 µg/mL.

, MIC₅₀: 4.0

--The study was performed in the U.S., 85% of the isolates were collected between 1994-1995 at the Ohio State University Medical Center and 15%, all representing uncommon species, were isolated from 1978-1995 in the same hospital

There are data on very few isolates and the MIC₉₀ is 8.0 µg/mL. *Brevundimonas diminuta* will not be allowed in the label

Burkholderia cepacia One study, 16 isolates, MIC range: MIC₅₀: 2.0
µg/mL, MIC₉₀: 4.0 µg/mL.

--The study was performed in the U.S., 85% of the isolates were collected between 1994-1995 at the Ohio State University Medical Center and 15%, all representing uncommon species, were isolated from 1978-1995 in the same hospital-

There are data on very few isolates and the MIC₉₀ is 4.0 µg/mL. *Burkholderia cepacia* will not be allowed in the label

Citrobacter diversus Six studies, 77 isolates, MIC range MIC₉₀
range median MIC₉₀: 0.06 µg/mL.

--One U.S. study had 17 isolates collected in summer of 1990 at Massachusetts General Hospital and University of Washington. MIC range was , MIC₅₀ was 0.062 µg/mL, and MIC₉₀ was 0.25 µg/mL.

--One U.S. study had 10 isolates collected at University of Iowa hospitals and clinics in 1991-1992. MIC range was MIC₅₀ was 0.03 µg/mL, and MIC₉₀ was 0.06 µg/mL.

--One U.S. study had 10 isolates collected at Columbia Presbyterian Medical Center before 1992. MIC range was , MIC₅₀ was 0.03 µg/mL, and MIC₉₀ was 0.06 µg/mL.

--One study had 10 U. S. isolates which according to the authors were neither recent clinical isolates nor typical of a consecutive clinical isolate distribution. They had known quinolone resistance. The MIC range was not given, the MIC₅₀ was 0.008 µg/mL and the MIC₉₀ was 0.016 µg/mL.

--One U.S. study had 20 isolates collected at Yale-New Haven Hospital. The age of the isolates were not indicated. MIC range was , MIC₅₀ was ≤0.015 µg/mL, and MIC₉₀ was 0.03 µg/mL.

--One U.S. study had 10 isolates collected from cancer patients admitted to The University of Texas M. D. Anderson Cancer Center at Houston during the past 5 years. The MIC range was , MIC₅₀ was 0.03 µg/mL and MIC₉₀ was 0.06 µg/mL.

Less than 100 isolates were tested in a number of different centers. However, majority of the isolates were older than 5 years. Even though the median MIC₉₀ was 0.06 µg/mL and this organism may be associated with pneumonia, *Citrobacter diversus* will not be allowed into the

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Citrobacter freundii

Six studies, 123 isolates, MIC range:
MIC₉₀ range: median MIC₉₀: 0.375 µg/mL.

--One U.S. study had 28 isolates collected in summer of 1990 at Massachusetts General Hospital and University of Washington. MIC range was MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.25 µg/mL.

--One U.S. study had 20 isolates collected at University of Iowa hospitals and clinics in 1991-1992. MIC range was µg/mL, MIC₅₀ was 0.06 µg/mL, and MIC₉₀ was 0.5 µg/mL.

--One U.S. study had 20 isolates collected at Columbia Presbyterian Medical Center before 1992. MIC range was µg/mL, MIC₅₀ was 0.06 µg/mL, and MIC₉₀ was 0.25 µg/mL.

--One study had 15 U. S. isolates which according to the authors were neither recent clinical isolates nor typical of a consecutive clinical isolate distribution. They had known quinolone resistance. The MIC range was not given, the MIC₅₀ was 0.06 µg/mL and the MIC₉₀ was 0.5 µg/mL.

--One U.S. study had 25 isolates collected at Yale-New Haven Hospital. The age of the isolates were not indicated. MIC range was MIC₅₀ was 0.03 µg/mL, and MIC₉₀ was 4.0 µg/mL.

--One U.S. study had 15 isolates collected from cancer patients admitted to The University of Texas M. D. Anderson Cancer Center at Houston during the past 5 years. The MIC range was MIC₅₀ was 0.06 µg/mL and MIC₉₀ was 0.25 µg/mL.

More than 100 isolates were tested in a number of different centers. Majority of the isolates were older than 5 years. However, the recent study with 15 isolates indicates that *Citrobacter freundii* remains susceptible to trovafoxacin with an MIC₉₀ of 0.25 µg/mL. This organism may be associated with pneumonia, *Citrobacter freundii* will be allowed into the label.

Enterobacter aerogenes

Seven studies, 165 isolates, MIC range:
MIC₉₀ range: median MIC₉₀: 0.125 µg/mL.

--One U.S. study had 38 isolates collected in summer of 1990 at Massachusetts General Hospital and University of Washington. MIC range was MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.5 µg/mL.

--One U.S. study had 20 isolates collected at University of Iowa

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hospitals and clinics in 1991-1992. MIC range was _____
MIC₅₀ was 0.03 µg/mL, and MIC₉₀ was 0.06 µg/mL.

--One U.S. study had 20 isolates collected at Columbia
Presbyterian Medical Center before 1992. MIC range was _____
, MIC₅₀ was 0.06 µg/mL, and MIC₉₀ was 0.125
µg/mL.

--One Saudi study had 27 isolates collected between April, 1995
to September 1995. MIC range was _____
MIC₅₀ was <0.03 µg/mL, and MIC₉₀ was 0.125 µg/mL.

--One study had 10 U. S. isolates which according to the authors
were neither recent clinical isolates nor typical of a consecutive
clinical isolate distribution. They had known quinolone
resistance. The MIC range was not given, the MIC₅₀ was 0.03
µg/mL and the MIC₉₀ was 8.0 µg/mL.

--One U.S. study had 25 isolates collected at Yale-New Haven
Hospital. The age of the isolates were not indicated. MIC
range was _____, MIC₅₀ was 0.03 µg/mL, and
MIC₉₀ was 0.125 µg/mL.

--One U.S. study had 25 isolates collected from cancer patients
admitted to The University of Texas M. D. Anderson Cancer
Center at Houston during the past 5 years. The MIC range was _____
MIC₅₀ was 0.03 µg/mL and MIC₉₀ was
0.06 µg/mL.

This organism may be associated with pneumonia. More than 100 isolates were tested in a
number of different centers. However, majority of the isolates were older than 5 years. The two
recent studies were performed in Saudi Arabia with 27 isolates and in U.S. with 25 isolates. The
MIC₉₀s were 0.125 µg/mL and 0.06 µg/mL respectively. *Enterobacter aerogenes* will be allowed
into the label.

Morganella morganii

Nine studies, 195 isolates, MIC range:
MIC₉₀ range: _____, median MIC₉₀: 0.5 µg/mL.

--One U.S. study had 39 isolates collected in summer of 1990 at
Massachusetts General Hospital and University of Washington.
MIC range was _____, MIC₅₀ was 1.0 µg/mL, and
MIC₉₀ was 2.0 µg/mL.

--One U.S. study had 10 isolates collected at University of Iowa
hospitals and clinics in 1991-1992. MIC range was _____
MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.25 µg/mL.

--One U.K. study had 25 isolates collected at City Hospital NHS
Trust. The age of the isolates was not indicated. MIC range _____

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- was , MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 1.0 µg/mL
- One U.S. study had 20 isolates collected at Columbia Presbyterian Medical Center before 1992. MIC range was MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.25 µg/mL.
 - One Saudi study had 45 isolates collected between April, 1995 to September 1995. MIC range was , MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 2.0 µg/mL.
 - One Belgian study had 20 isolates collected in 1993 from ten large hospitals. MIC range was , MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 0.25 µg/mL.
 - One study had 10 U. S. isolates which according to the authors were neither recent clinical isolates nor typical of a consecutive clinical isolate distribution. They had known quinolone resistance. The MIC range was not given, the MIC₅₀ was 0.06 µg/mL and the MIC₉₀ was 0.125 µg/mL.
 - One U.S. study had 17 isolates collected at Yale-New Haven Hospital. The age of the isolates were not indicated. MIC range was , MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 0.5 µg/mL.
 - One U.S. study had 9 isolates collected from cancer patients admitted to The University of Texas M. D. Anderson Cancer Center at Houston during the past 5 years. The MIC range was , MIC₅₀ and MIC₉₀ was not given.

This is an opportunistic organism most commonly associated with urinary tract infections. Close to 200 isolates were tested in a number of different centers. However, majority of the isolates were older than 5 years. The three recent studies were performed in Saudi Arabia, Belgium and the U.S. with 45, 20, and 9 isolates respectively. The MIC₉₀ for the Saudi study was 2.0 µg/mL and for the Belgian study was 0.25 µg/mL. None of the U.S. isolated had MICs greater than 0.5 µg/mL. Even though both foreign studies followed NCCLS methodologies, the MIC₉₀ results for these studies are at conflict. The small U.S. study indicates that *Morganella morganii* remains susceptible to trovafloxacin and it will be allowed into the label.

Neisseria meningitidis

Two studies, 71 isolates, MIC range:
MIC₉₀ range: , median MIC₉₀: 0.005 µg/mL.

- One U.K. study had 10 isolates collected at City Hospital NHS Trust. The age of the isolates was not indicated. MIC range was 0.002 µg/mL, MIC₅₀ was 0.002 µg/mL, and MIC₉₀ was 0.002 µg/mL.

--One U.K. study had 61 isolates collected in University College Hospital in London. The authors indicate that some of the isolates were recent clinical isolates from the University College Hospital microbiology lab and some were frozen isolates from UK and European centers collected in 1993-1994. . MIC range was _____, MIC₅₀ was 0.004 µg/mL, and MIC₉₀ was 0.008 µg/mL.

Neisseria meningitidis is an organism that is implicated in community -acquired pneumonia, urethritis, and most importantly in meningitis. Due to the seriousness of meningococcal meningitis and the associated public health issues this organism will be listed ONLY if the efficacy of a drug is studied and demonstrated in well controlled clinical trials. *Neisseria meningitidis* will not be allowed in the label.

Proteus vulgaris

Six studies, 89 isolates, MIC range: _____ MIC₉₀
range: _____ median MIC₉₀: 0.5 µg/mL.

--One U.S. study had 10 isolates collected at University of Iowa hospitals and clinics in 1991-1992. MIC range was _____, MIC₅₀ was 0.06 µg/mL, and MIC₉₀ was 0.25 µg/mL.

--One U.K. study had 18 isolates collected at City Hospital NHS Trust. The age of the isolates was not indicated. MIC range was _____, MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 0.5 µg/mL.

--One U.S. study had 20 isolates collected at Columbia Presbyterian Medical Center before 1992. MIC range was _____, MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 0.5 µg/mL.

--One Belgian study had 21 isolates collected in 1993 from ten large hospitals. MIC range was _____, MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 0.5 µg/mL.

--One study had 10 U. S. isolates which according to the authors were neither recent clinical isolates nor typical of a consecutive clinical isolate distribution. They had known quinolone resistance. The MIC range was not given, the MIC₅₀ was 0.125 µg/mL and the MIC₉₀ was 0.25 µg/mL.

--One U.S. study had 10 isolates collected at Yale-New Haven Hospital. The age of the isolates were not indicated. MIC range was _____, MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 1.0 µg/mL.

This organism is most commonly associated with urinary tract infections. Only 89 isolates were

tested in a number of different centers. However, majority of the isolates were older than 5 years. The only recent study was performed in Belgium with 21 isolates and an MIC₉₀ of 0.5 µg/mL which indicates that *Proteus vulgaris* remains susceptible to trovafoxacin. Even though the number of isolates are less than 100 given the low frequency by which this organism is isolated from clinical samples, *Proteus vulgaris* will be allowed into the label.

Providencia rettgeri Three studies, 30 isolates, MIC range:
MIC₉₀ range: 0.5 µg/mL, median MIC₉₀: 0.5 µg/mL.

There are not enough isolates tested and *Providencia rettgeri* will not be allowed into the label.

Providencia stuartii Three studies, 40 isolates, MIC range
MIC₉₀ range , median MIC₉₀: 2.0 µg/mL.

There are not enough isolates tested and the median MIC₉₀ is 2.0 µg/mL. *Providencia stuartii* will not be allowed into the label.

P. fluorescens putida One study, 15 isolates, MIC range. MIC₉₀
range: 1.0 µg/mL, median MIC₉₀: 1.0 µg/mL.

There are not enough isolates tested and *Pseudomonas fluorescens putida* will not be allowed into the label.

Pseudomonas stutzeri One study, 23 isolates, MIC range MIC₉₀
range: 0.25 µg/mL, median MIC₉₀: 0.25 µg/mL.

There are not enough isolates tested and *Pseudomonas stutzeri* will not be allowed into the label.

Salmonella enteritidis Two studies, 15 isolates, MIC range
MIC₉₀ range median MIC₉₀: 0.075
µg/mL.

There are not enough isolates tested and Infectious diarrhea is not an indication for trovafoxacin. *Salmonella enteritidis* will not be allowed into the label.

Salmonella typhi Two studies, 34 isolates, MIC range MIC₉₀
range: 0.03 µg/mL, median MIC₉₀: 0.03 µg/mL.

There are not enough isolates tested and Infectious diarrhea is not an indication for trovafoxacin. *Salmonella typhi* will not be allowed into the label.

Salmonella spp. Four studies, 127 isolates, MIC range
MIC₉₀ range median MIC₉₀: 0.09 µg/mL.

Infectious diarrhea is not an indication for trovafoxacin. *Salmonella* spp. will not be allowed into the label.

Serratia marcescens Eight studies, 211 isolates, MIC range
MIC₉₀ range , median MIC₉₀: 2.5 µg/mL.

- One U.S. study had 36 isolates collected in summer of 1990 at Massachusetts General Hospital and University of Washington. MIC range was _____, MIC₅₀ was 2.0 µg/mL, and MIC₉₀ was 4.0 µg/mL.
- One U.S. study had 20 isolates collected at University of Iowa hospitals and clinics in 1991-1992. MIC range was _____ µg/mL, MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.5 µg/mL.
- One U.S. study had 25 isolates collected at Columbia Presbyterian Medical Center before 1992. MIC range was _____, MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 1.0 µg/mL.
- One Saudi study had 28 isolates collected between April, 1995 to September 1995. MIC range was _____, MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 1.0 µg/mL.
- One Belgian study had 22 isolates collected in 1993 from ten large hospitals. MIC range was _____, MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 16 µg/mL.
- One study had 25 U. S. isolates which according to the authors were neither recent clinical isolates nor typical of a consecutive clinical isolate distribution. They had known quinolone resistance. The MIC range was not given, the MIC₅₀ was 1.0 µg/mL and the MIC₉₀ was >8.0 µg/mL.
- One U.S. study had 25 isolates collected at Yale-New Haven Hospital. The age of the isolates were not indicated. MIC range was _____, MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 4.0 µg/mL.
- One U.S. study had 30 isolates collected from cancer patients admitted to The University of Texas M. D. Anderson Cancer Center at Houston during the past 5 years. The MIC range was _____, MIC₅₀ was 0.25 µg/mL and MIC₉₀ was 0.25 µg/mL.

Serratia marcescens is an important cause of extraintestinal infections, having caused many nosocomial outbreaks associated with blood transfusions surgery, and the urinary tract. Most of the MIC₉₀s were above the susceptible breakpoint. *Serratia marcescens* will not be allowed in the label.

Shigella spp.

Five studies, 111 isolates, MIC range _____, MIC₉₀ range _____, median MIC₉₀: 0.03 µg/mL.

- One U.S. study had 31 isolates collected in summer of 1990 at

Massachusetts General Hospital and University of Washington.
MIC range was MIC₅₀ was 0.031 µg/mL,
and MIC₉₀ was 0.031 µg/mL.

--One U.S. study had 10 isolates collected at University of Iowa
hospitals and clinics in 1991-1992. MIC range was
MIC₅₀ was ≤0.015 µg/mL, and MIC₉₀ was ≤0.015
µg/mL.

--One U.K. study had 48 isolates collected at University College
Hospital in London and other European centers between 1993
and 1994. MIC range was MIC₅₀ was
0.015 µg/mL, and MIC₉₀ was 0.03 µg/mL.

--One U.S. study had 12 isolates collected at Columbia
Presbyterian Medical Center before 1992. MIC range was
MIC₅₀ was 0.03 µg/mL, and MIC₉₀ was 0.06
µg/mL.

--Reference 42 is an abstract that does not address *Shigella* spp.

Infectious diarrhea is not an indication for trovafoxacin. *Shigella* spp. will not be allowed into
the label.

Stenotrophomonas maltophilia Seven studies, 227 isolates, MIC range
MIC₉₀ range: 0.5->8 µg/mL, median MIC₉₀: 2.0 µg/mL.

--One U.S. study had 10 isolates collected at University of Iowa
hospitals and clinics in 1991-1992. MIC range was
MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 2.0 µg/mL.

--One U.K. study had 10 isolates collected at City Hospital NHS
Trust. The age of the isolates was not indicated. MIC range
was MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was
1.0 µg/mL

--One U.S. study had 20 isolates collected at Columbia
Presbyterian Medical Center before 1992. MIC range was
MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 0.5
µg/mL.

--One U.S. study had 25 isolates collected at Yale-New Haven
Hospital. The age of the isolates were not indicated. MIC
range was MIC₅₀ was 0.25 µg/mL, and MIC₉₀
was 2.0 µg/mL.

--Reference 58 is an abstract that does not address checkerboard
titration with out reference to MIC range, MIC₅₀, or MIC₉₀.

--One U.S. study had 50 isolates. Eighty five percent of the isolates were collected in 1994-1995 and 15% were collected in 1991-1994 at The Ohio State University Medical Center. MIC range was MIC_{50} was 1.0 $\mu\text{g/mL}$, and MIC_{90} was $>8.0 \mu\text{g/mL}$.

--One U.S. study had 30 isolates collected from cancer patients admitted to The University of Texas M. D. Anderson Cancer Center at Houston during the past 5 years. The MIC range was MIC_{50} was 0.5 $\mu\text{g/mL}$ and MIC_{90} was 4.0 $\mu\text{g/mL}$.

Stenotrophomonas maltophilia is ubiquitous in nature and has also been isolated from the hospital environment. It is the third most frequently isolated nonfermentative gram-negative rod in the clinical laboratory. Strains may be colonizers (e.g., in cystic fibrosis) or infecting agents. Septicemia (often associated with intravenous catheters), pneumonia, and wound infections have been reported. Most of the isolates tested are not recent isolates and the MICs were greater than the susceptible breakpoint. The two recent studies with 50 and 30 isolates each reported the MIC_{90} to be $>8.0 \mu\text{g/mL}$ and 4.0 $\mu\text{g/mL}$ respectively. *Stenotrophomonas maltophilia* will not be allowed into the label.

Vibrio cholerae One study, 15 isolates, MIC range MIC_{90}
range: 0.03 $\mu\text{g/mL}$, median MIC_{90} : 0.03 $\mu\text{g/mL}$.

There are not enough isolates tested and *Vibrio cholerae* will not be allowed into the label.

Yersinia enterocolitica Two study, 45 isolates, MIC range
 MIC_{90} range: 0.06 $\mu\text{g/mL}$, median MIC_{90} : 0.06 $\mu\text{g/mL}$.

Infectious diarrhea is not an indication for trovafoxacin and there is not enough isolates tested therefore, *Yersinia enterocolitica* will not be allowed into the label.

c. Activity Against Anaerobes

Bacteroides distasonis Five studies, 245 isolates, MIC range MIC_{90}
range median MIC_{90} : 1.0 $\mu\text{g/mL}$.

--One U.S. study (reference 60) makes no reference to *Bacteroides distasonis*.

--One U.K. study had 12 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, and University of Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was MIC_{50} was 0.25 $\mu\text{g/mL}$, and MIC_{90} was 0.5 $\mu\text{g/mL}$.

--One U.S. study had 118 isolates collected at New England

Medical Center, Danbury Hospital, Duke University Medical Center, Loyola Medical Center, university Medical Center at University of Florida (Jacksonville), University of Michigan Medical Center, the Pittsburgh V.A. Medical Center, and the wadsworth V.A. Medical Center (Los Angeles) between 1992-1994. The MIC range was , MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 1.0 µg/mL.

--One U.S. study (reference 64) makes no reference to *Bacteroides distasonis*.

--One U.S. study had 43 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 1.0 µg/mL.

Bacteroides distasonis as a member of *Bacteroides fragilis* group is recovered from most intra-abdominal infections and may occur in infections at other sites. The MIC₉₀ of well over a 100 recent isolates was 1.0 µg/mL. *Bacteroides distasonis* may be included in the label.

Bacteroides ovatus

Five studies, 218 isolates, MIC range MIC₉₀
range median MIC₉₀: 2.0 µg/mL.

--One U.S. study (reference 60) makes no reference to *Bacteroides ovatus*.

--One U.K. study had 17 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, and University of Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 2.0 µg/mL.

--One U.S. study had 118 isolates collected at New England Medical Center, Danbury Hospital, Duke University Medical Center, Loyola Medical Center, university Medical Center at University of Florida (Jacksonville), University of Michigan Medical Center, the Pittsburgh V.A. Medical Center, and the wadsworth V.A. Medical Center (Los Angeles) between 1992-1994. The MIC range was MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 2.0 µg/mL.

--One U.S. study (reference 64) makes no reference to *Bacteroides ovatus*.

--One U.S. study had 24 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 2.0 µg/mL.

Bacteroides ovatus as a member of *Bacteroides fragilis* group is recovered from most intra-

abdominal infections and may occur in infections at other sites. The MIC₉₀ of well over a 100 recent isolates was 2.0 µg/mL. *Bacteroides ovatus* will be allowed in the label.

Bacteroides uniformis Four studies, 74 isolates, MIC range MIC₉₀
range, median MIC₉₀: 4.0 µg/mL.

--One U.K. study had 13 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, and University of Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 2.0 µg/mL.

--One U.S. study had 23 isolates collected at New England Medical Center, Danbury Hospital, Duke University Medical Center, Loyola Medical Center, university Medical Center at University of Florida (Jacksonville), University of Michigan Medical Center, the Pittsburgh V.A. Medical Center, and the wadsworth V.A. Medical Center (Los Angeles) between 1992-1994. The MIC range was MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 4.0 µg/mL.

--One U.S. study (reference 64) makes no reference to *Bacteroides uniformis*.

--One U.S. study had 23 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 4.0 µg/mL.

Bacteroides uniformis as a member of *Bacteroides fragilis* group is recovered from most intra-abdominal infections and may occur in infections at other sites. The MIC₉₀ of 46 recent isolates was 4.0 µg/mL. *Bacteroides uniformis* will not be allowed in the label.

Bacteroides vulgatus Five studies, 150 isolates, MIC range MIC₉₀
range: 0.5-4.0 µg/mL, median MIC₉₀: 4.0 µg/mL.

--One U.S. study (reference 60) makes no reference to *Bacteroides vulgatus*.

--One U.K. study had 18 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, and University of Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 1.0 µg/mL.

--One U.S. study had 55 isolates collected at New England Medical Center, Danbury Hospital, Duke University Medical Center, Loyola Medical Center, university Medical Center at

University of Florida (Jacksonville), University of Michigan Medical Center, the Pittsburgh V.A. Medical Center, and the Wadsworth V.A. Medical Center (Los Angeles) between 1992-1994. The MIC range was 0.125-16.0 µg/mL, MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 4.0 µg/mL.

--One U.S. study (reference 64) makes no reference to *Bacteroides vulgatus*.

--One U.S. study had 32 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 4.0 µg/mL.

Bacteroides vulgatus as a member of *Bacteroides fragilis* group is recovered from most intra-abdominal infections and may occur in infections at other sites. The MIC₉₀ of 87 recent isolates was 4.0 µg/mL. *Bacteroides vulgatus* will not be allowed in the label.

Clostridium difficile

Four studies, 71 isolates, MIC range _____, MIC₉₀ range _____, median MIC₉₀: 1.0 µg/mL.

--One U.K. study had 30 isolates collected at University College Hospital in London and other European centers between 1993 and 1994. MIC range was _____, MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 4.0 µg/mL.

--One U.S. study (reference 60) makes no reference to *Clostridium difficile*.

--One U.S. study had 15 isolates collected at the V.A. Wadsworth Medical Center in Los Angeles. The age of the isolates were not indicated except for stating that they were "recent clinical isolates." MIC range was _____, MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 1.0 µg/mL.

--One U.K. study had 14 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, _____, and University of Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was _____, MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 1.0 µg/mL.

Clostridium difficile is the major cause of antibiotic-associated diarrhea and pseudomembranous colitis. There were less than 100 isolates tested and the one U.K. study with one third of the isolates, reported the MIC₉₀ to be 4.0 µg/mL. *Clostridium difficile* will not be allowed in the label.

Clostridium perfringens

Six studies, 179 isolates, MIC range _____, MIC₉₀ range _____, median MIC₉₀: 0.25 µg/mL.

- One U.K. study had 52 isolates collected at University College Hospital in London and other European centers between 1993 and 1994. MIC range was _____, MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.25 µg/mL.
- One U.S. study, 1 isolate with MIC of 0.03 µg/mL.
- One U.S. study had 20 isolates collected at the V.A. Wadsworth Medical Center in Los Angeles. The age of the isolates were not indicated except for stating that they were "recent clinical isolates." MIC range was _____, MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.125 µg/mL.
- One U.K. study had 16 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, _____ and University of Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was _____, MIC₅₀ was 0.06 µg/mL, and MIC₉₀ was 0.25 µg/mL.
- One U.S. study had 13 isolates. The age and the geographical location from which the isolates were recovered were not indicated. MIC range was _____, MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.125 µg/mL.
- One U.S. study had 53 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.25 µg/mL.

Clostridium perfringens is encountered in a wide variety of clinical settings ranging from simple contamination of wounds to traumatic or nontraumatic myonecrosis, clostridial cellulitis, intra-abdominal sepsis, gangrenous cholecystitis, postabortion infections, bacteremia in various clinical settings, aspiration pneumonia, necrotizing pneumonia, and brain abscess. Considering that the MIC₉₀ for 106 recent isolates is 0.25 µg/mL, *Clostridium perfringens* will be allowed in the label.

Clostridium ramosum One study, 15 isolates, MIC range: _____, MIC₉₀ range: 0.5 µg/mL, median MIC₉₀: 0.5 µg/mL.

There are not enough isolates tested and *Clostridium ramosum* will not be allowed into the label.

Fusobacterium mortiferum There is no *in vitro* data presented in the NDA to support the inclusion of this organism. *Fusobacterium mortiferum* will not be allowed in the label.

Fusobacterium nucleatum Four studies, 68 isolates, MIC range: _____, MIC₉₀ range _____, median MIC₉₀: 0.375 µg/mL.

- One U.S. study (reference 60) makes no reference to *Fusobacterium nucleatum*.

- One U.S. study had 28 isolates collected at the V.A. Wadsworth Medical Center in Los Angeles. The age of the isolates were not indicated except for stating that they were "recent clinical isolates." MIC range was MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 0.5 µg/mL.
- One U.K. study had 17 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, and University of Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 0.5 µg/mL.
- One U.S. study had 12 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 0.5 µg/mL.

There are only 12 isolates that may be considered as "recent" isolates. The reported MIC₉₀ was 0.5 µg/mL. There is not enough *in vitro* data presented to justify the inclusion of *Fusobacterium nucleatum* in the label. *Fusobacterium nucleatum* will not be allowed in the label.

Prevotella bivia

Three studies, 118 isolates, MIC range
MIC₉₀ range: median MIC₉₀: 1.5 µg/mL.

- One U.S. study (reference 60) makes no reference to *Prevotella bivia*.
- One U.S. study had 17 isolates. The age and the geographical location from which the isolates were recovered were not indicated. MIC range was MIC₅₀ was 1.0 µg/mL, and MIC₉₀ was 1.0 µg/mL.
- One U.S. study had 45 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 2.0 µg/mL, and MIC₉₀ was 2.0 µg/mL.

Only data for 62 isolates could be found in the NDA. One study with the majority of the isolates reported the MIC₉₀ to be 2.0 µg/mL. *Prevotella bivia* will not be allowed in the label.

Prevotella intermedia

Two studies, 27 isolates, MIC range
range: 1.0 µg/mL, median MIC₉₀: 1.0 µg/mL. MIC₉₀

- One U.S. study (reference 60) makes no reference to *Prevotella intermedia*.
- One U.K. study had 13 isolates collected at Southmead Hospital, Bristol Dental Hospital, the PHLS Anaerobe Reference Unit, Cardiff, and University of

Bristol, Department of Medical Microbiology. The age of the isolates was not stated. The MIC range was MIC₅₀ was 0.5 µg/mL, and MIC₉₀ was 1.0 µg/mL.

Only data for 13 isolates could be found in the NDA. There is not enough *in vitro* data presented to justify the inclusion of *Prevotella intermedia* in the label. *Prevotella intermedia* will not be allowed

Prevotella melaninogenica Two studies, 21 isolates, MIC range , MIC₉₀
range median MIC₉₀: 1.5 µg/mL.

--One U.S. study had one isolate with MIC of 1.0 µg/mL.

--One U.S. study had 10 isolates collected from several Chicago area medical centers during 1994. The MIC range was not stated, MIC₅₀ was 0.25 µg/mL, and MIC₉₀ was 2.0 µg/mL.

Only data for 11 isolates could be found in the NDA. There is not enough *in vitro* data presented to justify the inclusion of *Prevotella melaninogenica* in the label. *Prevotella melaninogenica* will not be allowed

d. Activity Against "Other" Organisms

APPROXIMATELY
CONFIDENTIAL

Legionella dumoffii
Legionella micdadei
Legionella longbeacheae
Legionella maltophilia

There were no *in vitro* data presented in the NDA to support inclusion of *Legionella dumoffii*, *Legionella micdadei*, *Legionella longbeacheae*, or *Legionella maltophili*?. These organisms will not be allowed in the label.

Mycoplasma hominis

Three studies, 121 isolates, MIC range: 0.008-0.125 µg/mL,
MIC₉₀ range median MIC₉₀: 0.03 µg/mL.

--One U.K. study had 10 isolates collected at University College Hospital in London and other European centers between 1993 and 1994. MIC range was , MIC₅₀ was not reported, and MIC₉₀ was 0.125 µg/mL.

--One U.S. study had tested 42 isolates at University of Washington in Seattle. The age and the geographical location of the isolates were not reported. MIC range was MIC₅₀ was 0.06 µg/mL, and MIC₉₀ was 0.06 µg/mL.

--One U.S. study had tested 69 clinical isolates at University of Alabama at Birmingham. The age of the isolates were not reported. MIC range was , MIC₅₀ was 0.016 µg/mL, and MIC₉₀ was 0.031 µg/mL.

The role of *Mycoplasma hominis* in genitourinary tract infections is controversial. Difficulty in accepting *Mycoplasma hominis* as cause of disease has arisen either because samples cannot be obtained easily from the affected site (for example, the fallopian tube) or because the organisms are recovered from asymptomatic individuals. Never the less, there is evidence that these species play etiologic role in some genital tract diseases of both men and women. *Mycoplasma hominis* has been isolated from the upper urinary tract only in patients with symptoms of acute pyelonephritis, often with an antibody response. *Mycoplasma hominis* will be included in the label.

Ureaplasma urealyticum

Three studies, 157 isolates, MIC range
MIC₉₀ range , median MIC₉₀: 0.5 µg/mL.

--One U.K. study had 10 isolates collected at University College Hospital in London and other European centers between 1993 and 1994. MIC range was MIC₅₀ was not reported, and MIC₉₀ was 0.5 µg/mL.

--One U.S. study had tested 46 isolates at University of Washington in Seattle. The age and the geographical location of the isolates were not reported. MIC range was MIC₅₀ was 0.125 µg/mL, and MIC₉₀ was 0.5 µg/mL.

--One U.S. study had tested 101 clinical isolates at University of Alabama at Birmingham. The age of the isolates were not reported. MIC range was MIC₅₀ was 0.063 µg/mL, and MIC₉₀ was 0.125

The role of *Ureaplasma urealyticum* in genitourinary tract is controversial. Difficulty in accepting *U. urealyticum* as cause of disease has arisen either because samples cannot be obtained easily from the affected site (for example, the fallopian tube) or because the organisms are recovered from asymptomatic individuals. Never the less, there is evidence that these species play etiologic role in some genital tract diseases of both men and women. *Ureaplasma urealyticum* has been associated with nonchlamydial nongonococcal urethritis in men and women. *Ureaplasma urealyticum* will be included in the label.

Toxoplasma gondii

There were no *in vitro* data presented in the NDA to support the inclusion of *Toxoplasma gondii* in the label. *Toxoplasma gondii* will not be allowed in the label.

In the label the *in vitro* organisms with MIC₉₀ values ≤1.0 µg/mL should, therefore, read as follows:

Aerobic gram-negative microorganisms:

Citrobacter freundii
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris

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Anaerobic microorganisms:

Bacteroides distasonis
Clostridium perfringens

Other microorganisms:
Mycoplasma hominis
Ureaplasma urealyticum

APPEARS THIS WAY
ON ORIGINAL

C. Effects of Miscellaneous Factors on Activity

1. Effect of Medium

Studies were performed in order to evaluate the effects of growth medium on the MICs to trovafloxacin with several aerobic and anaerobic organisms. In one study which included isolates of *S. aureus*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *E. cloacae*, and *P. aeruginosa*, the MICs and MBCs generally differed no more than fourfold (two tube dilutions) when determined in brain heart infusion broth, trypticase soy broth, nutrient broth, or cation-supplemented Mueller-Hinton broth (11).

In another study, the effects of various growth media on the activity of trovafloxacin against anaerobes was investigated (66). Supplemented brain heart infusion agar demonstrated the lowest MIC values, with correlation coefficients for most anaerobes of <0.65 when compared with Wilkens Chalgren agar. Wilkens Chalgren and supplemented Brucella agar gave comparative susceptibility results (correlation coefficients ≥ 0.90).

APPEARS THIS WAY
ON ORIGINAL

2. Effect of Inoculum

Increasing the initial cell inoculum from the MICs of trovafloxacin as determined in an agar dilution test (39).

had minimal effect on

3. Effect of pH

As with other fluoroquinolones, decreasing the pH of the test medium raised the MIC of most organisms (11,39). This effect was particularly noteworthy against *P. aeruginosa*, while little effect occurred with *S. aureus*.

APPEARS THIS WAY
ON ORIGINAL

Against anaerobes, the activity of trovafloxacin was twofold lower when agar media was adjusted to pH 6.0 in comparison to pH 7.0 or pH 7.5.

4. Effect of Divalent Cations

As with other fluoroquinolones, adding Mg^{+2} (9 mM) to Mueller-Hinton broth antagonized the *in vitro* activity of trovafoxacin, with MICs increasing fourfold over those obtained using unsupplemented medium (39).

5. Effect of Incubation Atmosphere

Incubation of the MIC test in aerobic or anaerobic conditions had little effect on the activity of trovafoxacin against two isolates each of *E. coli* and *S. aureus* (39).

6. Effect of Serum

The effect of serum protein binding on the antibacterial activity of trovafoxacin *in vitro* was studied by Child *et al.* (37). Protein binding values ranged between 70 and 88% (29,37), which is higher than values reported for most other fluoroquinolones (77). The addition of 20 or 70% human serum to susceptibility tests with Gram-positive and Gram-negative organisms indicated that MICs and MBCs increased by two to 32-fold (Table 8). The effect was most pronounced with two strains of *Klebsiella* sp.

Table 8. Effect of Human Serum (HS) on the *In Vitro* Activity of Trovafoxacin in Iso-Sensitest Broth (Iso) Against a Test Bacterial Inoculum of 10^5 CFU/mL

Organism	MIC Iso	MBC Iso	MIC Iso + 20% HS	MBC Iso + 20% HS	MIC Iso + 70% HS	MBC Iso + 70% HS
<i>E. coli</i>	0.03	0.03	0.06	0.06	0.06	0.125
<i>E. coli</i>	0.015	0.03	0.015	0.03	0.03	0.06
<i>Klebsiella spp.</i>	0.015	0.015	0.06	0.5	0.5	1.0
<i>Klebsiella spp.</i>	0.03	0.03	0.06	0.25	1.0	2.0
<i>S. aureus</i>	0.03	0.125	0.03	0.125	0.125	0.125
<i>S. aureus</i>	0.03	0.125	0.03	0.03	0.125	0.125
<i>M. catarrhalis</i>	0.008	0.008	0.015	0.015	0.03	0.03
<i>M. catarrhalis</i>	0.004	0.008	0.015	0.015	0.03	0.06

Data from (37)

D. Bactericidal Activity

The bactericidal activity of trovafoxacin has been assessed in two different types of assays. The first measures the minimum bactericidal concentration (MBC) in single time point susceptibility studies performed in broth. The MBC is defined as the lowest concentration of drug that kills 99.9% (>three $\log_{10}$) of the initial inoculum in 24 h. The second method, the Killing Curve studies, assessed bactericidal activity in broth over 24 h, sampling for viability at timed intervals.

One report describes the MBC values obtained for trovafoxacin for single isolates of *S. aureus*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *E. cloacae*, and *P. aeruginosa* (11). MBC values were within one dilution of the MIC determined in cation-supplemented Mueller-Hinton broth or brain heart infusion broth. Another study also found that MICs and MBCs were within one tube

dilution when five strains each of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and MRSA were studied (39).

Visalli *et al.* (71) studied the bactericidal activity of trovafoxacin against 10 isolates of *S. pneumoniae*: 4 penicillin-susceptible, 2 penicillin-intermediate, and 4 penicillin-resistant isolates. As observed with other organisms, the MBCs were within one dilution of the MIC for seven strains and within two dilutions for the remaining three strains.

The bactericidal activity of trovafoxacin was also evaluated against six species of anaerobes tested in Wilkens-Chalgren broth (72). The MIC/MBC values for trovafoxacin are shown in Table 9. MBC values were within one dilution of the MIC.

The kinetics of killing by trovafoxacin were examined by Gootz *et al.* (11). In these tests trovafoxacin and ciprofloxacin were found to be bactericidal within 24 h at the MIC against quinolone-susceptible *E. coli* (Fig. 1a), however, complete killing did not take place until after the first 6 hours of incubation. Sparfloxacin did not accomplish complete killing of this strain at the same MIC (Fig. 1a). Trovafoxacin and sparfloxacin were bactericidal within 24 h at the MIC against quinolone/methicillin-susceptible *S. aureus* (Fig. 1b), however, complete killing did not take place until after the first 6 hours of incubation. Ciprofloxacin exhibited a bacteriostatic effect and was not highly bactericidal even at four times the MIC (Fig. 1b). Trovafoxacin produced complete killing by 6 h at the MIC (2.0 µg/mL) against a ciprofloxacin- and methicillin-resistant *S. aureus* strain (Fig. 1c). Incomplete killing over 24 h was observed with this strain by ciprofloxacin and sparfloxacin at the MIC (32 µg/mL). In test with a quinolone-susceptible *P. aeruginosa* (Fig. 1d), ciprofloxacin was the most bactericidal agent when tested at the MIC (1 µg/mL). At 6 h, ciprofloxacin and trovafoxacin produced complete killing at 4X the MIC which was maintained after 24 h. Sparfloxacin at 4X the MIC was bactericidal at 24 h.

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Table 9. Bacteriostatic/Bactericidal Levels ($\mu\text{g}/\text{mL}$) at 48 h against anaerobes

Antibiotic	<i>Bacteroides fragilis</i>	<i>Bacteroides thetaiotaomicron</i>	<i>Prevotella melaninogenica</i>	<i>Fusobacterium mortiferum</i>	<i>Peptostreptococcus magnus</i>	<i>Clostridium perfringens</i>
Trovafoxacin	0.25/0.5	0.25/0.5	1.0/1.0	0.5/1.0	0.015/0.06	0.03/0.03
Ciprofloxacin	16.0/32.0	8.0/16.0	4.0/4.0	2.0/2.0	1.0/2.0	0.25/0.25
Sparfloxacin	2.0/8.0	0.5/1.0	2.0/4.0	0.5/1.0	1.0/1.0	0.06/0.06
Metronidazole	1.0/1.0	2.0/2.0	1.0/1.0	1.0/2.0	64.0/64.0	1.0/1.0
Cefoxitin	16.0/32.0	1.0/1.0	0.5/1.0	2.0/2.0	4.0/8.0	0.125/0.125
Piperacillin	64.0/64.0	16.0/32.0	8.0/8.0	1.0/1.0	0.25/0.5	0.125/0.125
Piperacillin/ tazobactam	2.8/8.0	2.0/4.0	0.125/0.25	1.0/1.0	0.25/0.5	0.06/0.125

From Spangler, Jacobs, and Appelbaum (72).

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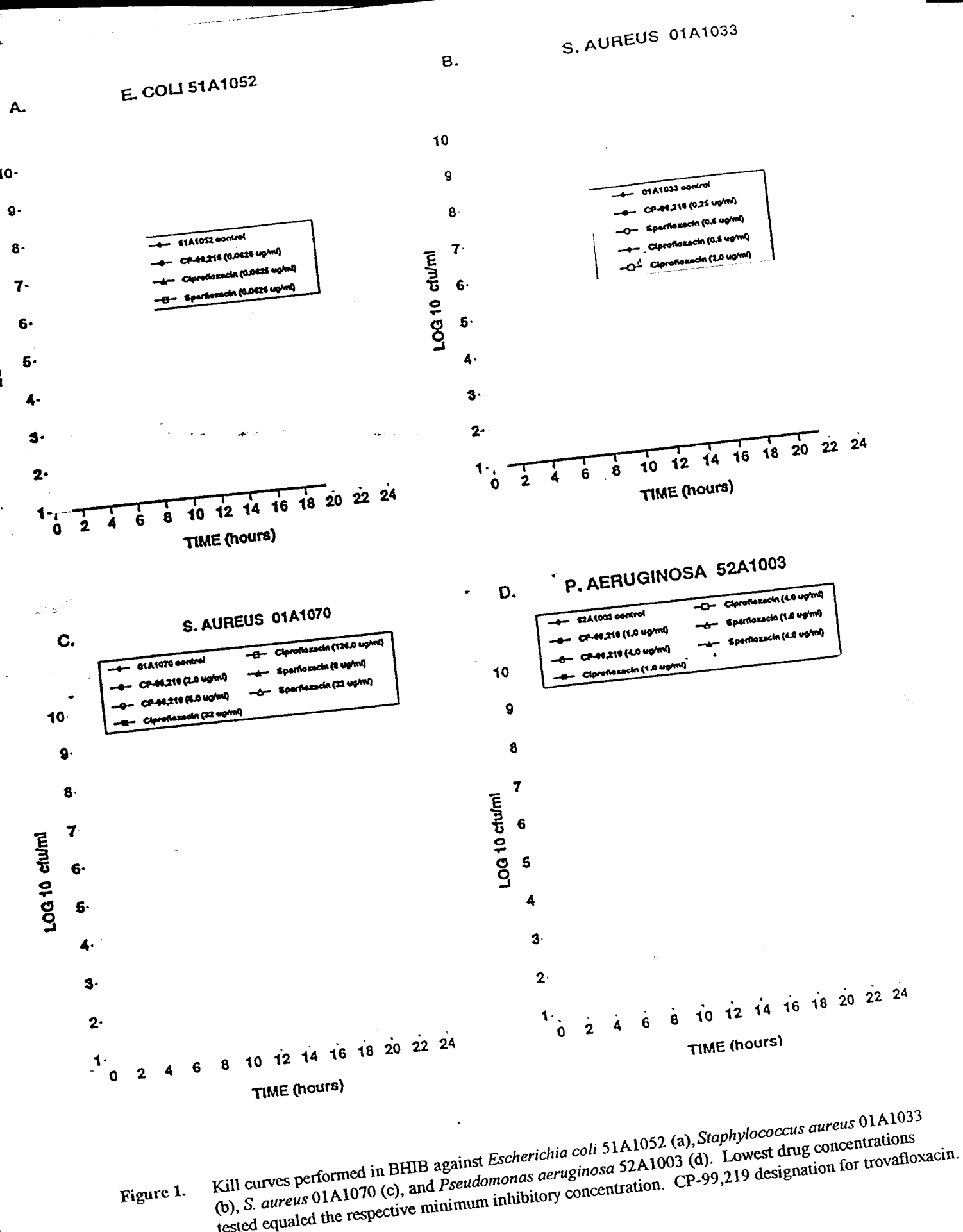


Figure 1. Kill curves performed in BHIB against *Escherichia coli* 51A1052 (a), *Staphylococcus aureus* 01A1033 (b), *S. aureus* 01A1070 (c), and *Pseudomonas aeruginosa* 52A1003 (d). Lowest drug concentrations tested equaled the respective minimum inhibitory concentration. CP-99,219 designation for trovafloxacin.

In time kill curve studies by Visalli *et al.* (71) against penicillin-resistant pneumococci, trovafoxacin was bacteriostatic after 24 h at MIC (0.03 µg/mL) and 2X MIC. At 4X the MIC it was bactericidal after 24 h and at 8X the MIC it was bactericidal at 6 h.

In studies designed to determine the optimum bactericidal concentration (OBC) of trovafoxacin, it was found that trovafoxacin, like ciprofoxacin, was more efficient in killing *E. coli* KL16 than *S. aureus* E3T (18) while sparfoxacin killed both organisms equally well. Against *E. coli* KL16 the OBC of ciprofoxacin < sparfoxacin, ofloxacin < trovafoxacin. Against *S. aureus* E3T the OBC of sparfoxacin < trovafoxacin < ciprofoxacin and ofloxacin. In tests with *S. pneumoniae* C3LN4, the OBC for trovafoxacin < ciprofoxacin < ofloxacin. When *Enterococcus faecalis* was treated with trovafoxacin, weak bactericidal activity occurred after the first 3 h, however, when incubation extended to 6 and 24 h, greater bactericidal activity was apparent. This slow bactericidal activity against *E. faecalis* is a characteristic shared by the majority of quinolone(18). This study demonstrated that after 3 h incubation at OBC, trovafoxacin was bactericidal (at least a 3 log kill) only for *E. coli* KL16 and *S. aureus* E3T. The killing of *S. pneumoniae* C3LN4 under the same conditions was incomplete. Trovafoxacin was not able to kill *E. faecalis* even after 24 h incubation (18). The studies by this author demonstrated that against *E. coli* trovafoxacin works with in 3 h post incubation by inhibiting DNA gyrase and against *S. aureus* it works by both inhibiting DNA gyrase and topoisomerase IV. Against *E. faecalis* trovafoxacin works by inhibiting DNA gyrase only after 24.h incubation. With *S. pneumoniae* complete inhibition of DNA gyrase did not take place within the 3 h post incubation.

Another study evaluated the bactericidal activity of trovafoxacin against six *E. faecalis* and five *E. faecium* isolates using a time kill method with a fixed drug concentration of 3 µg/mL (52). Trovafoxacin demonstrated bactericidal activity (at least a 3 log kill) at 24 h against all isolates, including *E. faecalis* resistant to aminoglycosides and/or producing beta-lactamase and one *E. faecalis* vancomycin-resistant isolate, except when the MICs of ciprofoxacin were ≥ 4 µg/mL and those of trovafoxacin were ≥ 2 µg/mL. Comparable degrees of cidity were obtained over 24 h whether the initial inoculum was 10^5 or 10^7 CFU/mL (52).

In another study, Zinner *et al.* (73) investigated the activity of 3 µg/mL trovafoxacin in time kill assays against five strains of *E. faecium* and two strains of *E. faecalis* with variable susceptibility to ampicillin, vancomycin and gentamicin as follows: *E. faecium*, Amp R, Van S; *E. faecium*, Amp R, VanB R; *E. faecium*, Amp R, VanA R; *E. faecium*, Amp R, Gent R; *E. faecium*, Strep R, Van R; *E. faecalis*, VanB R; and *E. faecalis*, Gent R. A ≥ 3 log decrease in the viability of enterococci was observed after 24 h incubation only for the following two strains: *E. faecium*, Amp R, Van S and *E. faecium*, Amp R, VanB R.

The overall conclusion of these bactericidal studies is that trovafoxacin's MBCs are generally 1-2 tube dilutions greater than the MICs when the MICs are less than 2 µg/mL. Trovafoxacin has a reduced bactericidal activity against *P. aeruginosa*, Enterococci, and penicillin-resistant *S. pneumoniae* as compared to its good bactericidal activity against *S. aureus* and *E. coli*. From studies by Ian Morrissey (18) one may conclude that the enhanced activity of trovafoxacin against *S. aureus* is a result of DNA gyrase, and topoisomerase IV both being targets for trovafoxacin.

E. Intracellular Accumulation and Bacterial Cell Killing

Fluoroquinolones are known to accumulate in phagocytic cells at levels significantly higher than extracellular blood levels. The intracellular accumulation and antibacterial activity of trovafoxacin has been studied in several systems.

One study measured the accumulation of trovafoxacin into guinea pig alveolar macrophages (56) after 1 h incubation. Intracellular levels of trovafoxacin were 23-fold above original extracellular test concentrations. One hour after addition of radiolabelled drug, intracellular trovafoxacin levels were $1.2 (\pm 0.02)$ mg per 10^7 cells, which was similar to the intracellular level of erythromycin obtained in these experiments. Accumulation was reversible, since about 50% of the drug egressed from the cells after one hour incubation in antibiotic-free medium (56).

In the same report, trovafoxacin was significantly more inhibitory than ofloxacin or erythromycin against two strains of *L. pneumoaphila* grown inside the alveolar macrophages. Erythromycin ($1.0 \mu\text{g/mL}$) and ofloxacin ($0.25 \mu\text{g/mL}$) were only partially inhibitory, with rapid regrowth of the organisms occurring after drug washout. Ofloxacin ($1.0 \mu\text{g/mL}$) and trovafoxacin ($0.25 \mu\text{g/mL}$), in contrast, were bactericidal, with no measurable regrowth detected up to 4 days after drug washout. Trovafoxacin at $0.1 \mu\text{g/mL}$ was bactericidal but the organisms grew rapidly after removal of the drug (56).

Another study evaluated the penetration of trovafoxacin into human neutrophils (PMN), peritoneal macrophages (PM), and tissue cultured epithelial cells (McCoy) (78). The accumulation of trovafoxacin into human PMNs was rapid, reversible, nonsaturable (at extracellular concentration ranging from 0.5 to $25 \mu\text{g/mL}$), not energy dependent, and significantly increased at pH 6. At extracellular concentrations of $2 \mu\text{g/mL}$, the cellular to extracellular ratios (C/E ratios) of trovafoxacin in PMN, PM, and McCoy cells were 10.2 ± 2.0 , 10.2 ± 2.0 and 9.6 ± 1.9 respectively (20 min; 37°C). Trovafoxacin uptake by PMNs was significantly higher at pH 6 ($C/E = 16.5 \pm 0.4$, $p < 0.05$) than at pH 7.2 (11.3 ± 0.8). The phagocytosis of opsonized *S. aureus* did not affect the intracellular accumulation of trovafoxacin in PMNs (C/E ratios of 9.0 ± 1.7 and 8.2 ± 1.6 , respectively). The phagocytosis of opsonized zymosan, however, significantly increased the accumulation of trovafoxacin by PMNs (C/E ratio of 13.9 ± 1.7 $p < 0.05$).

The available data indicate that like other fluoroquinolones, trovafoxacin reaches intracellular concentrates within phagocytic and non-phagocytic cells 10- to 23-fold above extracellular concentrations, while remaining active intracellularly.

F. Postantibiotic Effect

Postantibiotic effect (PAE) refers to the recovery period or persistent suppression of bacterial growth after short antimicrobial exposure. It is generally accepted that a prolonged PAE will extend the chemotherapeutic action of an antimicrobial drug beyond the time that the agent is available in inhibitory concentrations at the site of infection in the host. The PAE reflects the amount of time required for a cell culture to increase by one log of growth after removal of antimicrobial, with the value corrected for any delay seen in a drug-free control culture of the same organism. Previous studies with fluoroquinolones indicate that the PAE is both strain and

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drug specific. Also, higher levels of fluoroquinolone above the MIC produce a more prolonged PAE (75). The length of time of the initial exposure of drug before its removal can also affect the length of the PAE. For staphylococci and *P. aeruginosa*, exposure to ciprofloracin at for 2-3 h resulted in a PAE of approximately 2 h (75). Under similar conditions, PAE against *E. coli* was 4 h, but against *E. faecalis*, no measurable postantibiotic effect was found (75).

One study determined the PAE of trovafloracin against one strain each of *E. coli*, *S. aureus*, and *P. aeruginosa*. After a one hour exposure to drug, the PAE's were between 0.3 and 2.5 h (74). Ciprofloracin tested under the same conditions produced PAEs of 0 to 1.0 h.

In a study by Dubois J. et al. (76) trovafloracin, sparfloracin, ciprofloracin, erythromycin and rifampicin were evaluated against *Legionella* spp. The PAE of trovafloracin (3.85 h) and ciprofloracin (2.86 h) was greater than PAE of rifampicin (0.90 h) and sparfloracin (0.68 h) against erythromycin-resistant *L. pneumophila* strains. Against erythromycin-susceptible *L. pneumophila* strains the PAE of , ciprofloracin (3.61 h) and rifampicin (2.86 h) were grater than the PAE of trovafloracin (1.63 h). The PAE of trovafloracin (2.73 h) was greater than PAE of ciprofloracin (2.13 h) and sparfloracin (0.72 h) against erythromycin-resistant *Legionella* other than pneumophila strains.

From the small number of PAE studies that were performed with trovafloracin, it appears that the observed time for the effect is highly variable and similar to that expected for other fluoroquinolones.

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G. Synergy Studies

Limited *in vitro* synergy studies have been performed with trovafloracin. Ciprofloracin in combination with an aminoglycoside or a beta-lactam is generally indifferent or additive and synergy is generally not demonstrated (Eliopoulos, *Am. J. Med.* 87: Suppl. 5A, 17S-22S, 1989). In one study, trovafloracin and ciprofloracin were tested by a checkerboard MIC method for synergy with gentamicin or ampicillin/sulbactam (2:1) against *P. aeruginosa*, *E. aerogenes*, *S. marcescens*, and *Stenotrophomonas maltophilia* (53). The effect of trovafloracin or ciprofloracin in combination with either gentamicin, ampicillin/sulbactam (2:1), or vancomycin was tested with non multi-drug resistant *E. faecium* and *E. faecalis*, as well as a multi-drug (vancomycin and ampicillin-resistant with or without high-level gentamicin resistant) *E. faecium* and multi-drug resistant (ampicillin and high-level gentamicin-resistant) *E. faecalis*. Synergy was defined as a four-fold reduction in the MIC of the antibiotic combination compared to the MIC with each antibiotic alone. The results from these studies are shown in Table 10. From a total of 168 strains studied, synergy was seen for trovafloracin in only 4 strains of enterococci (2 with gentamicin, 2 with ampicillin-sulbactam). An additive effect was shown for over 50% of the multi-drug resistant *E. faecium* isolates tested with the combination of trovafloracin and ampicillin/sulbactam and for over 50% of the *E. faecalis* isolates tested with the combination of trovafloracin and vancomycin (53).

In another study involving checkerboard titration techniques, trovafloracin was tested alone and in combination with ceftazidime, imipenem, or amikacin against 120 nonfermenters (58). These

included 47 *P. aeruginosa*, 4 *P. fluorescens/putida*, 14 *S. maltophilia*, 15 *Burkholderia cepacia*, 15 *Acinetobacter*, 16 *Alcaligenes*, and 9 *Flavobacteria/Chryseobacteria*. MIC₉₀s of trovafoxacin, ceftazidime, amikacin, and imipenem were: *P. aeruginosa* (4, 128, 32, 128 µg/mL), *P. fluorescens/putida* (8, 32, 8, 8 µg/mL), *S. maltophilia* (4, 128, 32, 128 µg/mL), *B. cepacia* (64, 128, 32, 8 µg/mL), *Acinetobacter* (8, 128, 32, 1 µg/mL), *Alcaligenes* (32, 128, 32, 8 µg/mL), and *Flavobacteria/Chryseobacteria* (4, 128, 32, 128 µg/mL). The percent of strains showing synergy (fractional inhibitory concentration or FIC ≤0.5) in these studies was highly variable and strain-dependent. In most instances, less than 33% of the strains from any species showed synergy with any of the three drug combinations. The most frequent synergy was seen in the case of *P. aeruginosa*: trovafoxacin plus ceftazidime 28%, trovafoxacin plus imipenem 26%, and trovafoxacin plus amikacin 11%. Antagonism (FIC >1) was observed with trovafoxacin and imipenem with 60% of *B. cepacia* and 63% of *Alcaligenes*. The combination of trovafoxacin plus amikacin was antagonistic for 21% of *P. aeruginosa* and 73% of *B. cepacia*. If the antagonism was defined as FIC > 4.0, then no antagonism was observed.

Table 10. *In vitro* Studies of Antibiotic Combinations

Antibiotic Combination (No. of Isolates)	Synergy	Addition	Indifference
Multi-drug resistant <i>Enterococcus faecium</i> (20)			
Trovafoxacin + ampicillin / sulbactam	0	12	8
Trovafoxacin + gentamicin	2	3	15
Trovafoxacin + vancomycin	0	5	15
Ciprofloxacin + ampicillin / sulbactam	0	2	18
Ciprofloxacin + gentamicin	0	0	20
Ciprofloxacin + vancomycin	0	5	15
Non multi-drug resistant <i>Enterococcus faecium</i> (24)			
Trovafoxacin + ampicillin / sulbactam	0	8	16
Trovafoxacin + gentamicin	0	3	21
Trovafoxacin + vancomycin	0	5	19
Ciprofloxacin + ampicillin / sulbactam	0	7	17
Ciprofloxacin + gentamicin	0	1	23
Ciprofloxacin + vancomycin	0	4	20
Non multi-drug resistant <i>Enterococcus faecalis</i> (24)			
Trovafoxacin + ampicillin / sulbactam	2	10	12
Trovafoxacin + gentamicin	0	6	18
Trovafoxacin + vancomycin	0	18	6
Ciprofloxacin + ampicillin / sulbactam	0	0	24
Ciprofloxacin + gentamicin	0	0	24
Ciprofloxacin + vancomycin	0	4	20
<i>Pseudomonas aeruginosa</i> (25)			

Antibiotic Combination (No. of Isolates)	Synergy	Addition	Indifference
Trovafloracin + ampicillin / sulbactam	0	2	23
Trovafloracin + gentamicin	0	3	22
Ciprofloracin + ampicillin / sulbactam	0	0	25
Ciprofloracin + gentamicin	0	3	22
<i>Enterobacter aerogenes</i> (25)			
Trovafloracin + ampicillin / sulbactam	0	0	25
Trovafloracin + gentamicin	0	3	22
Ciprofloracin + ampicillin / sulbactam	0	0	25
Ciprofloracin + gentamicin	0	0	25
<i>Serratia marcescens</i> (25)			
Trovafloracin + ampicillin / sulbactam	0	2	23
Trovafloracin + gentamicin	0	2	23
Ciprofloracin + ampicillin / sulbactam	0	1	24
Ciprofloracin + gentamicin	0	2	23
<i>Stenotrophomonas maltophilia</i> (25)			
Trovafloracin + ampicillin / sulbactam	0	3	22
Trovafloracin + gentamicin	0	4	21
Ciprofloracin + ampicillin / sulbactam	0	0	25
Ciprofloracin + gentamicin	1	6	18

From Dembry and Andriole (53).

In order to rule out possible antagonistic interaction of trovafloracin with a beta-lactam against organisms that can cause meningitis, kill curves were performed with trovafloracin alone and in combination with ceftriaxone (74). Strains of *S. pneumoniae* (including a penicillin-resistant strain), *Haemophilus influenzae* (beta-lactamase positive and negative), and *Neisseria meningitidis* were tested in a timed kill curve assay where the degree of killing obtained at 24 h with each drug combination was compared to the amount of killing achieved at the same level of each drug alone. No cases of synergy or antagonism were found in any of these tests (74).

Quite different results were found in a study in which the *in vitro* combination of trovafloracin and sulbactam/ampicillin was examined (105). Of the 110 gram negatives examined, synergy or partial synergy was demonstrable for 91 (83%). Included were 10 isolates of *P. aeruginosa*, 10 strains of *Acinetobacter baumannii*, and 10 isolates of *Stenotrophomonas maltophilia*. An additive interaction was observed with an additional 12 (11%) isolates. Antagonism was noted with 2 (1.8%) of the gram negatives tested. Synergy or partial synergy was likewise demonstrable for 9/10 (90%) enterococci and 12/30 (40%) *S. pneumoniae* tested (including penicillin-resistant strains). A lack of interaction (indifference) was noted with 13/30 (43%) of the pneumococci.

In another study (106) the combination of trovafloracin and ceftazidime was tested against 459 Gram-negative non-fermentative organisms using an agar dilution MIC method. While synergy

with these antimicrobials was infrequently observed with this collection of non-fermenters, synergy was detected in 32/36 strains of *S. maltophilia* tested.

The overall results obtained with combinations of trovafoxacin with beta-lactams and aminoglycosides indicate that synergy is strain specific and not commonly encountered. This agrees with results obtained previously with other fluoroquinolones (Eliopoulos, *Am. J. Med.* 87:Suppl. 5A, 17S-22S, 1989).

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H. Assessment of Mechanisms of Resistance

Previous studies with fluoroquinolones indicate that selection of resistant mutants *in vitro* occurs at a relatively low frequency of 1×10^{-8} - 1×10^{-9} mutants per cell plated (91). Resistance to fluoroquinolones is not plasmid-encoded, nor inducible; single mutations in chromosomal genes have been shown to be responsible for step-wise selection of resistance (91). Such step-wise increases in resistance usually involve cumulative mutations at multiple genes in a given strain.

One of the first studies to assess the development of resistance to trovafoxacin *in vitro* involved a daily passage of strains in media containing increasing concentrations of drug (39). As observed previously with other fluoroquinolones, after 5 daily subcultures in the presence of trovafoxacin, MICs increased by 4 to 500-fold above those obtained before passage. The large increases in resistance did not occur with all of the *S. aureus*, *E. coli*, and *P. aeruginosa* strains tested. Such observations indicate that certain bacterial isolates possess the potential to become resistant to trovafoxacin under the appropriate selection conditions. The same study determined the frequency of mutation to trovafoxacin resistance in strains of *S. aureus*, *S. epidermidis*, *E. coli*, *Enterobacter* spp., and *P. aeruginosa*. The method used involved a direct plating technique and selection concentrations of 4X MIC. Resistance frequencies generally ranged from 10^{-7} or 10^{-8} to 10^{-10} . Such frequencies are typical for currently available fluoroquinolones.

One report compared the *in vitro* frequency of mutation observed with isolates of staphylococci using ciprofoxacin and trovafoxacin as the selecting agents (92). Rather than testing for selection at a standard multiple of the MIC, these investigators tested both drugs at the clinically relevant concentrations. At 1 $\mu\text{g/mL}$, the frequency of resistance selection with trovafoxacin for two MSSA and two MSSE strains were consistently $< 8 \times 10^{-10}$. This level of trovafoxacin was 16-fold above the MIC of each susceptible parent organism. In contrast, at 1 μg of ciprofoxacin per mL, selection frequencies ranged from 10^{-7} to 10^{-9} . Studies with two MRSA and two MRSE gave similar results.

These studies may suggest that at drug concentrations at the breakpoint for ciprofoxacin (1 $\mu\text{g/mL}$), resistance mutations are selected less frequently (less than 1 mutant from 10^{10} cells plated) with trovafoxacin than with ciprofoxacin. However the data is very limited and one must confirm this observation.

A detailed analysis of *in vitro* selection to fluoroquinolone resistance in *S. pneumoniae* was described in one report (13). In this study the mutation frequency to resistance was studied using ciprofoxacin or trovafoxacin at the clinically relevant selecting concentrations.

At the breakpoint for ciprofoxacin (1 $\mu\text{g/mL}$) mutation frequency for four pneumococcal strains ranged from 10^{-7} to 10^{-9} . At this level of trovafoxacin, mutation frequencies to

resistance were $\leq 8.9 \times 10^{-9}$. Trovafloracin MICs to these five strains of pneumococci were generally 16-fold lower than those for ciprofloracin, accounting for the lower frequency of mutation to resistance with trovafloracin.

This study also elucidated the mechanism of resistance to fluoroquinolones in mutants obtained in a step-wise selection with ciprofloracin. The exact changes occurring in the quinolone resistance determining region (QRDR) of the DNA gyrase and topoisomerase IV A subunits were determined by PCR analysis. First-step mutants selected by plating parent cells on medium containing 4X MIC ciprofloracin occurred at a frequency of 1×10^{-9} and possessed changes in the A subunit of topoisomerase IV (GrlA) only, involving substitution of Phe or Tyr at Ser80 (13). It is noteworthy that while these mutants had MICs to ciprofloracin of _____, they were still inhibited by 0.5 $\mu\text{g}/\text{mL}$ of trovafloracin (Table 11).

Table 11. Activity of Trovafloracin Against Topoisomerase IV Mutants of *Streptococcus pneumoniae*

Strain	MIC ($\mu\text{g}/\text{mL}$)			PCR Results for <i>grlA</i> and <i>gyrA</i> ^a	
	Trovafloracin	Ciprofloracin	Tetracycline	Topoisomerase IV	Gyrase
<i>S. pneumoniae</i> 1016 parent	0.125	1.0	0.125	- ^b	-
<i>S. pneumoniae</i> 1056 parent	0.125	1.0	0.25	-	-
<i>S. pneumoniae</i> 1016-30	0.5	4.0	0.125	Ser ⁸⁰ to Phe	-
<i>S. pneumoniae</i> 1016-36	0.5	4.0	0.125	Ser ⁸⁰ to Tyr	-
<i>S. pneumoniae</i> 1056-79	0.5	4.0	0.25	Ser ⁸⁰ to Phe	-
<i>S. pneumoniae</i> 1056-100	0.5	8.0	0.25	Ser ⁸⁰ to Phe	-

^a Both topoisomerase IV *grlA* and DNA gyrase *gyrA* genes were amplified and sequenced using specific primers to the quinolone resistance determining region (QRDR) of each gene (Gootzt *et al.*, 1996).

^b (-) denotes wild-type gene sequence found.

Second-step mutants were derived from *S. pneumoniae* mutants altered in *grlA* by plating concentrated cell suspensions on agar medium containing 4X MIC of ciprofloracin (32 $\mu\text{g}/\text{mL}$). Second-step mutants were similarly obtained at the low frequency of 1×10^{-9} (13).

PCR analysis of the QRDR of *grlA* and *gyrA* of these mutants revealed that they had a second change in the DNA gyrase A subunit corresponding to a substitution in Ser84 to Tyr or Phe, or in Glu88 to Lys (13). The second-step mutants had MICs to ciprofloracin of _____ and had trovafloracin MICs _____. While such double mutants could be selected in two distinct steps in the laboratory, such *S. pneumoniae* strains have been rarely isolated from clinical samples (94).

These observations in *S. pneumoniae* appear to parallel resistance selection in other Gram-positives. The first step to fluoroquinolone resistance in *S. aureus* also occurs in topoisomerase IV (9). Second-step mutants with high-level resistance to ciprofloracin contain an additional mutation in *gyrA* of DNA gyrase. While such double mutants have been documented in *S. aureus* (9), they have not been shown to date to occur in other Gram-positive organisms.

The activity of trovafoxacin against a collection of genetically defined strains of *S. aureus* and *E. coli* is summarized in Table 12 (95). The activity observed against *S. aureus* mutants parallels that observed in the mutants of *S. pneumoniae* just described above. In *S. aureus* mutants with changes in topoisomerase IV (MT111-MT5224C4) MICs to trovafoxacin were increased 8-fold over those of the parent, but remained at 0.25 µg/mL. A mutant with a change in both DNA gyrase and topoisomerase IV (EN1252a) had a trovafoxacin MIC of 4.0 µg/mL, representing a 128-fold increase over the parent (95). Interestingly, no effect was observed in a mutant (MT23142) overexpressing the NorA efflux protein, suggesting that trovafoxacin is not a substrate for this efflux transporter. This was also the case in *S. aureus* MT1222 which contained resistance mutations in *gyrA* and *gla* in addition to having an up-regulated NorA. Such up-regulation of drug efflux in *S. aureus* is known to markedly affect susceptibility to ciprofloxacin (95).

The impact of resistance mutations is more complex in Gram-negative organisms. Here, single mutations in the DNA gyrase A subunit increase the MIC to trovafoxacin 32-fold over that for the wild type. Combinations of *gyrA* mutations and those in the outer membrane, such as in *E. coli* EN226, lead to higher levels of resistance (Table 12). Such Gram-negative strains with multiple mechanisms of fluoroquinolone resistance have been isolated from clinical material (95).

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Table 12. Activity of Trovafoxacin Against Genetically Defined Strains of *Staphylococcus aureus* and *Escherichia coli*^a

Strain	Genotype	MIC (µg/mL)	Fold Change
<i>Staphylococcus aureus</i>			
ISP794	wild type	0.0312	1
ISP86	nov		
MT5224c4	<i>grlA</i> (Ser80Phe)	0.25	8
MT5222	<i>grlA</i> (Ser80Phe)	0.25	8
MT111	<i>grlA</i> (Ala116Glu)	0.25	8
EN1252a	<i>grlA</i> (Ser80Phe) <i>gyrA</i> (Ser84Leu)		
MT23142	<i>flqB</i> (↑ NorA) ^b	0.0312	1
MT1222	<i>grlA</i> (Ala116Glu) <i>gyrA</i> (Ser84Leu) <i>flqB</i>	2.0	64
<i>Escherichia coli</i>			
KL16	wild type	0.032	1
KF130	<i>gyrA</i>	1.0	32
EN226-3	<i>gyrA</i>	1.0	32
EN226-8	<i>marR</i>	0.512	16
EN226	<i>gyrA</i> <i>marR</i> others	>2	>64

^a Data from reference (95).

^b Mutant with increased expression of NorA efflux protein.

Observations with groups of clinical isolates that are resistant to ciprofloxacin indicate that a substantial degree of cross resistance to trovafoxacin occurs. In one study (96) of such resistant *E. coli* isolates with an MIC₉₀ to ciprofloxacin of 64 µg/mL, the MIC₉₀ to trovafoxacin was 128 µg/mL. Similarly, no potency advantage with trovafoxacin was observed against ciprofloxacin-resistant strains of *Klebsiella* spp., *E. cloacae*, *P. aeruginosa*, *Acinetobacter* spp., and *B. cepacia*.

The available data indicate that trovafoxacin possesses greater potency than ciprofloxacin against many gram-positive organisms. Single mutations in genes which confer resistance to ciprofloxacin (*grlA*) also decrease susceptibility to trovafoxacin but usually to a lesser degree. In terms of gram-negative clinical isolates, trovafoxacin appears to have no consistent advantage over strains which demonstrate high-level resistance to ciprofloxacin.

III. PRECLINICAL EFFICACY (IN VIVO)

A. Pharmacokinetics and Bioavailability

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1. Oral Administration: Bioavailability

The sponsor states that trovafoxacin is readily absorbed in humans after oral administration with peak blood levels of 1.1, 2.2, and 3.1 µg/mL observed following single doses of 100, 200, and 300 mg, respectively. Absorption is rapid, with a time to peak of approximately 1.1 h. Bioavailability has been measured to be 88%. Peak blood levels are dose-proportional through 1,000 mg, the top dose studied. The terminal elimination half-life of trovafoxacin is approximately 11 h.

In multiple dosing experiments at 100 and 300 mg once daily, consecutive dosing resulted in mean AUC₀₋₂₄ values from 9.4 µg-h/mL on day 1 to 11.8 µg-h/mL on day 17 for the 100 mg dose and from 26.2 µg-h/mL on day 1 to 34.6 µg-h/mL on day 17 for the 300 mg dose (Table 13). This resulted in an accumulation factor of 1.25 for the 100 mg dose and of 1.32 for the 300 mg dose. Inspection of the predose trovafoxacin concentrations on days 6, 10, 14, and 17 indicated that at both dose levels steady state had been obtained by the third daily dose. Mean renal clearance values observed in this study ranged , suggesting that repetitive daily dosing did not affect renal clearance (21).

Table 13. Pharmacokinetic Parameters (mean ± SD) for Trovafoxacin Following Oral Administration at Single and Multiple Doses of 100 and 300 mg to Healthy Male Volunteers (data from ref. 21)

Pharmacokinetic parameters	Trovafoxacin dose (mg)				Mean ^a
	100		300		
	Day 1 (n = 8)	Day 17 (n = 8)	Day 1 (n = 8)	Day 17 (n = 6)	
C _{max} (µg/mL)	1.0 ± 0.3	1.1 ± 0.2	2.9 ± 0.4	3.3 ± 0.5	
T _{max} (h)	0.9 ± 0.4	1.0 ± 0.5	1.2 ± 0.6	1.3 ± 0.7	1.1 ± 0.6
AUC ₀₋₂₄ (µg-h/mL)	9.4 ± 1.5	11.8 ± 1.8	26.2 ± 4.5	34.6 ± 6.5	
AUC _{0-∞} (µg-h mL)	11.2 ± 2.2		33.3 ± 5.5		
CL _r (L/h)	0.44 ± 0.08	0.47 ± 0.11	0.44 ± 0.08	0.35 ± 0.05	0.43 ± 0.09
f _e (%)	5.3 ± 0.6	5.5 ± 1.2	5.1 ± 1.6	2.9 ± 0.7 ^b	5.3 ± 1.1 ^c
f _u (%)	20.3 ± 7.4	22 ± 4.3	25.6 ± 3.7	28.3 ± 6.0	23.8 ± 6.1
T _{1/2} (h)	9.2 ± 1.2	10.5 ± 0.7	10.5 ± 1.4	12.2 ± 1.9	10.5 ± 1.9

^a Includes all subjects in all dose groups.

^b 12-24 h urine samples were lost.

^c Excluded the day 17 data.

2. Intravenous Administration

The pharmacokinetics following a single dose of the prodrug alatrofoxacin are shown in Table 14. The infusate concentration was 5 µg/mL for the 30-mg dose and the first three subjects in the 100-mg dose group, and it was 1 µg/mL for all subsequent dose groups. Alatrofoxacin prodrug was not detected in plasma at any time point following the end of the infusion. Urine concentrations of alatrofoxacin were not detected at the 300-mg dose level. Consequently, urine samples from the lower-dose were not analyzed for alatrofoxacin content.

Table 14. Mean Pharmacokinetic Values of Trovafoxacin Following Single Dose Alatrofoxacin Infusion in Man During Phase I Studies

Dose ^a	Day	n	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-∞} (µg·h/mL)	CL (mL/min)	V _{dss} (L)	T _{1/2} (h)	CL _r (mL/min)
30	1	4	0.4	0.9	--	--	--	--	15.1
100	1	4	1.8	1.0	16.4	104.9	89.1	10.4	12.0
200	1	3	2.3	1.0	31.2	107.7	110.2	12.3	9.8
300	1	4	4.3	1.0	43.4	116.0	99.2	10.8	13.1

^a Infused over 1 h, data from Trovafoxacin Investigator's Brochure

Multiple doses of alatrofoxacin showed an accumulation factor of 1.3 between days 1 and 10 for the 300 mg dose group (22). Following once-daily doses of 300 mg infused over one hour, mean peak blood levels of 3.6 and 4.4 µg/mL were obtained on days 1 and 10, respectively. On day 10, a mean of 0.8 µg/mL of trovafoxacin was present in serum 24 h after the infusion (22). It seems that the prodrug is immediately converted to trovafoxacin and the pharmacokinetics of both formulations are similar.

Table 15 summarizes the pharmacokinetic parameters for the proposed oral doses of 100 and 200-mg QD and IV 200 and 300 QD. It is not clear to this reviewer as to why some of the parameters presented in Table 16 differ from the parameters presented in table 15 above for similar doses.

Table 15. Trovafoxacin Pharmacokinetic Parameters.

	C _{max} (µg/mL)	T _{max} (h)	AUC ^a (µg·h/mL)	T _{1/2} (h)
Trovafoxacin 100 mg				
Single dose	1.0 ± 0.3	0.9 ± 0.4	9.4 ± 1.5	9.2
Multiple dose	1.1 ± 0.2	1.0 ± 0.5	11.8 ± 1.8	10.5
Trovafoxacin 200 mg				
Single dose	2.1 ± 0.5	1.8 ± 0.9	26.7 ± 7.5	9.6
Multiple dose	3.1 ± 1.0	1.2 ± 0.5	34.4 ± 5.7	12.2
Alatrofoxacin 200 mg^b				

Single dose	2.7 ± 0.4	1.0 ± 0	28.1 ± 5.1	9.4
Multiple dose	3.1 ± 0.6	1.0 ± 0	32.2 ± 7.3	11.7
<u>Alatrofoxacin 300 mg^b</u>				
Single dose	3.6 ± 0.6	1.3 ± 0.4	46.1 ± 5.2	11.2
Multiple dose	4.4 ± 0.6	1.2 ± 0.2	46.3 ± 3.9	12.7

^a Single dose: AUC₀₋₂₄, Multiple dose: AUC_{0-∞}

^b trovafoxacin equivalents

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These data indicates that for comparable doses, no dose adjustment is necessary when switching from parenteral to oral administration.

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3. Tissue Distribution

The sponsor states that the volume of distribution of trovafoxacin in humans following intravenous administration of 100, 200, or 300 mg alatrofoxacin ranged from 89.1 to 110.2 L. This suggests that trovafoxacin distributes extensively into body tissues and results in significantly higher trovafoxacin concentrations in most target tissues than in plasma or serum. Table 16 summarizes trovafoxacin levels in various tissues post administration.

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Table 16. Trovafoxacin distribution into tissues.

Fluid or Tissue	Tissue-Fluid/Serum Ratio	µg/mL or µg/g	Time/Interval Post Dose, (hr)
bronchial macrophages	24.1	34.3	6
lung mucosa	1.1	1.7	6
lung epithelial lining fluid			
single dose	2.3		6
multiple dose	5.8	10.2	6
lung	2.1	2.0	2-25
brain	0.3		2-8
cerebrospinal fluid (CSF, adults)	0.25	0.91	5-24
bowel	0.5		2-8
heart	1.8		2-8
colonic tissue	0.7	2.8	1-15
kidney	2.0		2-8
liver	5.2		2-8
bile	14.9	18-38	0-24
skin	1.0	1-2	2-27
subcutaneous tissue	0.4	1-2	2-25
skin blister fluid	0.7-0.9 (blister/plasma)	1.14	4-24
peritoneal fluid	0.4		0-15
skeletal muscle	1.5	1-2	2-27
bone	1.0	1-2	2-27
prostatic tissue	1.0	>1.0	3-10
cervix (single dose)	0.5	1.4	3-29
(multiple dose)	0.6		3-16
ovary	1.6	3.8	3-11
fallopian tube	0.7	1.72	3-29
myometrium (single dose)	0.5	1.0	5-13
(multiple dose)	0.6		7-16
uterus	0.6	1.3	3-29
vaginal fluid(single dose)	1.8		2-23
(multiple dose)	4.7	2-3	2-24

The penetration of trovafoxacin into the inflammatory fluid of cantharides-induced blister was assessed in eight humans given a single 200 mg oral dose(26). The mean peak concentration in plasma of 2.9 µg/mL was obtained at a mean time of 0.75 h post dose. The mean peak concentration in inflammatory fluid of 1.2 µg/mL (± 0.19) was obtained at 4.0 h. At 12 h the mean inflammatory fluid concentrations were 0.5 and 0.2 µg/mL, respectively. The overall penetration into inflammatory fluid was 64%.

The penetration of trovafoxacin into human bronchial tissues has also been studied. Following a single 200 mg dose the mean concentrations of trovafoxacin 1-6 h post dose were 2.2 µg/mL in

plasma and 6.1 $\mu\text{g/mL}$ in cells obtained by bronchiolar lavage(27). At 18-24 h after dosing, mean trovafoxacin concentrations were 1.1 $\mu\text{g/mL}$ and 5.2 mg/g in serum and cells, respectively.

In another study, nine patients given once daily 200 mg doses of trovafoxacin for four days were evaluated for drug levels in lung tissue. Six hours after the last dose, trovafoxacin levels in serum, alveolar macrophages, epithelial lining fluid, and bronchiolar mucosa were 1.5 $\mu\text{g/mL}$, 34.3 $\mu\text{g/mL}$, 10.2 $\mu\text{g/mL}$, and 1.7 $\mu\text{g/mL}$, respectively (100). These data suggests that extensive concentration of trovafoxacin occurs in cells present in the lung.

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4. Excretion and Metabolism

Following an oral dose of 200 mg (≈ 118 mCi) of [^{14}C]trovafoxacin, the mean percentage of radioactivity in urine and feces of normal volunteers was approximately 23% and 63%, respectively (102). Mass spectrometric analyses of fecal extracts indicated that the major fecal drug-related components were unchanged trovafoxacin and the N-acetyl conjugate (37% and 14% of administered dose, respectively); the N-sulfamate conjugate and the diacid metabolite were minor fecal metabolites. The acyl glucuronides of both trovafoxacin and the N-acetyl conjugate were absent in the feces, which was attributed to their hydrolysis by gut microflora. In urine, the major drug-related components were the acyl glucuronide conjugate and unchanged trovafoxacin (11% and 7% of administered dose, respectively); the N-acetyl and N-acetyl/acyl glucuronide conjugates and diacid and hydroxy carboxylic acid metabolites were minor urinary metabolites. In human serum, circulating radioactivity consisted of 52% unchanged trovafoxacin and 22% acyl glucuronide; the N-acetyl and N-acetyl/acyl glucuronide conjugates were minor circulating metabolites in man. Thus, this biotransformation study in man revealed that phase II metabolism (glucuronidation, N-acetylation, and N-sulfoconjugation) plays a major role in the elimination of trovafoxacin. A few oxidative metabolites such as the diacid, hydroxy carboxylic acid, and pyrroline were detected in man, but their percentage in the biological matrices was insignificant. The trovafoxacin metabolites identified in man had been previously identified in the rat and/or dog (28).

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5. Protein Binding

Over the clinically relevant serum/plasma trovafoxacin concentration range of 1 to 5 $\mu\text{g/mL}$, the protein binding of trovafoxacin is 70% as measured by the equilibrium dialysis method (29). A second study by Wise et al. measured serum protein binding of trovafoxacin by the same methodology and calculated a value of 88% at 1 $\mu\text{g/mL}$ (26).

6. Food Effects and Drug Interactions

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The pharmacokinetics of the suspension/solution and tablet formulations of trovafoxacin were examined in male and female subjects under fasted and fed conditions. The mean relative bioavailability estimate of trovafoxacin tablets, relative to the solution in a fasted state, were 91.9% and 95.7% in fed and fasted states, respectively. The mean relative bioavailability of the fed tablet treatment, compared with the

fasted tablet treatment was 98.0%
the bioavailability of trovafloracin (23).

indicating that food did not influence

Studies have indicated that coadministration of Maalox reduces the bioavailability of trovafloracin by 66% (24). Administration of 40 mg of omeprazole 2 h before trovafloracin slightly reduced the bioavailability of the quinolone (23).

Trovafloracin does not interfere with the metabolism of theophylline (25).

7. Effects of Age and Gender

There were only minor differences in the pharmacokinetics of trovafloracin in elderly subjects and between males and females (30).

8. Renal Impairment

Since trovafloracin is predominantly excreted by nonrenal routes of elimination, renal impairment has a limited effect on the pharmacokinetics of this fluoronaphthyridone.

IV. CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

A. Clinical Laboratory Susceptibility Test Methods

The information summarized in this section is to define the standardized methods to be used by clinical microbiology laboratories to determine the susceptibility of clinical isolates to trovafloracin.

1. Disk Content Studies

In a study by Fuchs et al. (51) several disk concentrations ranging from 5- to 60-mg trovafloracin were tested and the 10- μ g trovafloracin disk gave satisfactory results. The sponsor has proposed the use of this disk in Disk Diffusion method for performing *in vitro* susceptibility testing.

The 10- μ g disk may be used in performing Dish Diffusion test.

2. Quality Control

Studies by Fuchs et al. and Barry et al. (49,51,65) have been performed in order to establish quality control ranges for trovafloracin. All studies were conducted according to the standard procedures and guidelines established by the National Committee for Clinical Laboratory Standards. Due to the disk diffusion characteristics of trovafloracin, a 10- μ g disk content has

been chosen for all disk susceptibility procedures. The quality control ranges that have been proposed for trovafoxacin are shown in Table 17.

These quality control ranges may stand as proposed by the sponsor.

Table 17. Quality Control Ranges for Trovafoxacin

Organism (Strain)	MIC ($\mu\text{g/mL}$)	Zone diameter ^a (mm)
<i>E. coli</i> (ATCC 25922)	0.004-0.016	29-36
<i>S. aureus</i> (ATCC 29213)	0.008-0.03	ND ^b
<i>S. aureus</i> (ATCC 25923)	ND	29-35
<i>P. aeruginosa</i> (ATCC 27853)	0.25-2.0	21-27
<i>E. faecalis</i> (ATCC 29212)	0.06-0.25	ND
<i>H. influenzae</i> (ATCC 49247)	0.004-0.016	32-39
<i>S. pneumoniae</i> (ATCC 49619)	0.06-0.25	25-32
<i>N. gonorrhoeae</i> (ATCC 49226)	0.004-0.016	42-55
<i>B. fragilis</i> (ATCC 25285)		ND
<i>B. thetaiotaomicron</i> (ATCC 29741)		ND
<i>E. lentum</i> (ATCC 43055)		ND

^a All zone diameter studies performed with a 1 μg trovafoxacin disk

^b ND = not determined

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3. Susceptibility Interpretive Breakpoints for Dilution and Diffusion Tests

In two studies by Fuchs et al. (49,51) the authors state that MIC breakpoints of $\leq 1.0 \mu\text{g/mL}$ and $\leq 2.0 \mu\text{g/mL}$ were chosen based on the assumption that the oral dose of trovafoxacin would be 100 to 300 mg, which would result in a mean C_{max} of $1.5 \mu\text{g/mL}$ for the 100 mg dose and $4.4 \mu\text{g/mL}$ for the 300 mg dose. The error rate-bound method was used to calculate the zone diameter criteria corresponding to these two MIC breakpoints. For MIC breakpoints of $\leq 2.0 \mu\text{g/mL}$ (susceptible) and $\geq 8.0 \mu\text{g/mL}$ (resistant), the corresponding zone diameter breakpoints for the 10- μg disk were $\geq 14 \text{ mm}$ (susceptible) and $\leq 10 \text{ mm}$ (resistant). If MIC breakpoints of $\leq 1.0 \mu\text{g/mL}$ and $\geq 4.0 \mu\text{g/mL}$ were chosen, the corresponding zone diameter breakpoints for the 10- μg disk were $\geq 16 \text{ mm}$ (susceptible) and $\leq 12 \text{ mm}$ (resistant).

The authors suggested that these tentative breakpoints should be used for interpretation of *in vitro* susceptibility tests for aerobic (including fastidious) and anaerobic organisms until supporting clinical data are available to confirm the utility of these criteria.

The sponsor has proposed the following breakpoints (Table 18) for interpretation of *in vitro* susceptibility tests for aerobic (including fastidious except for *N. gonorrhoeae*) and anaerobic organisms.

Table 18. Tentative Breakpoints and Interpretive Criteria for Trovafloracin (10 µg disk) for Organisms Other than *Neisseria gonorrhoeae*

	Zone size (mm) (10 µg disk)	MIC (µg/mL)
Susceptible	≥ 14	≤ 2.0
Intermediate	11-13	4.0
Resistant	≤ 10	≥ 8.0

As it was state in Table 15 of section III.A.2. of this review, the steady state AUC_{0-∞} for 100 mg oral QD dose was 11.8 ± 1.8 mg.h/mL and for the 200 mg oral QD dose was 34.4 ± 5.7 mg.h/mL. The steady state AUC_{0-∞} for 200 mg I.V. QD dose was 32.2 ± 7.3 mg.h/mL and for the 300 mg I.V. QD dose was 46.3 ± 3.9 µg.h/mL. Since trovafloracin is a fluoroquinolone and it acts in a concentration dependent manner, the parameter that most closely relates to its efficacy is the AUC:MIC ratio.

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A comparison of the pharmacokinetic parameters for the common fluoroquinolones is presented in Table 19. The susceptible breakpoint (MIC B.P.) and the AUC:MIC ratio is included in this table for comparison. Historically, the MIC breakpoints have been set so that at the proposed dose the AUC:MIC ratio would be between 11 and 30. In the case of trovafloracin there are three proposed dose of 100, 200, and 300 mg QD. As one can see from Table 19 MIC susceptible breakpoint of 1 µg/mL would result in AUC:MIC ratio of 11.8 which is within the target range of 11-30. If one accepts the sponsor proposed MIC breakpoint of 2 µg/mL, then the AUC:MIC ratio for the 100 mg dose would be 5.9 which is way below the target range

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Table 19. Comparison of Pharmacokinetic Parameters for Fluoroquinolones

Drug	Dose (mg)	C _{max} (µg/mL)	AUC ₀₋₂₄ (µg.h/mL)	T _{max} (h)	T _{1/2} (h)	MIC B.P. (µg/mL)	AUC ₀₋₂₄ :MIC ratio
Ciprofloracin	500	2.4	11.6	1-2	4	1	11.6
Ofloxacin	400	4.6	61.0	1-2	4-5	2	30.5
Lomefloracin	400	3.2	26.1	0.8-1.4	~8	2	13.1
Enoxacin	400	2.0	---	1-3	3-6	2	---
Norfloxacin	400	1.5	---	~1	3-4	4	---
Sparfloracin	200	1.1	18.7			1	18.7
	400	1.3	20.6	3-4	18-20	1	20.6
Levofloxacin	250	2.8	27.2			2	13.6
	500	5.7	47.5	1-2	6.8	2	23.8
Grepafloxacin	400	1.35	14.08	2	7-12	1	14.1
	600	2.25	27.51	2	7-12	1	27.5
Trovafloracin	100	1.0	9.4	0.5-1.5	9.2	1	9.4
	200	2.1	26.7	0.9-2.7	9.6	1	26.7
	300	3.6	46.1	0.9-1.7	11.2	1	46.1

In addition when one looks at the frequency distribution curves presented in Figures 2 - 8 it becomes evident that with the exception of anaerobes and *Neisseria gonorrhoea* the susceptible breakpoint of 1 µg/mL nicely separates the susceptible from resistant populations and would allow for detection of resistance, should it develop, efficiently. For the anaerobes the breakpoint of 2 µg/mL is reasonable because the proposed dose is either 200 or 300 mg QD, which will put the AUC:MIC ratio For *Neisseria gonorrhoea* the sponsor has proposed a single 100 mg dose with the mean AUC of 9.4 µg.h/mL. Since the MIC₉₀ of these isolates is < 0.03 µg/mL, an MIC susceptible breakpoint of 0.25 µg/mL will give a satisfactory AUC:MIC ratio and would allow for rapid detection of resistance should it develop.

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Figure 2. TROVAFLOXACIN vs *Staphylococcus aureus*
(N = 458)

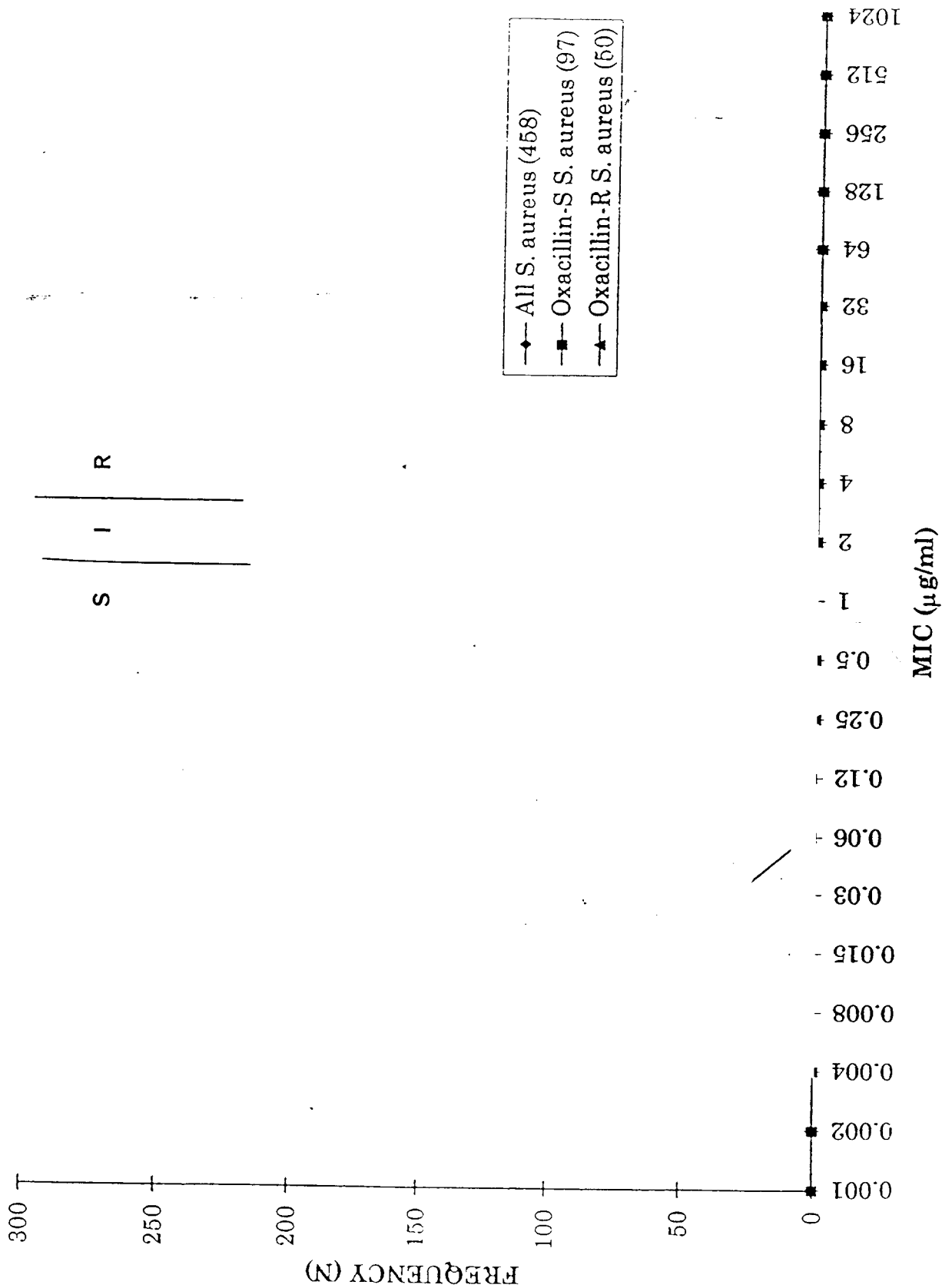


Figure 3. TROVAFLOXACIN vs Coagulase Negative Staphylococci (N = 336)

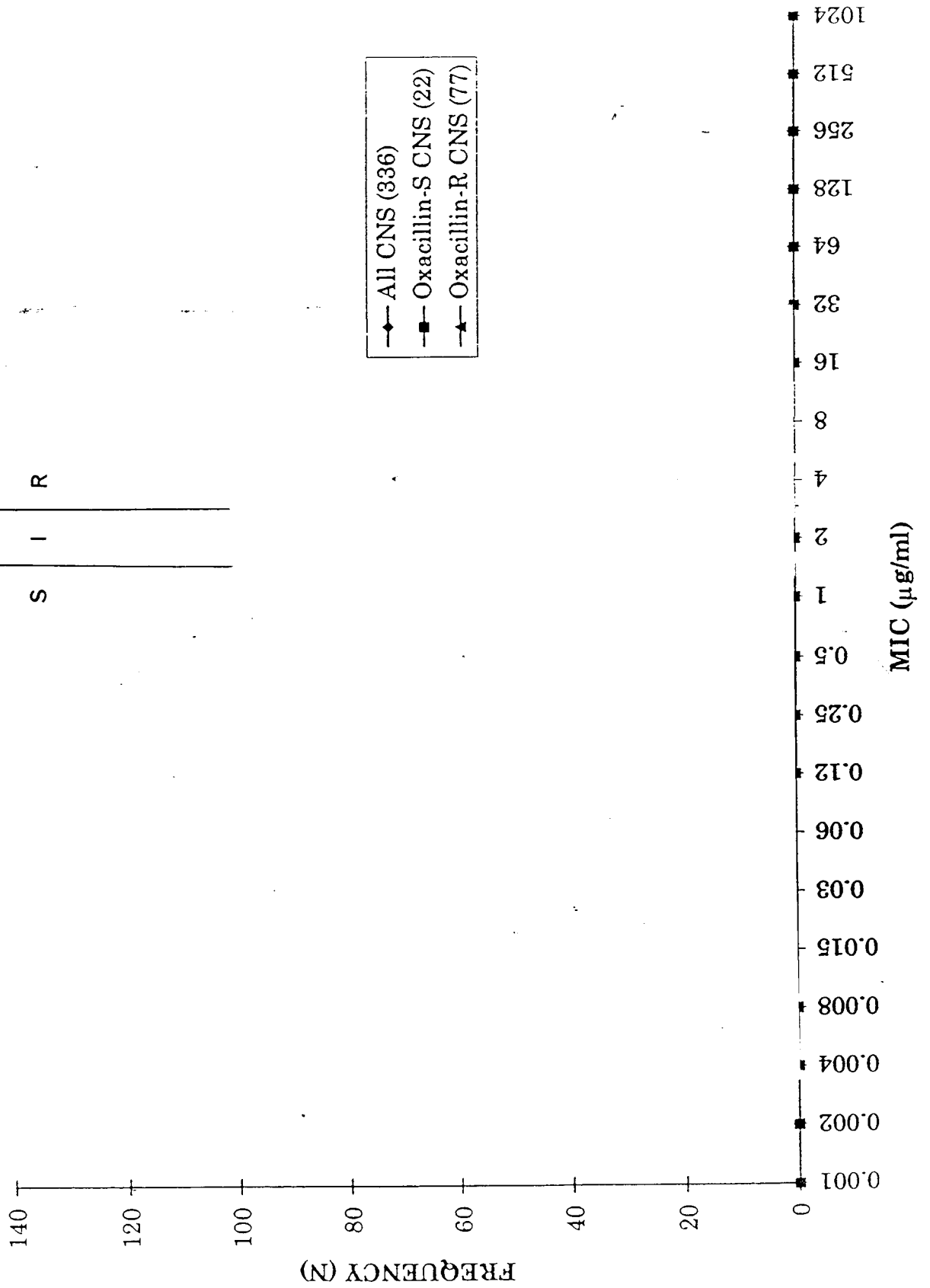


Figure 4. TROVAFLOXACIN vs All *Enterococcus* sp.
(n = 173)

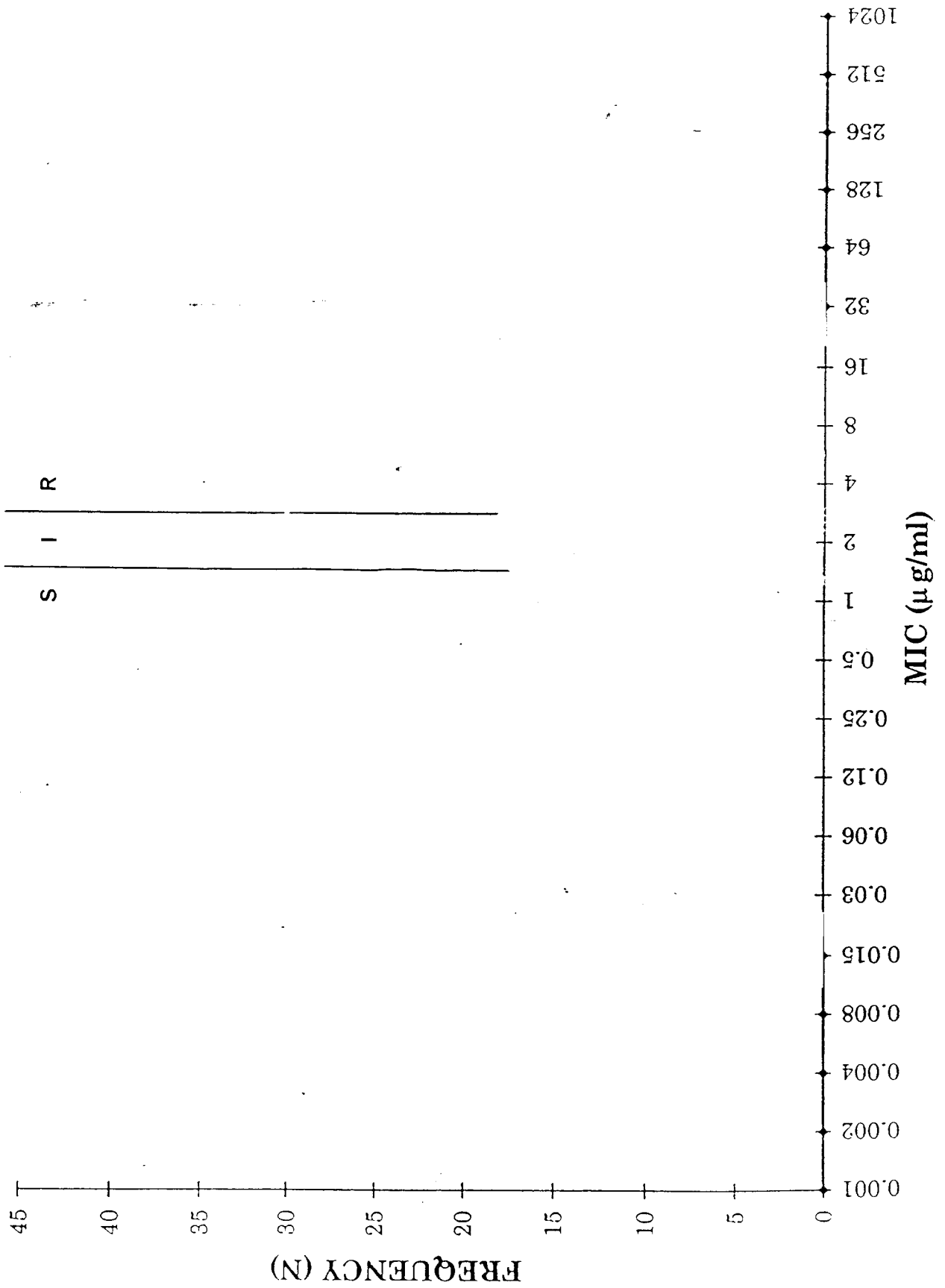


Figure 5. TROVAFLOXACIN vs *Streptococcus pneumoniae*
(N = 1330)

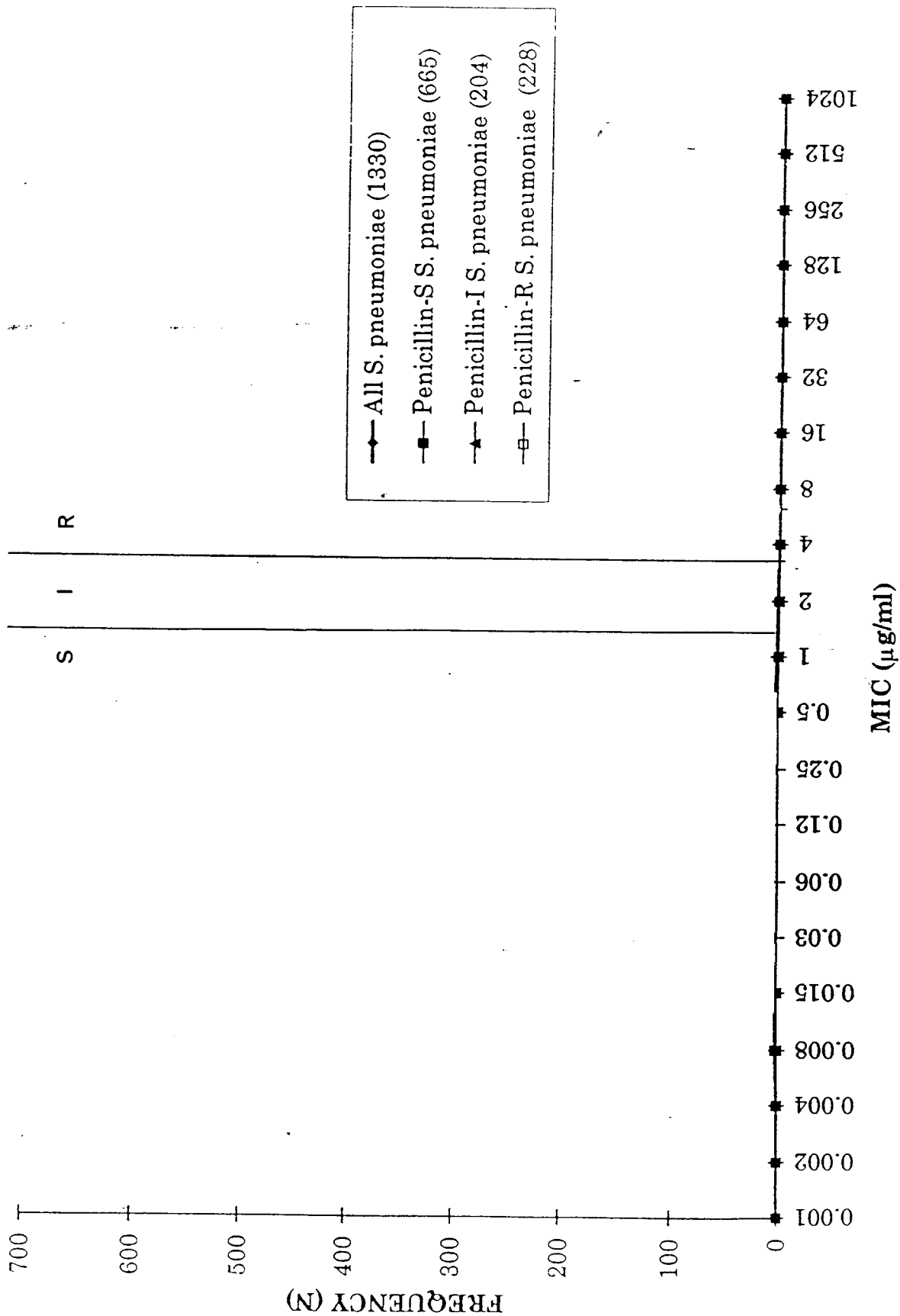


Figure 6. TROVAFLOXACIN vs *Enterobacteriaceae*
(n = 1356)

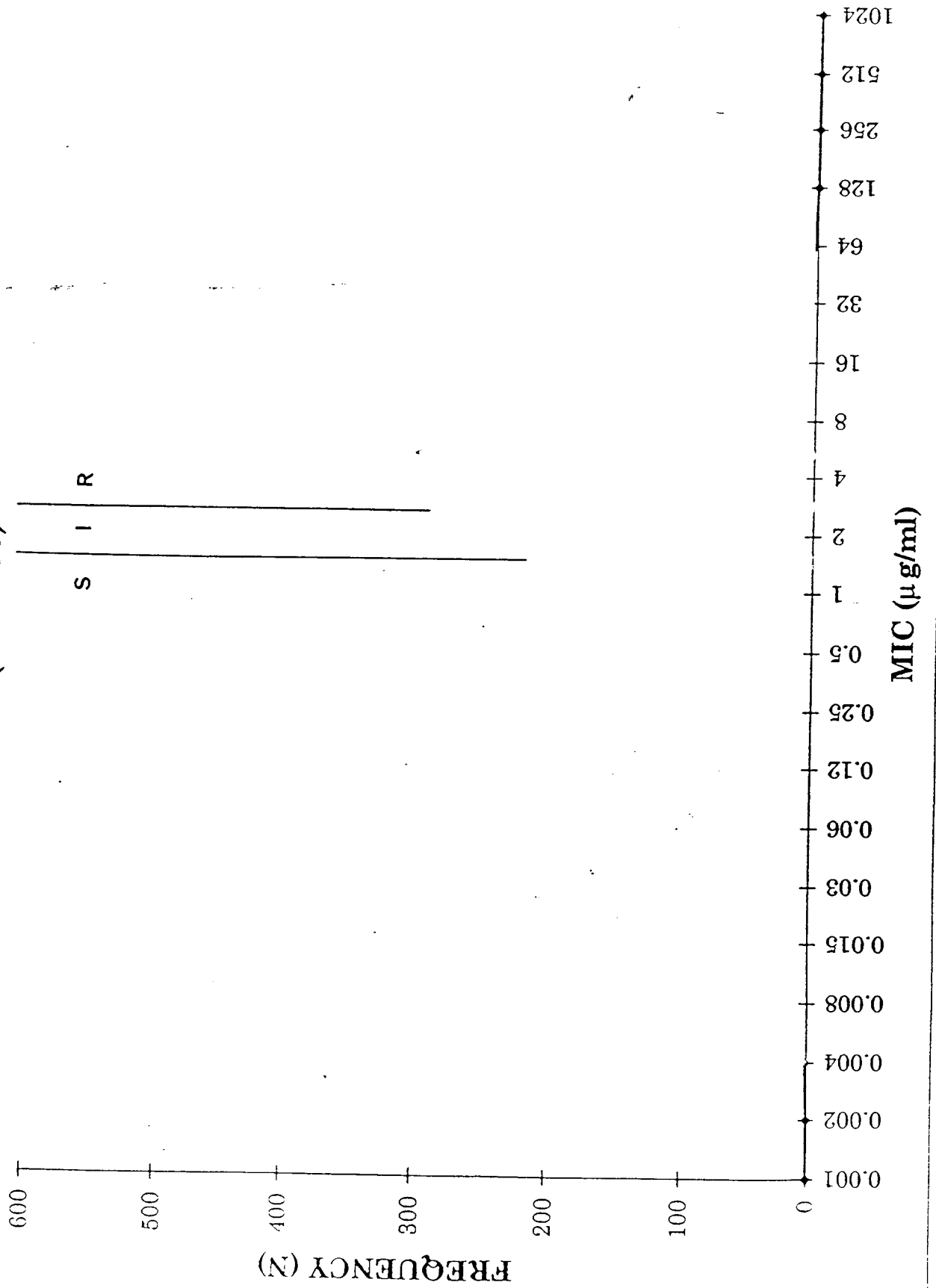


Figure 7. TROVAFLOXACIN vs Non-Enteric GNBs
(n = 365)

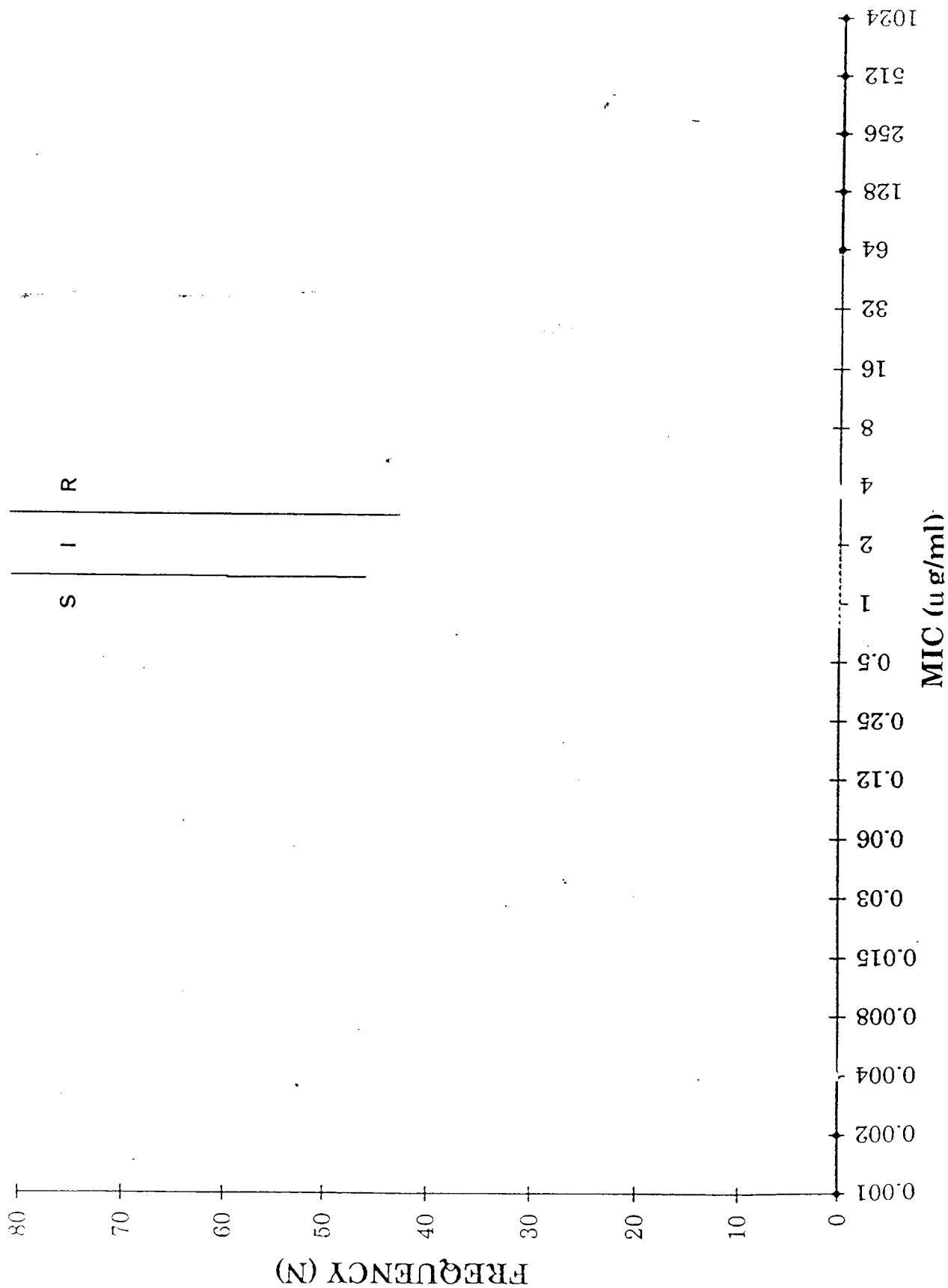
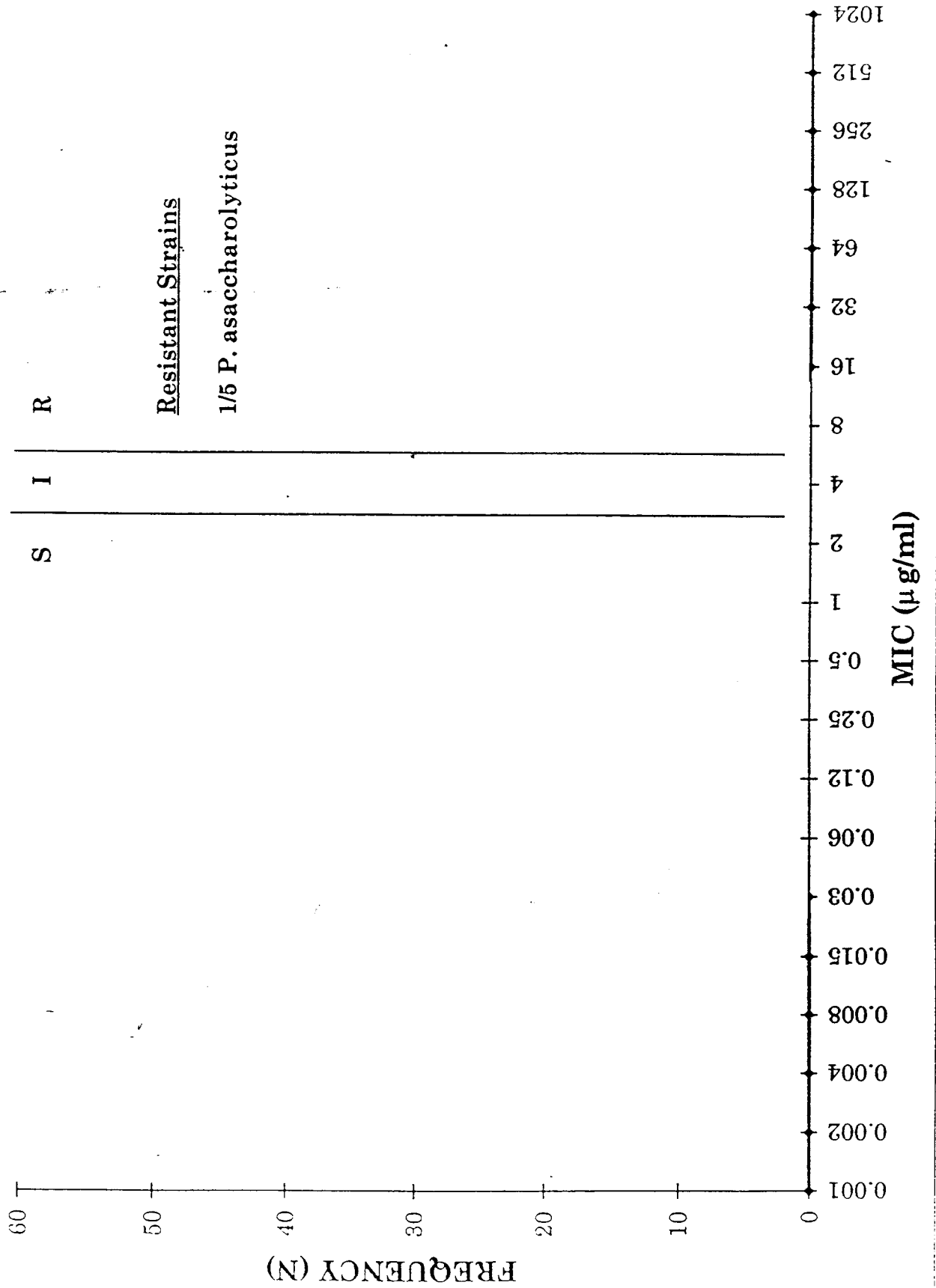


**Figure 8. TROVAFLOXACIN vs All Anaerobes
(n = 170)**



Therefore, it is the view of this reviewer that the breakpoints shown in Table 20. be used as a starting point for interpretation of clinical isolates.

Table 20. Tentative Breakpoints and Interpretive Criteria for Trovafoxacin (10 µg disk)

Organism	Zone size (mm) (10 µg disk)			MIC (µg/mL)		
	S	I	R	S	I	R
<i>N. gonorrhoeae</i>	--	--	--	≤ 0.25	--	--
All Other Aerobes	≥ 16	13-15	≤ 12	≤ 1.0	2.0	≥ 4.0
All Anaerobes	--	--	--	≤ 2.0	4.0	≥ 8.0

B. Bacteriological Efficacy

1. Activity of Trovafoxacin Against Bacteria Resistant to Non-Quinolone Antibacterial Agents

The following discussion will highlight the activity of trovafoxacin against organisms that are resistant to other classes of antimicrobials than fluoroquinolones. Some of these bacteria have been discussed in previous sections of this document and will not be covered extensively here. The major groups of pathogens to be discussed include: 1) penicillin/macrolide-resistant *S. pneumoniae*, 2) ampicillin-resistant *H. influenzae*, 3) MRSA, 4) gentamicin-resistant *E. faecalis*, 5) erythromycin-resistant *Mycoplasma* spp., 6) ceftazidime-resistant Gram-negative bacilli, and 7) *Mycobacterium tuberculosis*.

Trovafoxacin is active against isolates of pneumococci regardless of their susceptibility status to penicillin (Table 1). Trovafoxacin was active against 145 penicillin-resistant pneumococci tested in three *in vitro* studies (Table 21). The MIC₉₀ range for trovafoxacin was compared with for penicillin G, for ceftriaxone, and >16 µg/mL for erythromycin and azithromycin

The activity of trovafoxacin against isolates of MRSA has been reviewed in Table 1. The MIC₉₀ range of trovafoxacin against 487 MRSA (that also demonstrated high-level resistance to ciprofloxacin) was with a median MIC₉₀ of 2.0 µg/mL. Thus trovafoxacin can be expected to show inhibitory activity against only a few MRSA. In one study (98) the activity of trovafoxacin was compared with those of several new antimicrobials selected for their activity against MRSA. In this study, trovafoxacin was similar in potency to two new oxazolidinones (U 100592 and U 100766), and vancomycin. Rifampin was more potent than any of the other agents tested (Table 21).

The activity of trovafoxacin against clinical isolates of enterococci is variable. Against 574 isolates of vancomycin susceptible *E. faecalis* the MIC₉₀ range for trovafoxacin was 0.25-8.0 µg/mL with a median MIC₉₀ of 2.0 µg/mL (Table 2). In one study (52) trovafoxacin had an MIC₉₀ of 8 µg/mL against 17 isolates of *E. faecalis* demonstrating high-level resistance to gentamicin. In a study by Freeman *et al.* (97) MIC₉₀s for trovafoxacin were out of the clinically useful range for vancomycin-resistant enterococci containing either *vanA* or *vanB* (Table 21). Only ramoplanin had potent activity against this group of isolates. Collectively, the available data suggest that while trovafoxacin is active against a very few isolates of multi-drug resistant enterococci, achievable blood levels in man will not be above the MIC for many isolates rendering the drug useless in treating infections due to Enterococci.

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Table 21. Activity of Trovafoxacin Against Bacteria Resistant to Non-Quinolone Antibacterials

Organism	No. Strains	Compound	MIC ₉₀ Range (µg/mL)	Reference
<i>S. pneumoniae</i> Pen-R	(145) ^a	Trovafoxacin		
		Ciprofloxacin		48
		Penicillin G		48
		Ceftriaxone		
		Erythromycin	>16	
		Azithromycin	>16	
<i>S. aureus</i> MRSA	(118)	Trovafoxacin	1.0	98
		Ciprofloxacin	16.0	
		U 100592	1.0	
		U 100766	1.0	
		Synercid	0.5	
		Rifampin	0.006	
		Vancomycin	1.0	
Enterococci <i>vanA</i>	(27)	Trovafoxacin	32	97
		Vancomycin	1024	
		Teicoplanin	>64	
		Ciprofloxacin	>64	
		Ramoplanin	2.0	
		Fusidic acid	4.0	
		Minocycline	8.0	
		Synercid	0.5	
Enterococci <i>vanB</i>	(17)	Trovafoxacin	8.0	97
		Ciprofloxacin	32	
		Vancomycin	512	
		Teicoplanin	0.5	
		Ramoplanin	2.0	
		Fusidic acid	8.0	
		Minocycline	16.0	
		Synercid	8.0	

Organism	No. Strains	Compound	MIC ₉₀ Range (µg/mL)	Reference
<i>H. influenzae</i> (Amp-R) Beta-lactamase positive	(50)	Trovafloracin	0.03	40
		Ciprofloracin	0.03	
		Amoxicillin	>16	
		Amoxicillin/ clavulanate	2.0	
		Ceftriaxone	0.03	
		Trimethoprim/ sulphamethoxazole	32	
		Erythromycin	4.0	
<i>E. cloacae</i>	(47)	Trovafloracin	0.5	41
		Ciprofloracin	0.5	
		Ceftazidime	128	
		Augmentin	128	
		Amikacin	2.0	
		Gentamicin	16.0	
<i>K. pneumoniae</i>	(124)	Trovafloracin	0.5	41
		Ciprofloracin	4.0	
		Ceftazidime	128	
		Augmentin	64	
		Amikacin	64	
		Gentamicin	64	
<i>M. morgani</i>	(45)	Trovafloracin	2.0	41
		Ciprofloracin	0.125	
		Ceftazidime	16	
		Augmentin	>128	
		Amikacin	4.0	
		Gentamicin	8.0	
<i>P. mirabilis</i>	(57)	Trovafloracin	4.0	41
		Ciprofloracin	1.0	
		Ceftazidime	4.0	
		Augmentin	4.0	
		Amikacin	8.0	
		Gentamicin	8.0	
<i>S. marcescens</i>	(28)	Trovafloracin	1.0	41
		Ciprofloracin	1.0	
		Ceftazidime	16	
		Augmentin	>128	
		Amikacin	>128	
		Gentamicin	128	
<i>P. aeruginosa</i>	(92)	Trovafloracin	2.0	41
		Ciprofloracin	2.0	
		Ceftazidime	32	
		Amikacin	16	
		Gentamicin	128	

Organism	No. Strains	Compound	MIC ₉₀ Range (µg/mL)	Reference
<i>Mycobacterium tuberculosis</i>	(33)	Trovafloracin	32	37,38
		Ciprofloracin	0.5	
		Ofloxacin	1.0	
<i>M. avium intracellulare</i>	(22)	Trovafloracin	64	37,38
		Ciprofloracin	32	
		Ofloxacin	32	

^a The number of isolates in parenthesis were already presented in Table 1, page 10 of this review.

The *in vitro* activity of trovafloracin against ampicillin-resistant beta-lactamase-positive *H. influenzae* was investigated by Sefton *et al.* (40). Trovafloracin was equivalent in potency to ciprofloracin, with an MIC₉₀ of 0.03 µg/mL (Table 21). Ceftriaxone had an identical MIC₉₀. Trovafloracin was at least 500-fold more active than amoxicillin and 67-fold more active than amoxicillin/clavulanate against these strains. This collection of fifty isolates was multi-resistant, as MIC₉₀s to trimethoprim/sulphamethoxazole and erythromycin were 32 and 4.0 µg/mL, respectively. Comparable results were obtained in another report (41) involving 28 isolates of *H. influenzae* demonstrating MIC₉₀s to ampicillin and cefuroxime of 16 µg/mL. The MIC₉₀s for trovafloracin and ciprofloracin were ≤0.03 and 0.06 µg/mL, respectively.

Trovafloracin is active against multi-resistant isolates of *Enterobacteriaceae* that are susceptible to ciprofloracin. One report (41) evaluated the activity of trovafloracin against Gram-negative bacilli that were resistant to ceftazidime and gentamicin. MIC₉₀s for trovafloracin ranged between 0.5 and 4.0 µg/mL for species including *E. cloacae*, *K. pneumoniae*, *M. morgani*, *P. mirabilis*, *S. marcescens*, and *P. aeruginosa* (Table 21). MIC₉₀s to ceftazidime and gentamicin ranged from 4.0 to 128 µg/mL and 8.0 to 128 µg/mL, respectively. Such high-level aminoglycoside resistant strains often contain multiple drug modifying determinants including enzymes for acetylating, adenylating, and phosphorylating aminoglycosides. In this regard, the isolates *K. pneumoniae*, *S. marcescens*, and *P. aeruginosa* had MIC₉₀s to amikacin of 16.0 to >128 µg/mL. The MIC₉₀s for trovafloracin against these three species ranged from 0.5 to 2.0 µg/mL. The data suggest that trovafloracin could be active against Gram-negative bacilli that are resistant to beta-lactams and aminoglycosides. Clearly, the potency of trovafloracin against such isolates is dependent upon them being generally susceptible to the newer fluoroquinolones.

Multi-resistant isolates of *Mycobacterium tuberculosis* and *M. avium-intracellulare* are being isolated from a broad range of clinical settings. Preliminary results indicate that trovafloracin does not possess good activity against these mycobacteria. The data in Table 21 indicate that the MIC₉₀s of trovafloracin for these two species are 32 and 64 µg/mL, respectively (37,38). Against *M. tuberculosis*, trovafloracin appears to be significantly less active than ciprofloracin or ofloxacin.

2. Summary of Clinical Trials

Thirty three clinical studies were conducted in order to determine the safety and efficacy of trovafoxacin in treating the following infections:

- Community Acquired Pneumonia
- Nosocomial Pneumonia
- Acute Bacterial Exacerbation of Chronic Bronchitis
- Sinusitis
- Intra-Abdominal Infections
- Gynecologic and Pelvic Infections
- Pelvic Inflammatory Disease
- Skin and Skin Structure Infections
- Uncomplicated Urinary Tract Infections
-
- Prostatitis
- Sexually Transmitted Disease (Gonorrhea and Chlamydia)
- Surgical Prophylaxis

(b)(4)

Tablet and I.V. formulations were studied. In most protocols, dosages included 300 or 200 mg I.V. followed by 200 mg oral QD. Some of the protocols had a dosage of 100 mg QD. Different protocols studied different dosing protocols any where from a single dose for treatment of gonorrhea to 28 days for treatment of prostatitis. A summary of all pivotal and supporting clinical studies are shown in Table 22. A total of 6,205 patients were randomized in these studies.

Table 22. Summary of Clinical Trials Which Evaluated the Effectiveness of Trovafoxacin

Protocol	Dose	No.	Type of Study
Community Acquired Pneumonia (Oral Regimen)			
154-102	200 mg QD (10 days) 300 mg QD (10 days)	50	Phase II Double-Blind
154-112	200 mg QD (7 or 10 days)	150	Phase III Double-Blind
154-134	200 mg QD (7 or 10 days)	179	Phase III Double-Blind
Community Acquired Pneumonia (IV/PO Regimen)			
154-110	Alatrofoxacin 200 mgQD IV → trovafoxacin 200 mg QD PO (7 to 10 days total)	198	Phase III Double-Blind
145-111	Alatrofoxacin 200 mgQD IV → trovafoxacin 200 mg QD PO (7 to 10 days total)	218	Phase III Double-Blind
Nosocomial pneumonia			
154-113	Alatrofoxacin 300 mgQD IV → trovafoxacin 200 mg QD PO (7 to 14 days total)	129	Phase III Double-Blind
154-137	Alatrofoxacin 300 mgQD IV → trovafoxacin	135	Phase III Open Randomized

	200 mg QD PO (7 to 10 days total)		
Acute Bacterial Exacerbation of Chronic Bronchitis			
154-101	100 mg QD (10 days)	74	Phase II Double-Blind
	300 mg QD (10 days)	76	
154-109	100 mg QD (7 days)	210	Phase III Double-Blind
154-141	100 mg QD (7 days)	131	Phase III Double-Blind
Sinusitis			
154-114	200 mg QD (10 days)	255	Phase III Open Non-randomized
154-115	200 mg QD (10 days)	206	Phase III Double-Blind
154-138	200 mg QD (10 days)	207	Phase III Open Randomized
Intra-Abdominal Infections			
154-124	Alatrofoxacin 300 mg QD IV → trovafoxacin 200 mg QD PO (max 14 days total)	204	Phase III Double-Blind
Gynecologic and Pelvic Infections			
154-144	Alatrofoxacin 300 mg QD IV → trovafoxacin 200 mg QD PO (14 days total)	161	Phase III Double-Blind
Pelvic Inflammatory Disease			
154-122	Alatrofoxacin 200 mg QD IV → trovafoxacin 200 mg QD PO (max 14 days total)	79	Phase III Investigator-Blind
154-125	200 mg QD PO (14 days)	155	Phase III Double-Blind
Uncomplicated Skin and Skin Structure Infections			
154-129	100 mg QD (7 days)	141	Phase III Double-Blind
154-130	100 mg QD (7 to 10 days)	221	Phase III Double-Blind
Complicated Skin and Skin Structure Infections			
154-131	Alatrofoxacin 200 mg QD IV → trovafoxacin 200 mg QD PO (10 or 14 days total)	145	Phase III Double-Blind
154-132	200 mg QD PO (10 or 14 days)	255	Phase III Open
154-139	200 mg QD PO (10 or 14 days)	166	Phase III Open Randomized
Uncomplicated Urinary Tract Infection			
154-103	100 mg QD (7 days)	72	Phase II Double-Blind
	300 mg BID (7 days)	74	
154-116	100 mg BID (7 days)	182	Phase II Double-Blind
		182	

Prostatitis			
154-119	200 mg QD (28 days)	142	Phase III Double-Blind
Gonorrhea			
154-120	100 mg single dose	311	Phase III Double-Blind
Chlamydia			
154-105	200 mg QD (7 days)	31	Phase II Open Randomized
	200 mg QD (5 days)	34	
	100 mg QD (7 days)	28	
	50 mg QD (7 days)	37	
154-123	200 mg QD (5 days)	495	Phase III Double-Blind
Elective Colo-Rectal Surgery Prophylaxis			
154-128	Alatrofoxacin 200 mg single dose IV	269	Phase III Double-Blind
Elective Hysterectomy Prophylaxis			
154-146	200 mg single dose PO	196	Phase III Double-Blind

(b)(4)

3. Correlation of MIC Interpretive criteria with Therapeutic Outcome

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If interpretive breakpoints are accurate, susceptibility test results should predict the therapeutic efficacy of an antibiotic. To validate proposed trovafloxacin interpretive breakpoints, bacteriologic eradication and clinical cure rates obtained during clinical studies were examined for correlation with MIC and disk diffusion results.

For analyses in this section, the sponsor has included all clinically and microbiologically evaluable trovafloxacin-treated patients that had a baseline isolate with both MIC and zone size values. Data are presented in Tables G. 33.1a. to G. 45.1b. in Appendix A. Using the MIC breakpoint of ≤ 1.0 , 2.0, and ≥ 4 $\mu\text{g/mL}$ for susceptible, intermediate and resistant respectively, 1,954 isolates from clinical trials were tested, 55 (2.8%) were resistant, 28 (1.4%) were intermediate and 1871 (95.8%) were susceptible to trovafloxacin. As might be predicted, resistance was observed most frequently in isolates of enterococci, *P. aeruginosa*, and members of the *Enterobacteriaceae*. Few resistant isolates of *S. aureus*, *S. epidermidis*, and *S. haemolyticus*, Streptococci, and *Corynebacterium*, were also encountered.

Tables 23 and 24 show overall trends in the data demonstrating that the proposed MIC interpretive breakpoints serve as good predictors of therapeutic outcome for all target species. There is a direct correlation between a susceptible MIC result and both bacterial eradication and

clinical cure rates. As seen in Table 23, when all organisms are considered, susceptible MIC results correspond with 87% bacterial eradication rate and 89% clinical cure rate.

The correlation between susceptible results and positive therapeutic outcome was generally uniform among bacterial species (Tables 24). Two exceptions are the lower eradication and clinical cure rates seen for gram-negative nonfermenters (including *Acinetobacter* spp., *Pseudomonas* spp. and *S. maltophilia*) and *Enterococcus* spp.

As seen in Table 23, there is an overall trend for lower eradication and cure rates with intermediate and resistant isolates. Specifically there were 83/1954 (4.3%) isolates that had resistant or intermediately resistant MICs to trovafloxacin. Among these isolates 57/83 (69%) were eradicated as compared to an eradication rate of 87% for the isolates with susceptible MICs. The cure rates were also lower for isolates with intermediate and resistant MICs (72/83, 87%) as compared to isolates with susceptible MICs with cure rates of 89%.

The clinical efficacy and pathogen eradication data obtained supports the use of a ≤ 1 $\mu\text{g/mL}$ susceptibility breakpoint for trovafloxacin

TABLE 23. Overall Summary of Results Relationship Between Susceptibility to Trovafoxacin and Pathogen Eradication and Clinical Cure Rates

Methodology	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated ^a	% Eradicated ^a	No. of Patients	No. of Patients Cured ^b	% Cured ^b
MIC	R (≥ 4.0 $\mu\text{g/mL}$)	55	42	76	55	49	89
	I (2.0 $\mu\text{g/mL}$)	28	15	54	28	23	82
	S (≤ 1.0 $\mu\text{g/mL}$)	1854	1613	87	1854	1659	89

^a Including eradicated and presumed eradicated pathogens

^b Including cured and improved patients

TABLE 24. Relationship Between MIC and Pathogen Eradication and Clinical Cure Rates in patients treated with Trovafoxacin I.V. and Tablets

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated ^a	% Eradicated ^a	No. of Patients	No. of Patients Cured ^b	% Cured ^b
<i>Haemophilus</i> spp.	R (≥ 4.0 $\mu\text{g/mL}$)	0	--	--	0	--	--
	I (2.0 $\mu\text{g/mL}$)	0	--	--	0	--	--
	S (≤ 1.0 $\mu\text{g/mL}$)	165	158	96	165	151	92
<i>S. pneumoniae</i>	R (≥ 4.0 $\mu\text{g/mL}$)	0	--	--	0	--	--
	I (2.0 $\mu\text{g/mL}$)	0	--	--	0	--	--
	S (≤ 1.0 $\mu\text{g/mL}$)	100	91	91	100	91	91
<i>Streptococcus</i> spp	R (≥ 4.0 $\mu\text{g/mL}$)	1	1	100	1	1	100

other than <i>S. pneumoniae</i>	I (2.0 µg/mL)	3	0	0	3	3	100
	S (< 1.0 µg/mL)	149	127	85	149	134	90
<i>M. catarrhalis</i>	R (≥ 4.0 µg/mL)	0	--	--	0	--	--
	I (2.0 µg/mL)	0	--	--	0	--	--
	S (< 1.0 µg/mL)	58	55	95	58	53	91
<i>N. gonorrhoeae</i>	R (≥ 4.0 µg/mL)	0	--	--	0	--	--
	I (2.0 µg/mL)	0	--	--	0	--	--
	S (< 1.0 µg/mL)	25	25	100	25	23	92
<i>S. aureus</i>	R (≥ 4.0 µg/mL)	4	2	50	4	4	100
	I (2.0 µg/mL)	4	3	75	4	3	75
	S (< 1.0 µg/mL)	321	264	82	321	293	91
<i>Staphylococcus</i> spp. other than <i>S. aureus</i>	R (≥ 4.0 µg/mL)	12	10	83	12	12	100
	I (2.0 µg/mL)	9	6	67	9	7	78
	S (< 1.0 µg/mL)	202	182	90	202	185	92
<i>Enterococcus</i> spp.	R (≥ 4.0 µg/mL)	9	6	67	9	7	78
	I (2.0 µg/mL)	1	1	100	1	1	100
	S (< 1.0 µg/mL)	116	92	79	116	100	86
<i>Enterobacteriaceae</i> spp. ^c	R (≥ 4.0 µg/mL)	15	11	73	15	12	80
	I (2.0 µg/mL)	3	1	33	3	2	67
	S (< 1.0 µg/mL)	577	513	89	577	530	92
Gram-negative nonfermenters ^d	R (≥ 4.0 µg/mL)	8	7	88	8	8	100
	I (2.0 µg/mL)	7	3	43	7	6	86
	S (< 1.0 µg/mL)	110	75	68	110	92	84

^a Including eradicated and presumed eradicated pathogens

^b Including cured and improved patients

^c Excluding all *Acinetobacter* spp., *Pseudomonas* spp., and *S. maltophilia*

^d Includes all *Acinetobacter* spp., *Pseudomonas* spp. and *S. maltophilia*

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Table 25 is an attempt to summarize all the data available for the anaerobic isolates recovered from patients treated with Trovafloracin regardless of the clinical outcome. The data indicates that a susceptible MIC interpretation correlate with a 86% bacterial eradication rate. When compared with other anaerobic organisms, susceptible determination corresponded to lower eradication rate for *Bacteroides* spp. The data is very limited and one is not able to determine whether these bacterial eradication rates correlates with successful clinical outcome. If one was to set susceptibility breakpoints for anaerobes at this point, this reviewer would reside to the pharmacokinetic and population distribution data and would suggest ≤ 2.0, 4.0, and ≥ 8.0 µg/mL for susceptible, intermediate, and resistant, respectively.

Table 25. Relationship Between MIC and Anaerobic Pathogen Eradication Rates in patients treated with Trovafloracin I.V. and Tablets

Organism Group	Susceptibility	Pathogen Eradication Rate		
		No. of Pathogens	No. of Pathogens Eradicated ^a	% Eradicated ^a
<i>Peptostreptococcus</i> spp.	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	9	8	98

	Missing	6	5	83
<i>Peptostreptococcus magnus</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	6	6	100
	Missing	3	2	67
<i>Propionibacterium acnes</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	1	1	100
	Missing	0	--	--
Anaerobic gram-positive cocci	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	0	--	--
	Missing	2	2	100
<i>Bacteroides distasonis</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	0	--	--
	Missing	1	1	100
<i>Bacteroides fragilis</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	4	3	75
	Missing	3	3	100
<i>Bacteroides spp.</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	4	2	50
	Missing	1	0	0
<i>Peptostreptococcus prevotii</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	1	1	100
	Missing	2	2	100
<i>Prevotella spp.</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	3	3	100
	Missing	1	1	100
<i>Actinomyces israelii</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	0	--	--
	Missing	1	1	100
<i>Bifidobacterium spp.</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	0	--	--
	Missing	1	1	100
<i>Eubacterium limosum</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	0	--	--
	Missing	1	1	100
<i>Bacteroides thalaitaomicron</i>	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--
	S ($\leq 2.0 \mu\text{g/mL}$)	0	--	--
	Missing	1	1	100
Total	R ($\geq 8.0 \mu\text{g/mL}$)	0	--	--
	I ($4.0 \mu\text{g/mL}$)	0	--	--

	S ($\leq 2.0 \mu\text{g/mL}$)	28	24	86
	Missing	22	20	91

* Including eradicated and presumed eradicated pathogens

4. Discussion of Disk Diffusion Interpretive Breakpoints for *Haemophilus* spp.

Figures 9 to 11 are scattergrams for clinical isolates of *Haemophilus* spp. obtained during the clinical trials. In this section the sponsor has included all the isolates regard less of the clinical outcome. When one compares the U.S./Canada strains (Figure 10) with the non-U.S./Canada strains (Figure 11) it becomes evident that there is not much difference between the susceptibility patterns of the two groups. The only two resistant isolates came from non-U.S./Canada studies and are not sufficient to warrant selection of a resistant break point either for MIC or disk diffusion methods. One can combine the data from the U.S. and non-U.S. studies (Figure 9) and using the error rate-bound method determine the disk diffusion breakpoint based on MIC susceptible breakpoint of $\leq 1 \mu\text{g/mL}$.

Using the error rate-bound method and the fact that the ideal (in the sense of reading accuracy) zone sizes should not be less than 15 mm, the disk diffusion susceptible breakpoint should be set at ≥ 22 mm. This would result in an acceptable very major and major error rates of 0.36% and 1.4% respectively (the acceptable limits for very major and major error rates are $< 1.5\%$ and $< 3\%$ respectively).

If one applies the error rate-bound method to the scattergram from U.S./Canada isolates (Figure 10), the ≥ 22 mm susceptible breakpoint would generate a 2.0% major error rate, which is within the acceptable limit. Similarly if one does the same thing with the scattergram from the non-U.S./Canada isolates (Figure 11), the very major error of 0.95% is within the acceptable limit.

Table 26 show overall trends in the data demonstrating that the above disk diffusion interpretive breakpoint serves as good predictors of therapeutic outcome for *Haemophilus* species. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 96% bacterial eradication and 92% clinical cure rates.

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Figure 9. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)
 All Hemophilus spp (n=562)

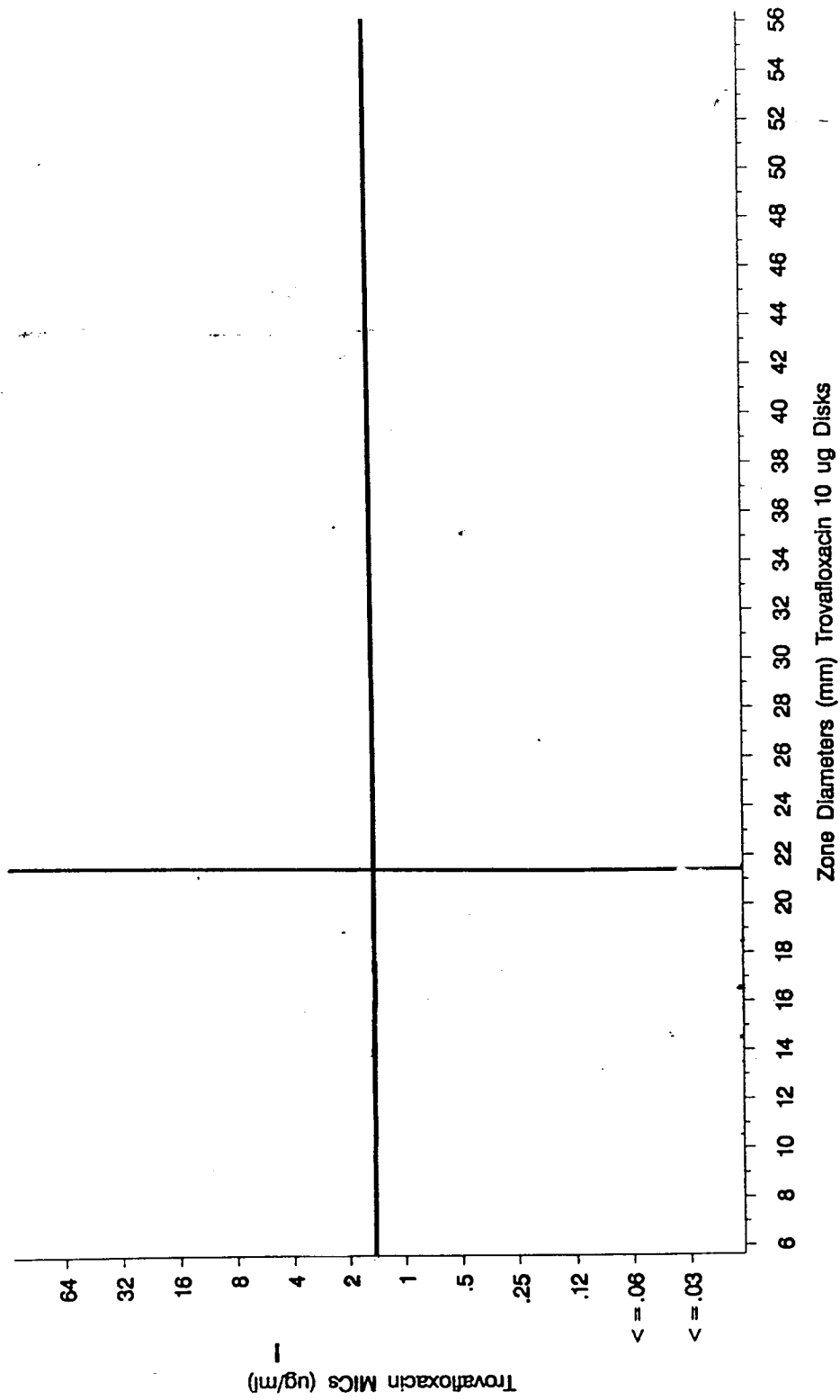


Figure 10. Trovafloxacin MICs ($\mu\text{g/ml}$) vs Zone Diameter (mm) USA/Canada
 All Hemophilus spp (n = 245)

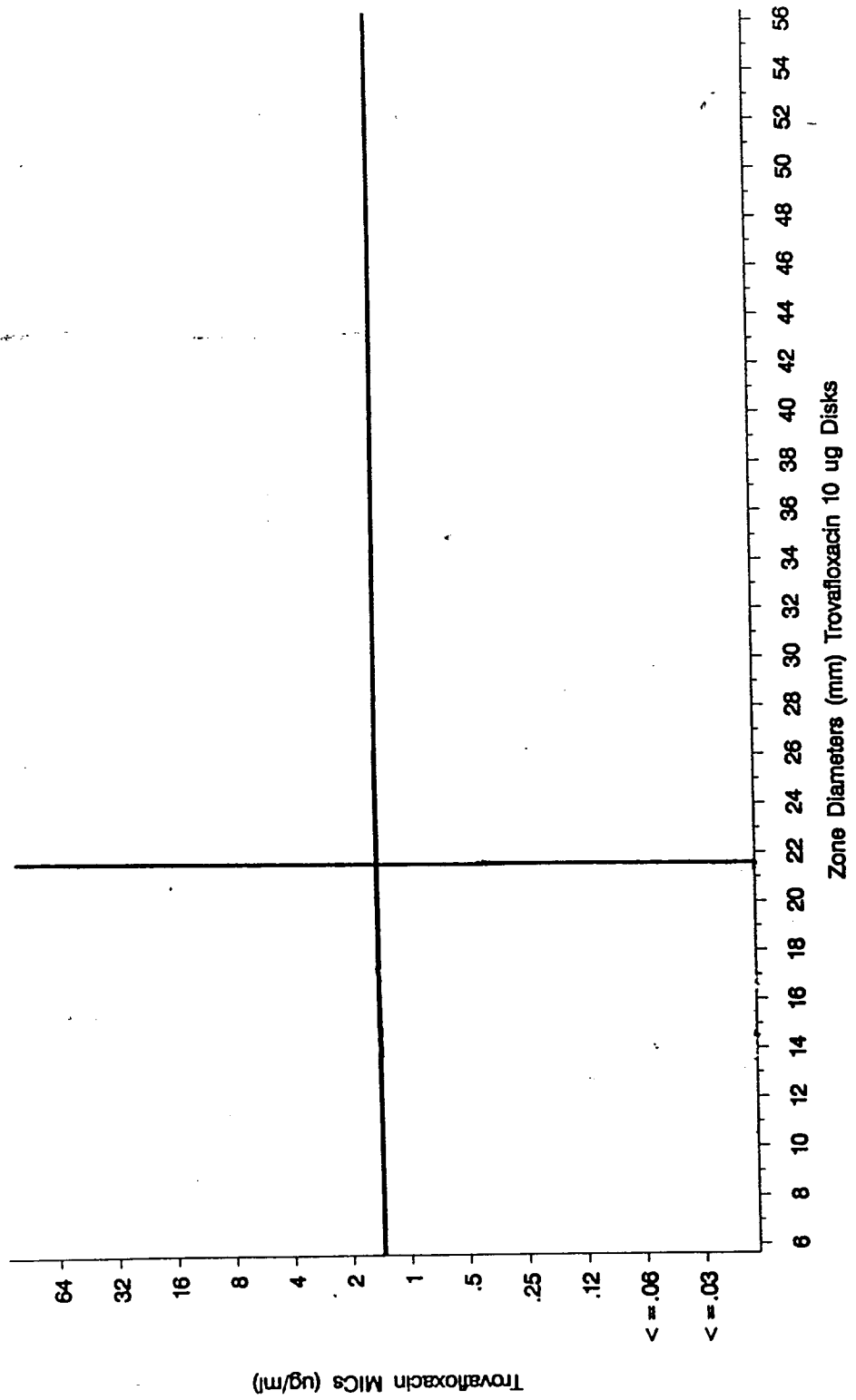
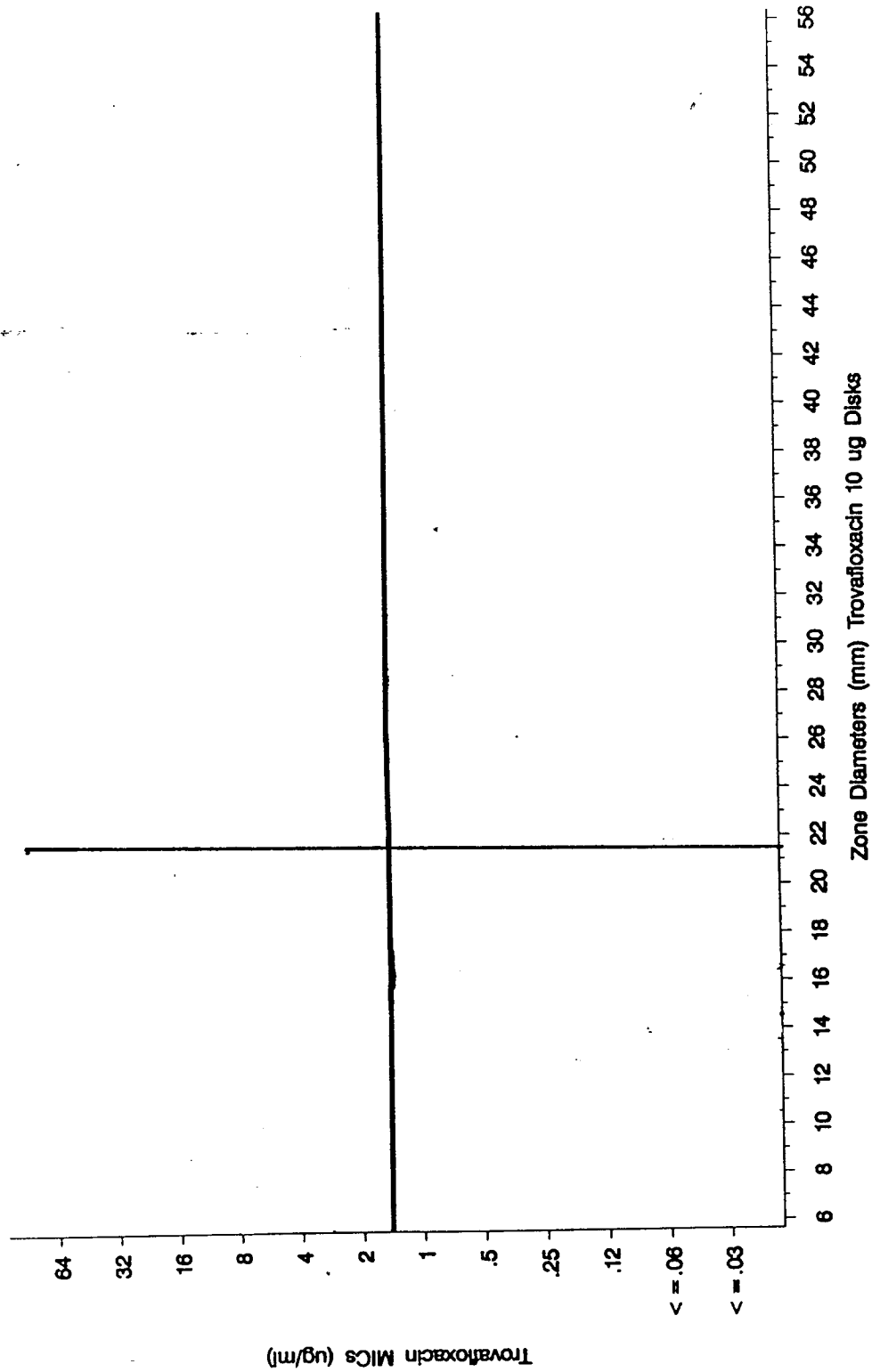


Figure 11. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)
 All Hemophilus spp (n = 317) Non - USA/Canada



5. Discussion of Disk Diffusion Interpretive Breakpoints for *Streptococcus pneumoniae*

Figure 12 is the scattergram for clinical isolates of *Streptococcus pneumoniae* obtained during the clinical trials. In this scattergram the sponsor has included all the U.S. and non-U.S. isolates regard less of the clinical outcome. The isolates were not divided into U.S. and non-U.S. because there were no resistant isolates recovered from the clinical studies. According to these data the highest MIC was 0.5 µg/mL so the proposed (by this reviewer) susceptible MIC breakpoint of 1 µg/mL would seem appropriate. The smallest zone diameter obtained was 21 mm. Using the error rate-bound method or the rule of 3 mm smaller than the zone for 99.9 % of the isolates, the disk diffusion susceptible breakpoint based on MIC susceptible breakpoint of ≤ 1 µg/mL would be ≥ 18 mm. Since there were no resistant isolates recovered in the clinical trials this reviewer will refer to two studies performed by Arthur Barry et al. and James Jorgensen et al. that were presented in the NCCLS fastidious organism working group during the general meeting on June 1-3, 1997. Arthur Barry presented a scattergram on 80 *Streptococcus pneumoniae* isolates (Figure 13). The highest MIC and lowest zone diameter obtained from these isolates were 0.25 µg/mL and 24 mm, respectively. This study like the sponsor's clinical trials did not allow for setting any breakpoints other than susceptible for both MIC and disk diffusion methods. However this study reconfirmed that the susceptible MIC of ≤ 1 µg/mL and susceptible zone diameter of ≥ 18 mm were appropriate. James Jorgensen presented a scattergram on 161 *Streptococcus pneumoniae* isolates (Figure 14). These isolates included ofloxacin resistant isolates (marked by an * in the scattergram in Figure 14) with known single *parC* (ofloxacin MIC,) and double *parC* and *gyrA* (ofloxacin MIC,) mutations that resulted in fluoroquinolone resistance. As it is shown in Figure 14 the MIC susceptible breakpoint of ≤ 1 µg/mL would separate all the double mutations and most of the single mutations from the non-mutated susceptible isolates. The intermediate MIC breakpoint of 2 µg/mL would allow for some of the organisms with single mutation to be categorized appropriately as such. Using the error rate-bound method the corresponding zone diameters would be ≥ 19 mm, , and ≤ 15 mm for susceptible, intermediate, and resistant, respectively. With these breakpoints there are no very major or major errors and only 5.6% minor errors. Of course based only on this scattergram one could set the disk diffusion breakpoints at ≥ 20 mm and ≤ 16 for susceptible , intermediate, and resistant respectively. With these breakpoints there are no very major or major errors and only 3.1% minor errors. And finally one could also choose ≥ 21 mm and ≤ 17 for Susceptible , intermediate, and resistant respectively. With these breakpoints there are no very major or major errors and only 1.9% minor errors. However for the sake of consistency with the clinical isolates this reviewer prefers the breakpoints of ≥ 19 mm and ≤ 15 mm for susceptible, intermediate, and resistant, respectively.

Table 26 shows overall trends in the data demonstrating that the above disk diffusion interpretive breakpoints serve as good predictors of therapeutic outcome for *Streptococcus pneumoniae*. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 91% bacterial eradication and 91% clinical cure rates.

**Figure 12. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)
Strep. Pneumoniae (n=336)**

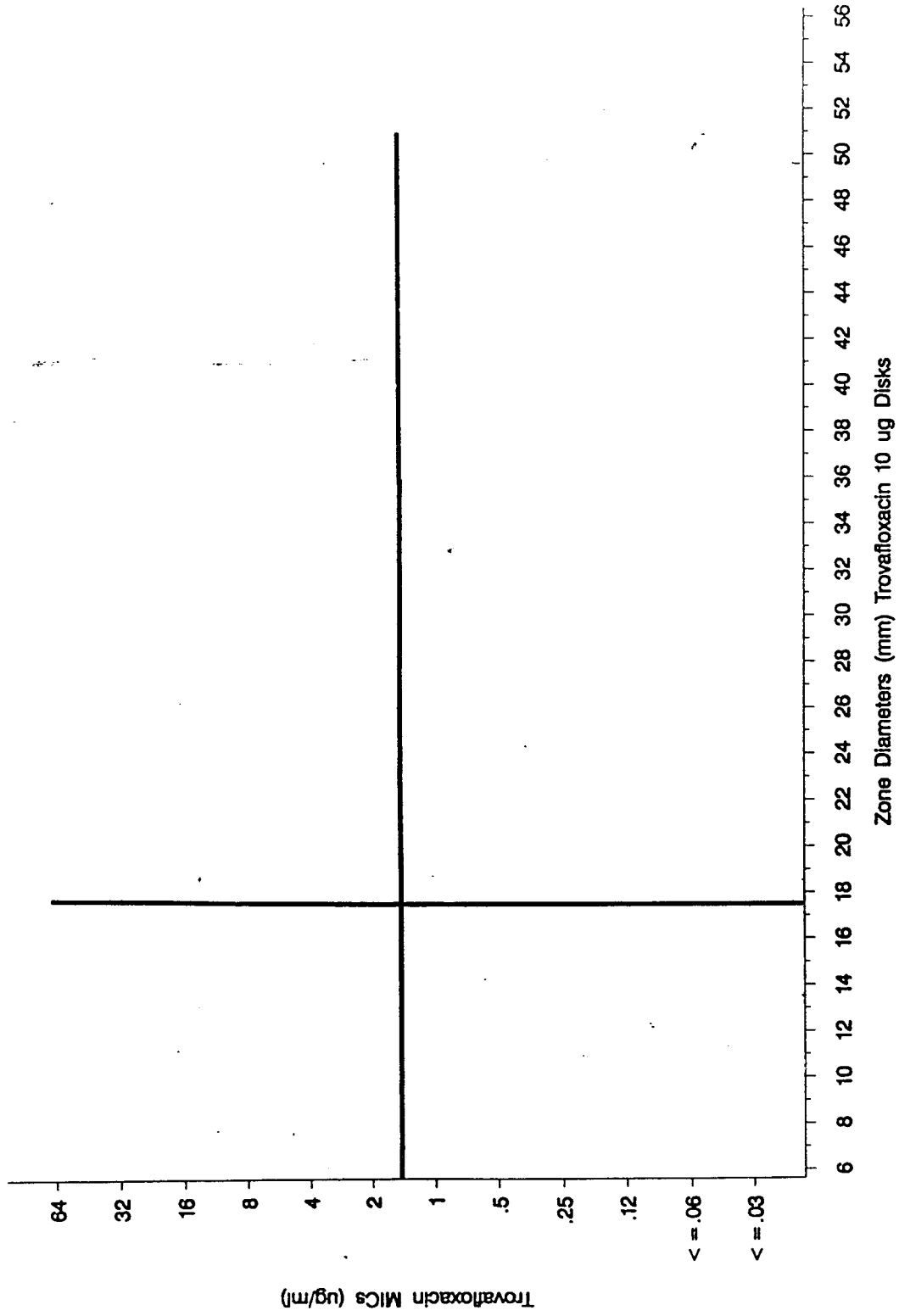


Figure 13. Scattergram generated from 80 selected pneumococcal culture collection against trovafloxacin.

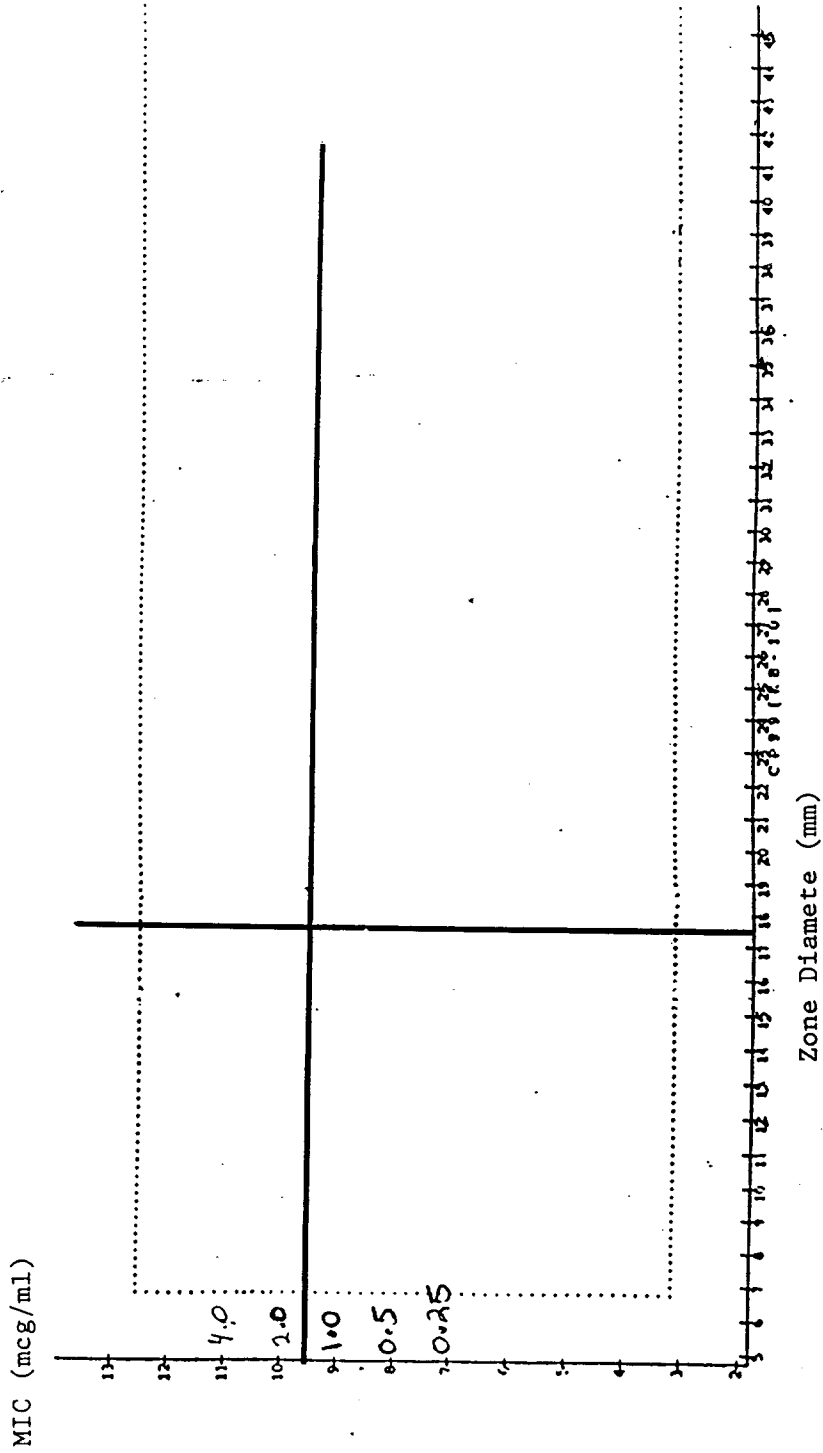
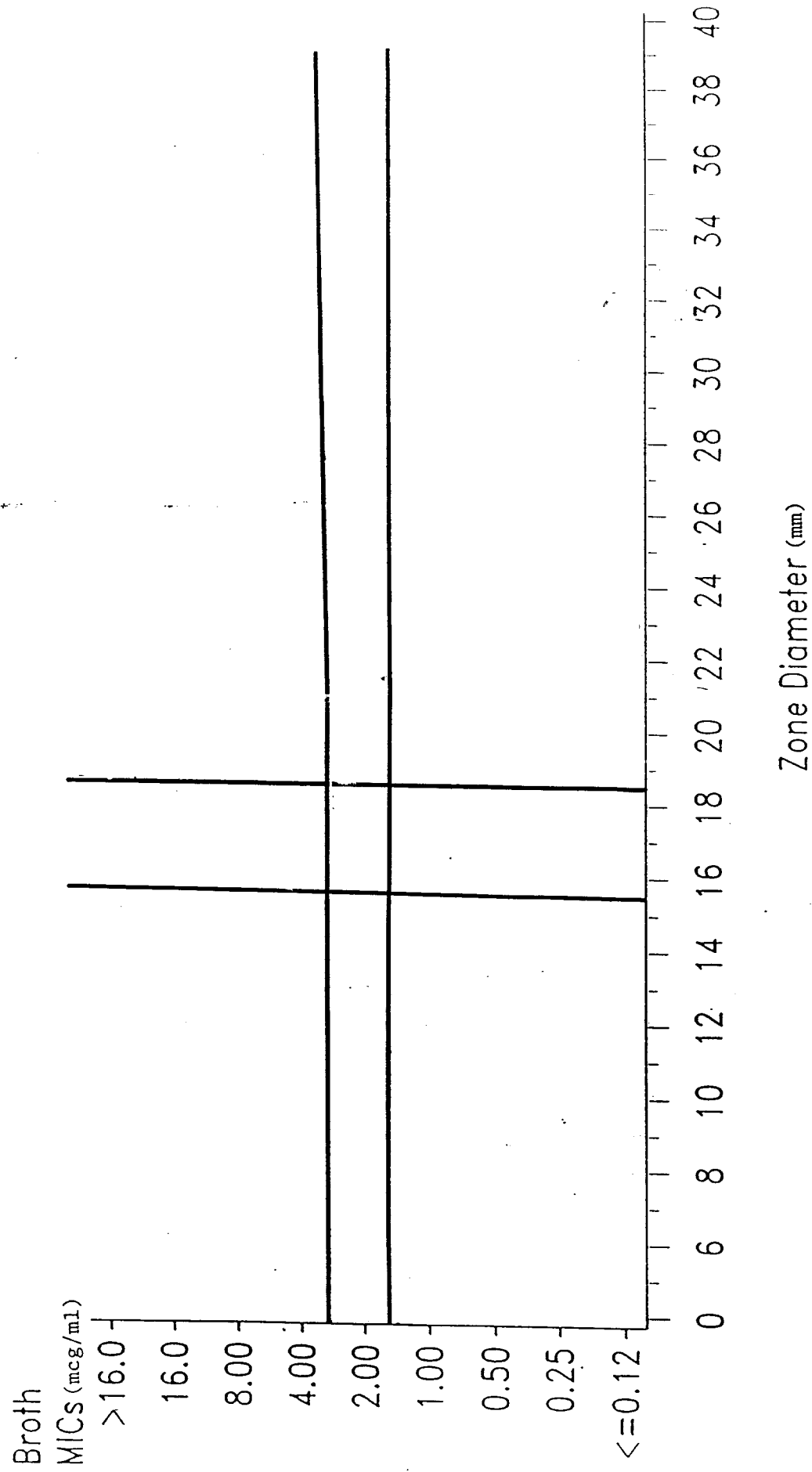


Figure 14. Scattergram generated from testing of 161 selected pneumococcal culture collection against trovafloxacin. The isolates marked with an * are resistant to ofloxacin and containe either single parC (MIC = 4-8 mcg/ml) or double parC & gyrA (MIC = 16-128 mcg/ml) mutations.



6. Discussion of Disk Diffusion Interpretive Breakpoints for *Streptococcus* spp. other than *Streptococcus pneumoniae*

Figures 15 to 17 are scattergrams for clinical isolates of *Streptococcus* spp. other than *S. pneumoniae* obtained during the clinical trials. In this section the sponsor has included all the isolates regardless of the clinical outcome. When one compares the U.S./Canada strains (Figure 15) with the non-U.S./Canada strains (Figure 16) it becomes evident that there is a tendency for the U.S./Canada isolates to have slightly higher MICs than the non-U.S./Canada strains. So it is the opinion of this reviewer that combining the data would strengthen the data. Figure 17 is the scattergram resulting from the combined data. There were only five resistant isolates, two from U.S./Canada and 3 from one-U.S./Canada. These five isolates are not sufficient to warrant selection of a resistant break point either for MIC or disk diffusion methods. However, it is apparent that the susceptible MIC breakpoint of 1 µg/mL nicely separates the susceptible from non-susceptible isolates. If one would want to set a resistant breakpoint despite the limited data for the resistant isolates, 4 µg/mL would seem appropriate leaving 2 µg/mL as intermediate.

Using the error rate-bound method and the fact that the ideal (in the sense of reading accuracy) zone sizes should not be less than 15 mm, the disk diffusion susceptible breakpoint should be set at ≥ 18 mm. This would result in an acceptable very major and major error rates of 0.27% and 0.53% respectively.

In a study by Arthur Barry et al. that was presented in the NCCLS fastidious organism working group during the general meeting on June 1-3, 1997 a scattergram was presented on 405 *Streptococcus* spp. other than *S. pneumoniae* isolates (Figure 18). The highest MIC and zone diameter obtained from these isolates were 2.0 µg/mL and 18 mm, respectively. This study like the sponsor's clinical trials did not allow for setting any breakpoints other than susceptible for both MIC and disk diffusion methods. However this study reconfirmed that the susceptible MIC of ≤ 1 µg/mL and susceptible zone diameter of ≥ 18 mm were appropriate.

For the sake of simplicity and consistency, despite the limited data for resistant Streptococcal isolates other than *S. pneumoniae*, this reviewer would like to also set intermediate and resistant breakpoints for both MIC and disk diffusion methods. If one chooses MICs of 1.0, 2.0, and 4.0 µg/mL for susceptible, intermediate, and resistant breakpoints respectively, then using the error rate-bound method, the corresponding zone sizes from the clinical data would be ≥ 19 and ≤ 15 for susceptible, intermediate, and resistant, respectively. These breakpoints would result in no very major error rate, 0.53% major error rate, and 0.8% minor error rate. The corresponding zone sizes from Arthur Barry's data would be the same with no very major or major error rates and only 0.25% minor error rate.

Table 26 shows overall trends in the data demonstrating that the above disk diffusion interpretive breakpoints serve as good predictors of therapeutic outcome for *Streptococcus* spp. other than *S. pneumoniae*. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 85% bacterial eradication and 88% clinical cure rates

Figure 15 . Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) USA/Canada
 All *Streptococcus* spp, except *S. Pneumoniae* (n = 314)

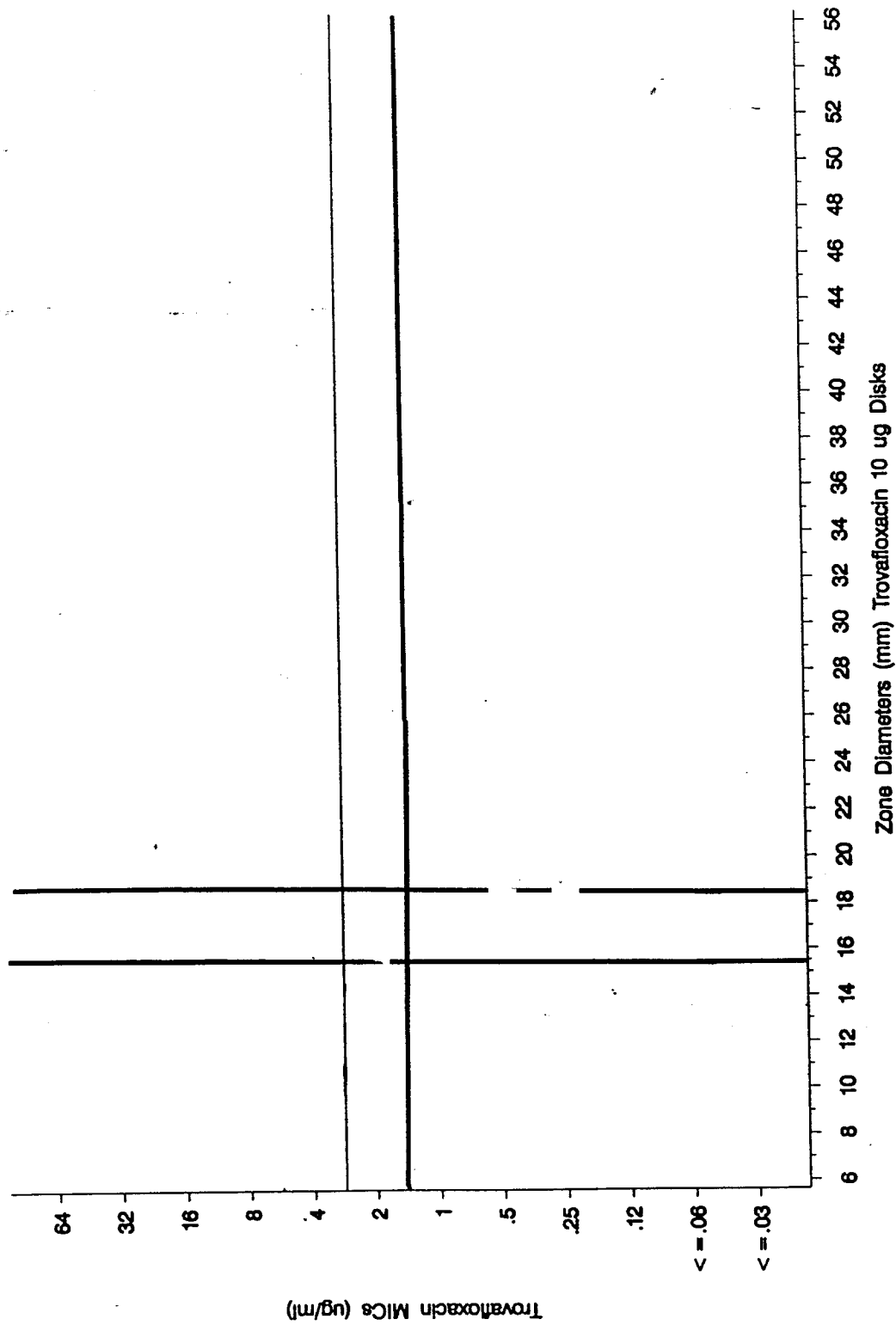


Figure 16. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) Non - USA/Canada
All Streptococcus spp, except S. Pneumoniae (n=61)

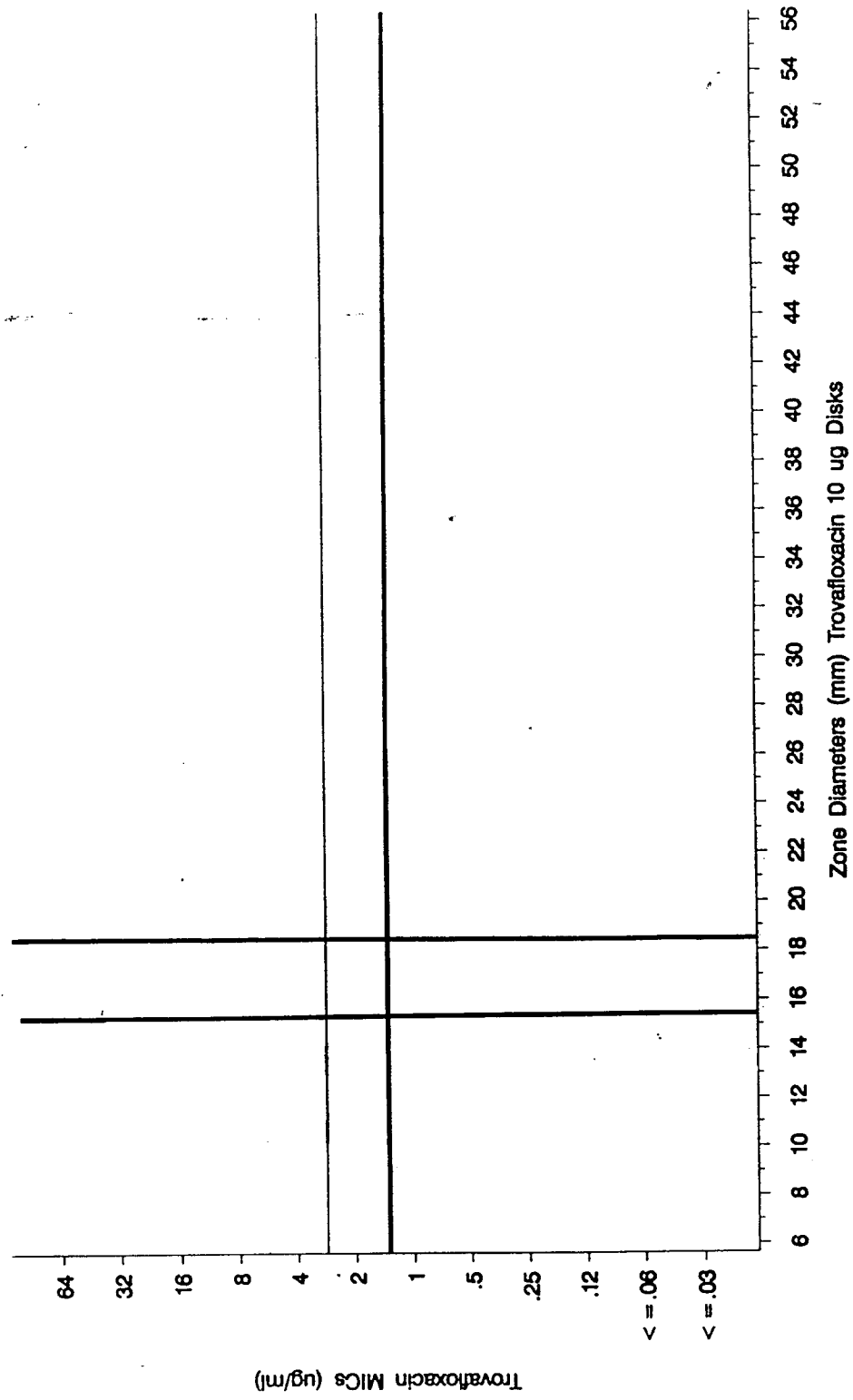


Figure 17. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)
 All *Streptococcus* spps, except *S. Pneumoniae* (n = 375)

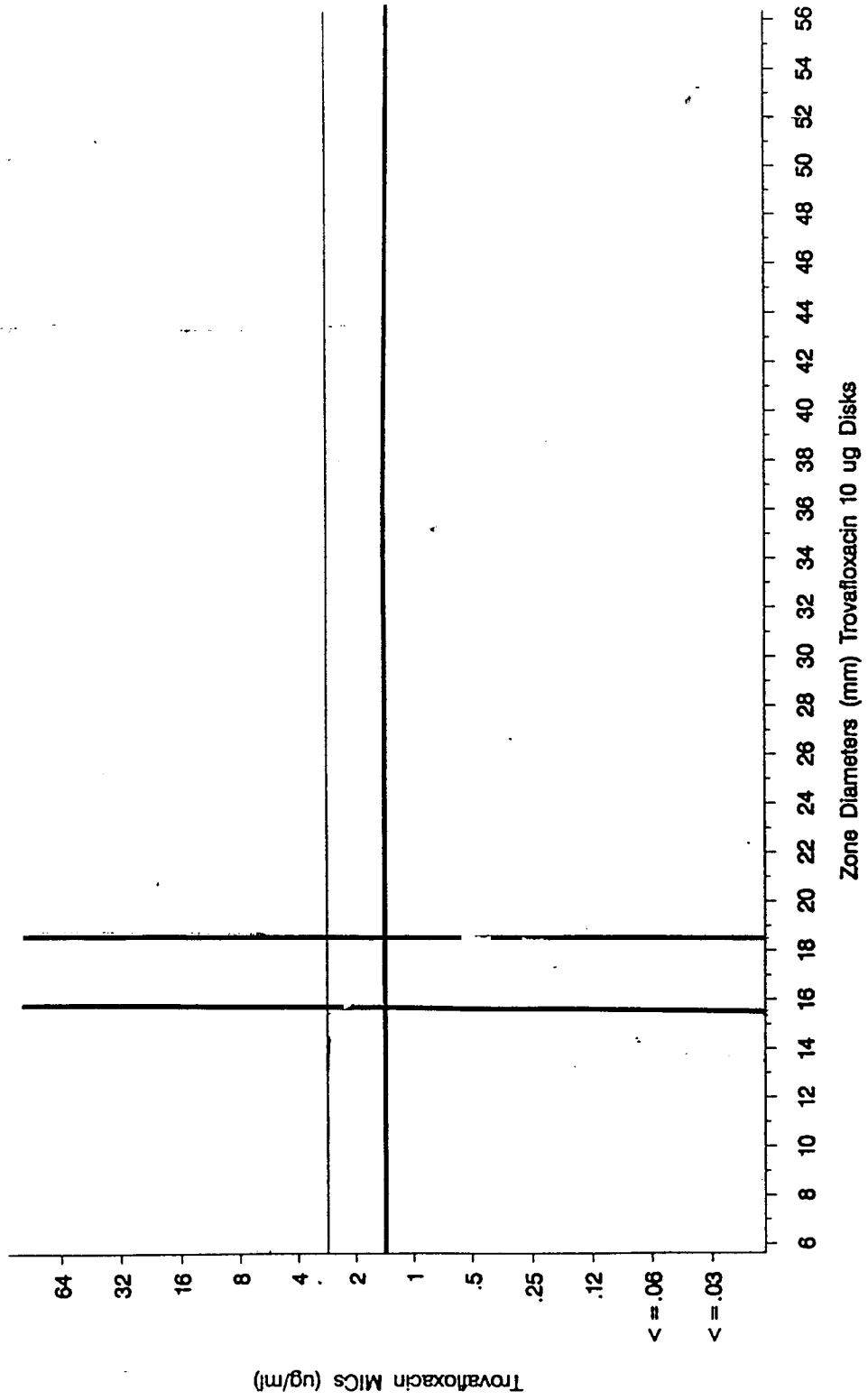
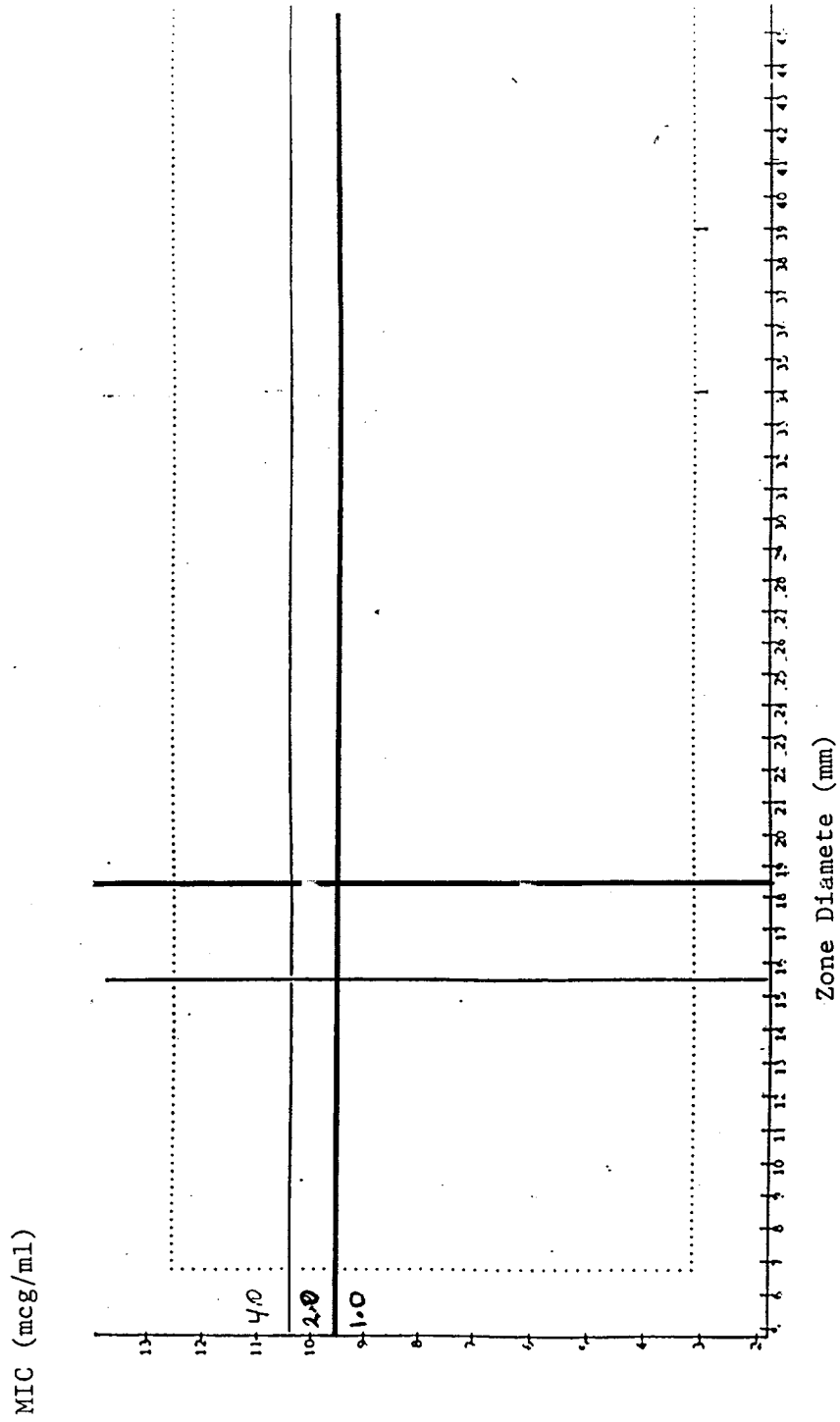


Figure 18. Scattergram generated from 405 selected *Streptococcus* spp. other than *S. pneumoniae* culture collection against Trovan



7. Discussion of Disk Diffusion Interpretive Breakpoints for *Neisseria gonorrhoeae*

Figure 19 is the scattergram for clinical isolates of *Neisseria gonorrhoea* obtained during the clinical trials. In this scattergram the sponsor has included all the U.S. isolates regard less of the clinical outcome. The isolates were not divided into U.S. and non-U.S. because there were no non-U.S. isolates in these studies. According to these data the highest MIC obtained was 0.03 $\mu\text{g}/\text{mL}$. Considering that the AUC_{0-24} for the proposed 100 mg single dose is $9.4 \pm 1.5 \mu\text{g} \cdot \text{h}/\text{mL}$, the MIC susceptible breakpoint of 0.125 $\mu\text{g}/\text{mL}$ would seem appropriate (AUC/MIC ratio would be 78). The smallest disk diffusion zone diameter obtained was 30 mm (excluding an out-lire at 6 mm). Using the error rate-bound method or the rule of 3 mm smaller than the zone for 99.9 % of the isolates, the disk diffusion susceptible breakpoint based on MIC susceptible breakpoint of $\leq 0.125 \mu\text{g}/\text{mL}$ would be ≥ 27 mm. Since there were no resistant isolates recovered in the clinical trials this reviewer will refer to a study performed by Ronald Jones et al. that was presented to the NCCLS fastidious organism working group during the general meeting on June 1-3, 1997. Ronald Jones presented a scattergram on 150 selected strains of *Neisseria gonorrhoeae* having defined mechanism of resistance (Figure 20). One hundred strains were classified as ciprofloxacin-susceptible. These ciprofloxacin-susceptible strains exhibited varied patterns of susceptibility to penicillin: seven strains susceptible, 54 strains intermediate, 24 strains resistant by means of beta-lactamase production, and 15 additional strains with chromosomally mediated resistance. Fifty strains demonstrated decreased susceptibility to ciprofloxacin: 44 strains were classified as having low-level resistance and six strains had high-level resistance. The MIC_{50} and MIC_{90} of these 50 isolates against trovafoxacin were 0.06 and 0.25 $\mu\text{g}/\text{mL}$. These strains were collected from diverse geographic locations with 27 strains coming from Japan, 17 strains from the U.S., and six strains from the Netherlands. The 27 strains from Japan included 16 strains with *gyrA*, and 11 strains with double *gyrA* and *parC* mutations. The highest MIC and lowest disk diffusion zone diameter obtained from these isolates were 0.5 $\mu\text{g}/\text{mL}$ and 29 mm, respectively. As it is shown in Figure 20 the MIC susceptible breakpoint of $\leq 0.125 \mu\text{g}/\text{mL}$ would separate most of the double mutations from the single and non-mutated isolates. Using the error rate-bound method the corresponding zone diameters would be ≥ 37 mm. Choosing 0.25 and $\geq 0.5 \mu\text{g}/\text{mL}$ for intermediate and resistant categories, respectively the corresponding intermediate and resistant zone diameters would be ≥ 37 mm and ≤ 33 mm respectively. With these breakpoints there are no very major or major errors and only 0.7% minor errors.

If these breakpoints are chosen, the error rate-bound examination of the scattergram from the clinical isolates (excluding an out-lire at 6 mm) would predict no very major or minor errors and 3.0% major errors. This major error rate, even thought on the high side, is acceptable. Therefore this reviewer would suggest the MIC and disk diffusion breakpoints of ≤ 0.125 , 0.25, $\geq 0.5 \mu\text{g}/\text{mL}$ and ≥ 37 , ≤ 33 mm for susceptible, intermediate, and resistant respectively.

Table 26 shows overall trends in the data demonstrating that the above disk diffusion interpretive breakpoints serve as good predictors of therapeutic outcome for *Neisseria gonorrhoea*. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and

clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 100% bacterial eradication and 91% clinical cure rates.

TABLE 26. Relationship Between Zone Diameter and Pathogen Eradication and Clinical Cure Rates in patients treated with Trovafloracin I.V. and Tablets

Organism Group	Susceptibility	Pathogen Eradication Rate			Clinical Cure Rate		
		No. of Pathogens	No. of Pathogens Eradicated ^a	% Eradicated ^a	No. of Patients	No. of Patients Cured ^b	% Cured ^b
<i>Haemophilus</i> spp.	S (≥ 22 mm)	164	157	96	164	150	92
	R (< 22 mm)	1	1	100	1	1	100
<i>S. pneumoniae</i>	R (≤ 15 mm)	0	--	--	0	--	--
	I (16-18 mm)	0	--	--	0	--	--
	S (≥ 19 mm)	100	91	91	100	91	91
<i>Streptococcus</i> spp other than <i>S. pneumoniae</i>	R (≤ 15 mm)	3	3	100	3	3	100
	I (16-18 mm)	3	1	33	3	3	100
	S (≥ 19 mm)	154	130	85	154	136	88
<i>M. catarrhalis</i>	R (≤ 14 mm)	0	--	--	0	--	--
	I (15-17 mm)	0	--	--	0	--	--
	S (≥ 18 mm)	58	55	95	58	53	91
<i>N. gonorrhoeae</i>	R (≤ 33 mm)	2	2	100	2	2	100
	I (34-36 mm)	0	--	--	0	--	--
	S (≥ 37 mm)	23	23	100	23	21	91
<i>S. aureus</i>	R (≤ 14 mm)	7	4	57	7	7	100
	I (15-17 mm)	17	12	70	17	15	88
	S (≥ 18 mm)	305	253	83	305	279	91
<i>Staphylococcus</i> spp. other than <i>S. aureus</i>	R (≤ 14 mm)	15	13	87	15	14	93
	I (15-17 mm)	9	7	78	9	7	78
	S (≥ 18 mm)	201	180	90	201	185	92
<i>Enterococcus</i> spp.	R (≤ 14 mm)	11	7	64	11	9	82
	I (15-17 mm)	7	7	100	7	7	100
	S (≥ 18 mm)	98	85	87	98	92	94
<i>Enterobacteriaceae</i> spp. ^c	R (≤ 14 mm)	28	18	64	28	22	79
	I (15-17 mm)	10	6	60	10	6	60
	S (≥ 18 mm)	560	503	89	560	508	91
Gram-negative nonfermenters ^d	R (≤ 14 mm)	9	7	78	9	9	100
	I (15-17 mm)	10	6	60	10	9	90
	S (≥ 18 mm)	100	67	67	100	85	85

^a Including eradicated and presumed eradicated pathogens

^b Including cured and improved patients

^c Excluding all *Acinetobacter* spp., *Pseudomonas* spp., and *S. maltophilia*

^d Includes all *Acinetobacter* spp., *Pseudomonas* spp. and *S. maltophilia*

Figure 19. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)
Neisseria gonorrhoea (n=66)

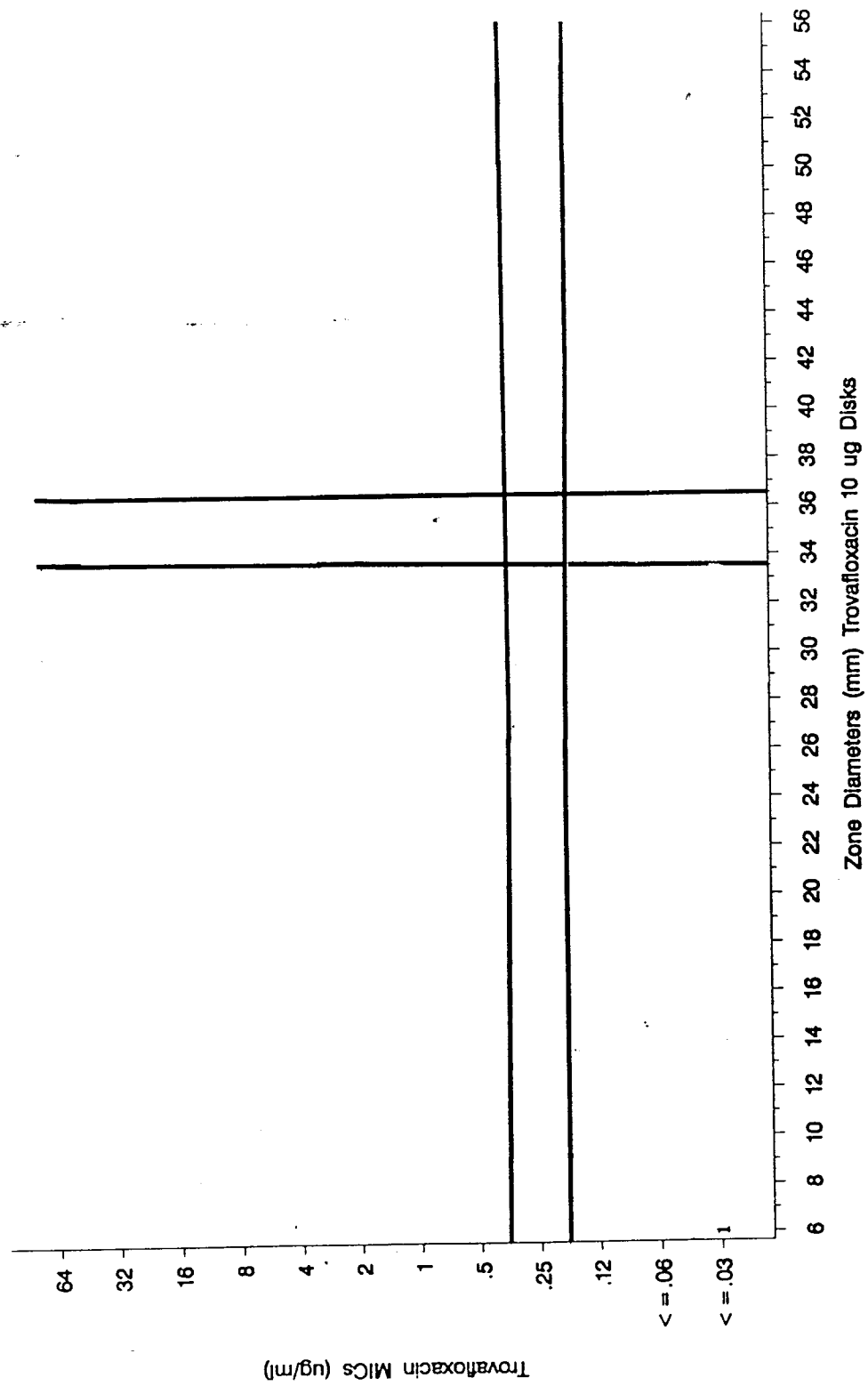
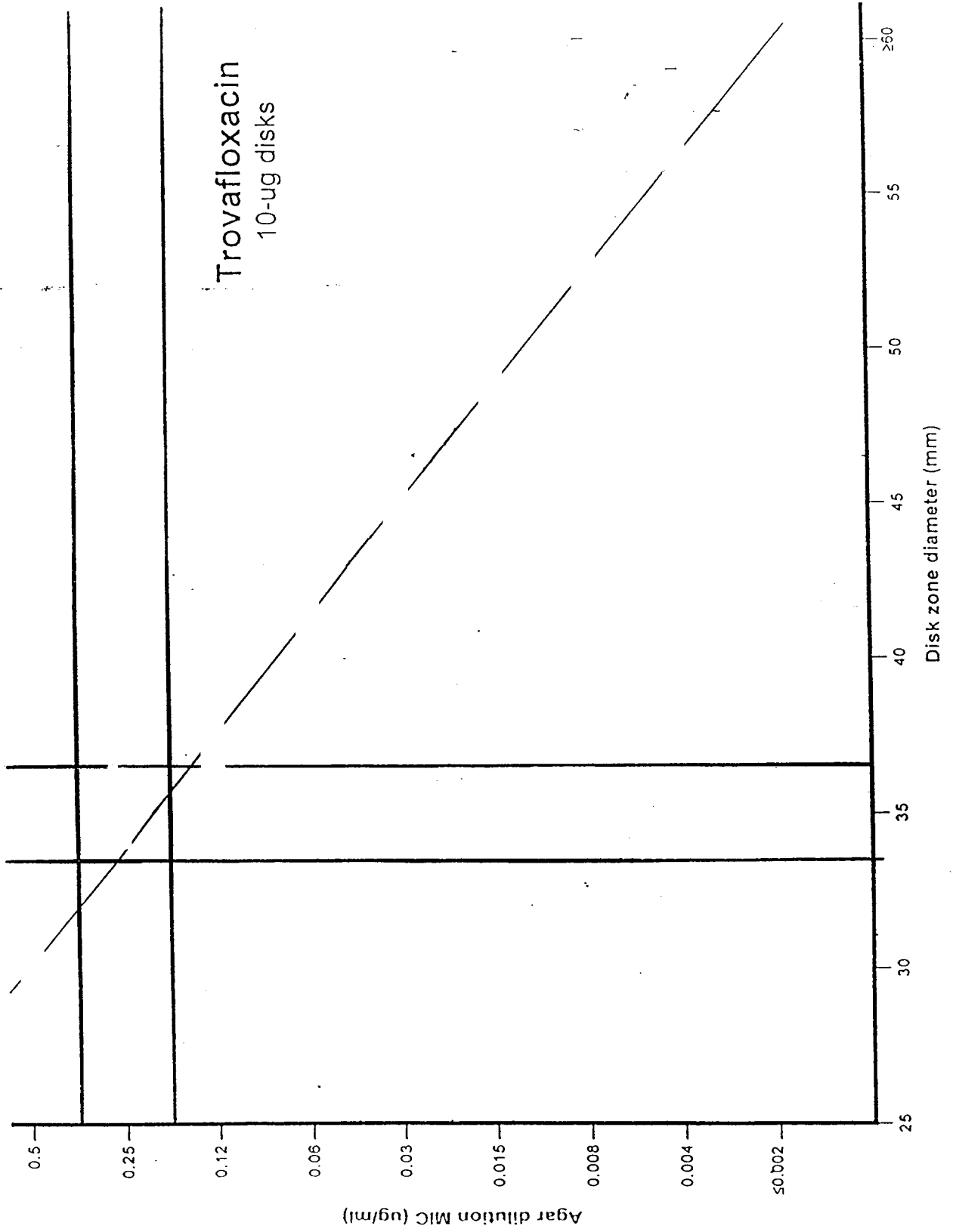


Figure 20. Scattergram of 150 gonococcal isolates including 50 strains from ciprofloxacin/ ofloxacin therapy failures,



8. Discussion of Disk Diffusion Interpretive Breakpoints for Non-Fastidious Aerobic Organisms

Figures 21 to 23 are scattergrams for clinical isolates of all non-fastidious aerobic organisms obtained during the clinical trials. In this section the sponsor has included all the isolates regardless of the clinical outcome. When one compares the U.S./Canada strains (Figure 21) with the non-U.S./Canada strains (Figure 22) it becomes evident that there is not much difference between the susceptibility patterns of the two groups. Therefore, one may combine the data from the U.S. and non-U.S. studies (Figure 23) and using the error rate-bound method determine the disk diffusion breakpoints based on MIC breakpoints of ≤ 1 , 2.0, and ≥ 4.0 $\mu\text{g/mL}$ for susceptible, intermediate and resistant, respectively.

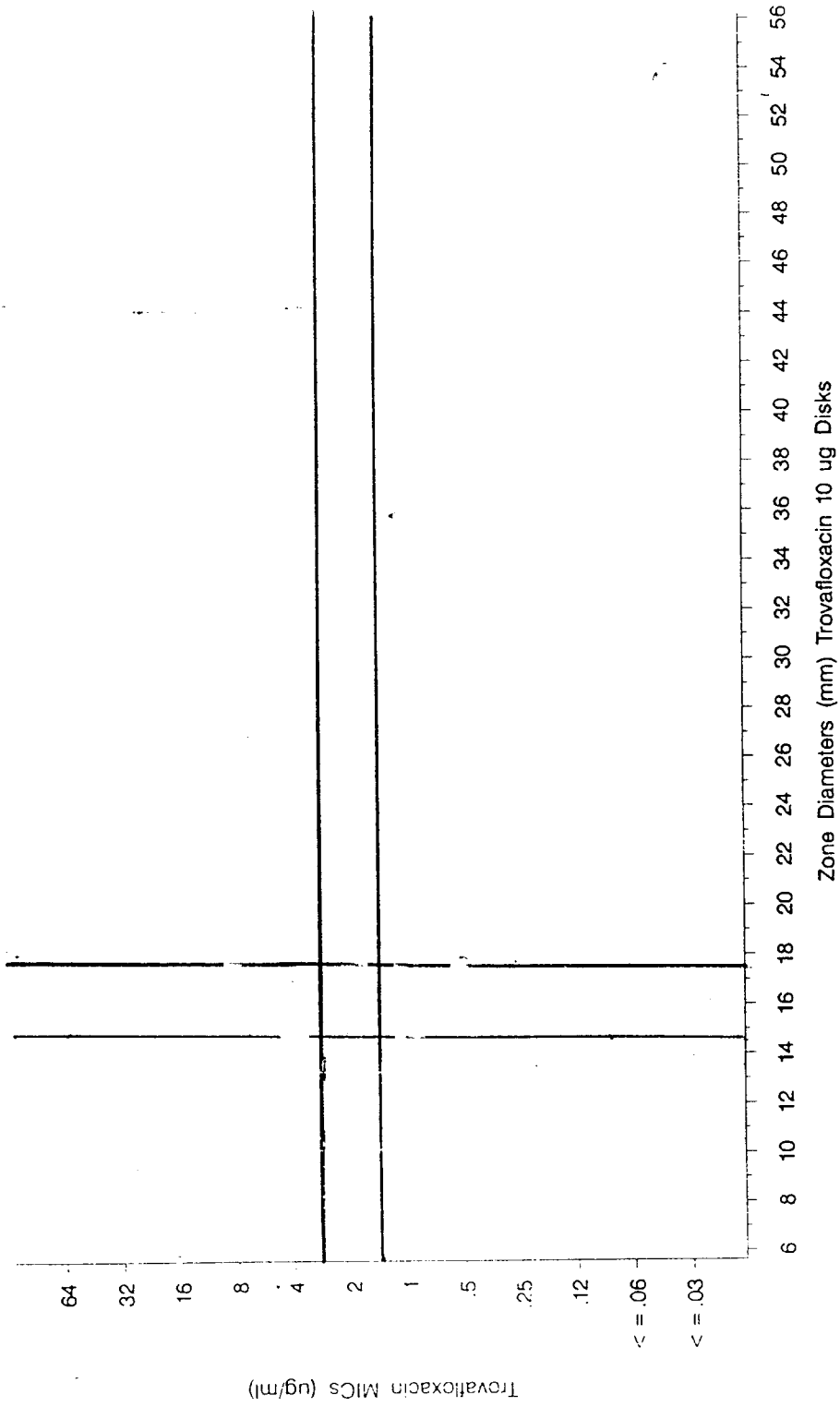
Using the error rate-bound method the disk diffusion susceptible, intermediate, and resistant breakpoints should be set at ≥ 18 , ≥ 17 , and ≤ 14 mm, respectively. This would result in an acceptable very major and major and minor error rates of 0.36%, 0.36%, and 3.4%, respectively.

If one considers MIC breakpoints of ≤ 2 , 4.0, and ≥ 8.0 $\mu\text{g/mL}$ for susceptible, intermediate and resistant, respectively, using the error rate-bound method the disk diffusion susceptible, intermediate, and resistant breakpoints should be set at ≥ 17 , ≥ 16 , and ≤ 13 mm, respectively. This would result in an acceptable very major and major and minor error rates of 0.17%, 0.54%, and 3.6%, respectively (See Figures 24-26 and addendum by Dr. Albert Sheldon)

Table 26 show overall trends in the data demonstrating that the above disk diffusion interpretive breakpoint serves as good predictors of therapeutic outcome for non-fastidious aerobic organisms. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, for *Moraxella catarrhalis*, susceptible disk diffusion result correspond with 95% bacterial eradication and 91% clinical cure rates; for *Staphylococcus aureus*, susceptible disk diffusion result correspond with 83% bacterial eradication and 91% clinical cure rates; for staphylococci other than *S. aureus*, susceptible disk diffusion result correspond with 90% bacterial eradication and 92% clinical cure rates; for *Enterococcus* spp., susceptible disk diffusion result correspond with 87% bacterial eradication and 94% clinical cure rates; for Enterobacteriaceae spp., susceptible disk diffusion result correspond with 89% bacterial eradication and 91% clinical cure rates; and for gram-negative non-fermenters, susceptible disk diffusion result correspond with 67% bacterial eradication and 85% clinical cure rates.

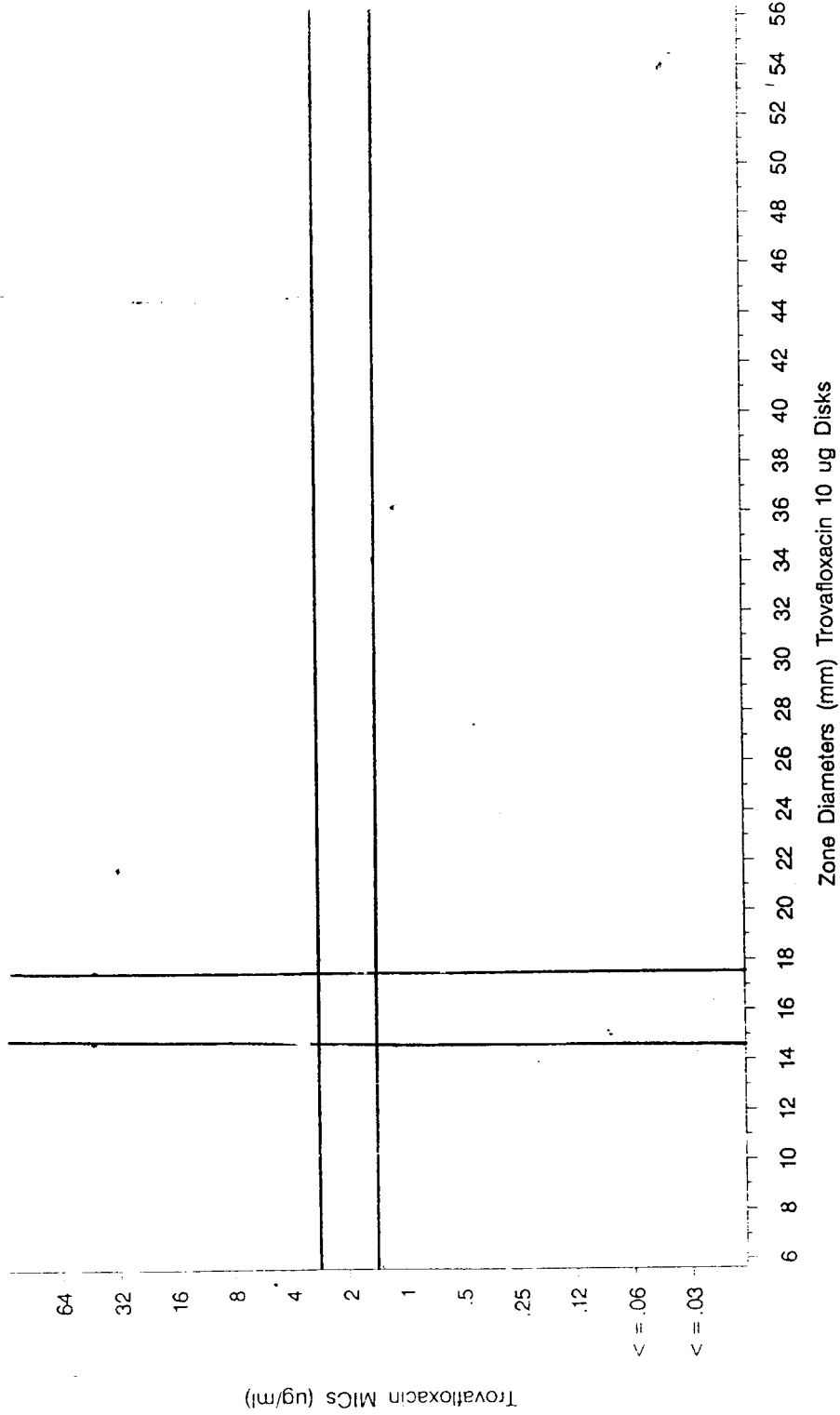
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Figure 21. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) USA/Canada
 All Staph spp, all Enterococcal spp, all Enterobacteriaceae and all gram negative nonfermenters (n = 2282)



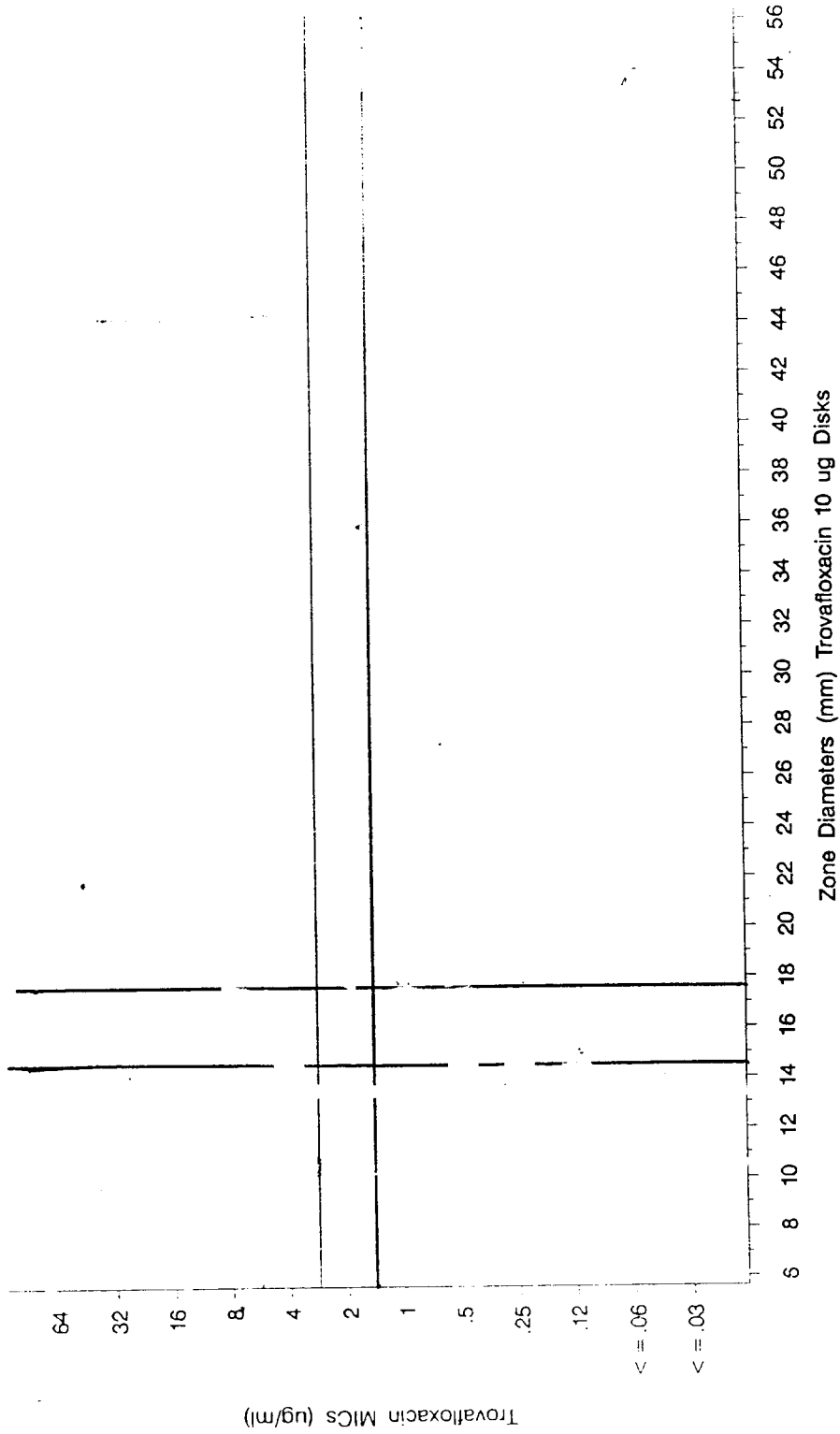
Very Major Errors = 3 (0.13% of Total or 2.94% of 67 Resistant Strains)
 Major Errors = 5 (0.22% of Total or 0.23% of 2175 Susceptible Strains)
 Minor Errors = 42 (1.84% of Total or 1.93% of 2175 Susceptible Strains)

Figure 22. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) Non - USA/Canada
 All Staph spp, all Enterococcal spp, all Enterobacteriaceae and all gram negative nonfermenters (n=1071)



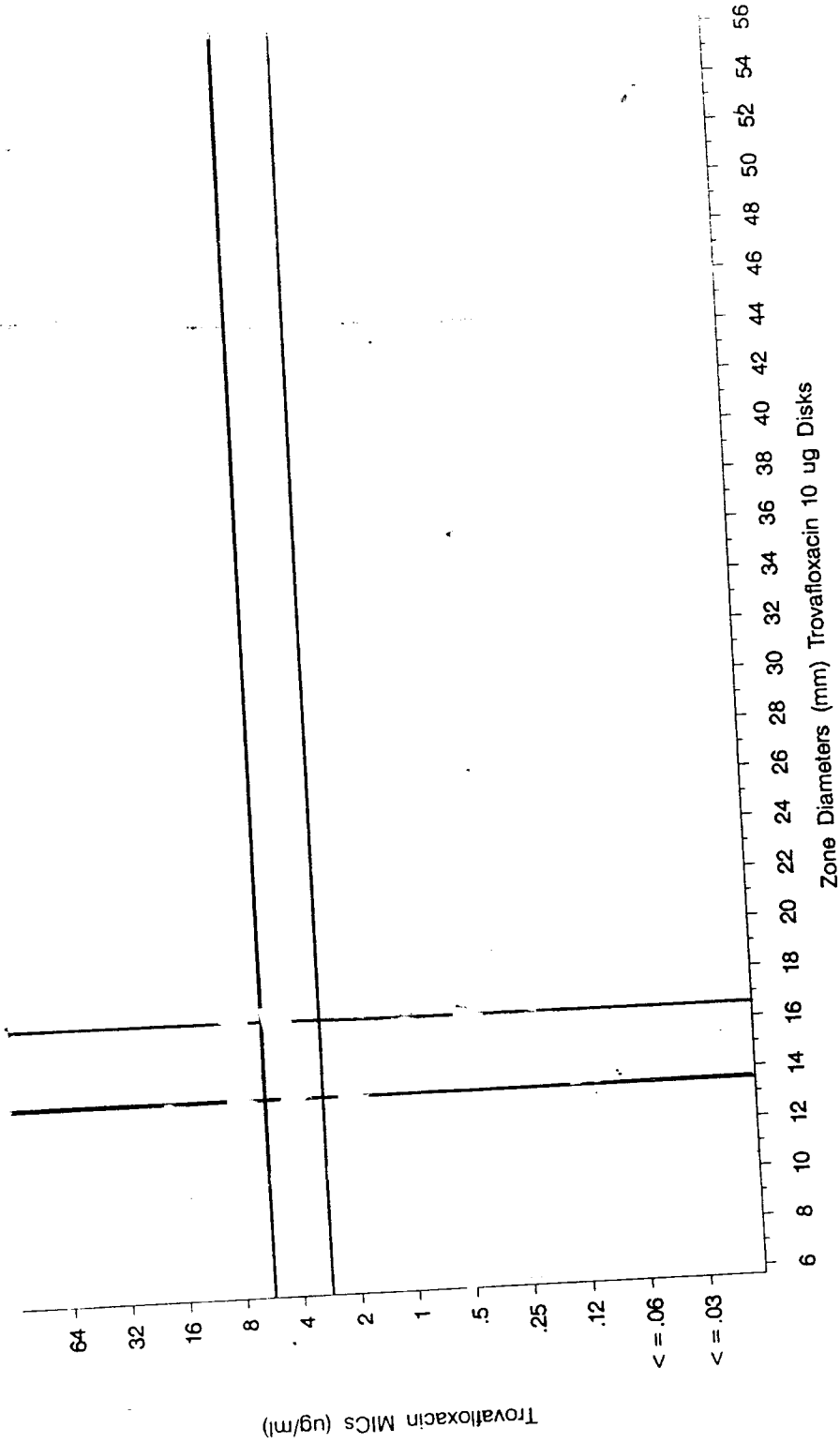
Very Major Errors = 3 (0.28% of Total or 3.45% of 37 Resistant Strains)
 Major Errors = 3 (0.28% of Total or 0.29% of 1022 Susceptible Strains)
 Minor Errors = 13 (1.21% of Total or 1.27% of 1022 Susceptible Strains)

Figure 23. Trovafloxacin MICs (ug/m) vs Zone Diameter (mm)
 All Staph spp, all Enterococcal spp, all Enterobacteriaceae and all gram negative nonfermenters (n = 3353)



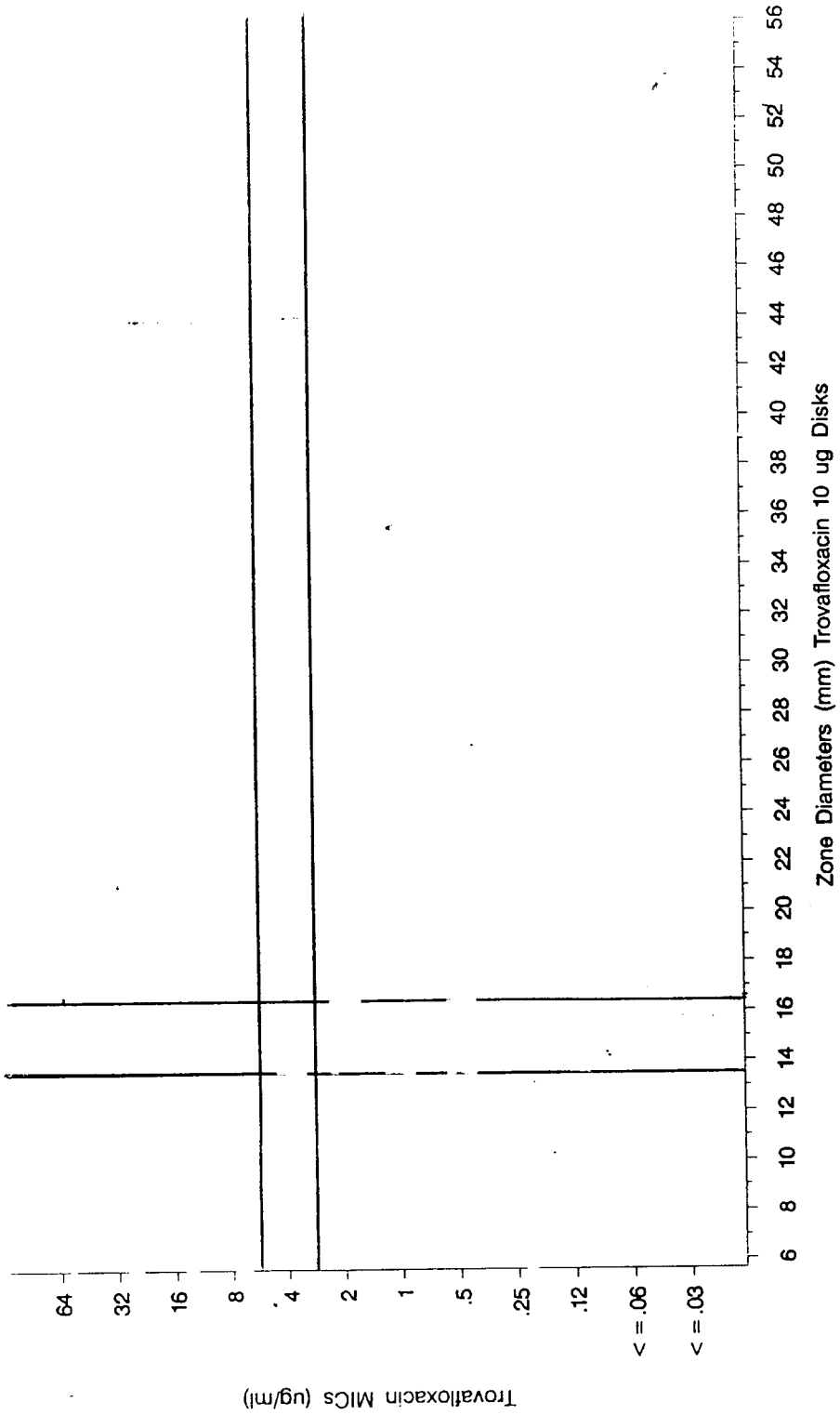
Very Major Errors = 6 (0.18% of Total or 3.10% of 104 Resistant Strains)
 Major Errors = 8 (0.24% of Total or 0.25% of 3197 Susceptible Strains)
 Minor Errors = 55 (1.64% of Total or 1.72% of 3197 Susceptible Strains)

Figure 24. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) USA/Canada
 All Staph spp, all Enterococcal spps, all Enterobacteriaceae and all gram negative nonfermenters (n = 2282)



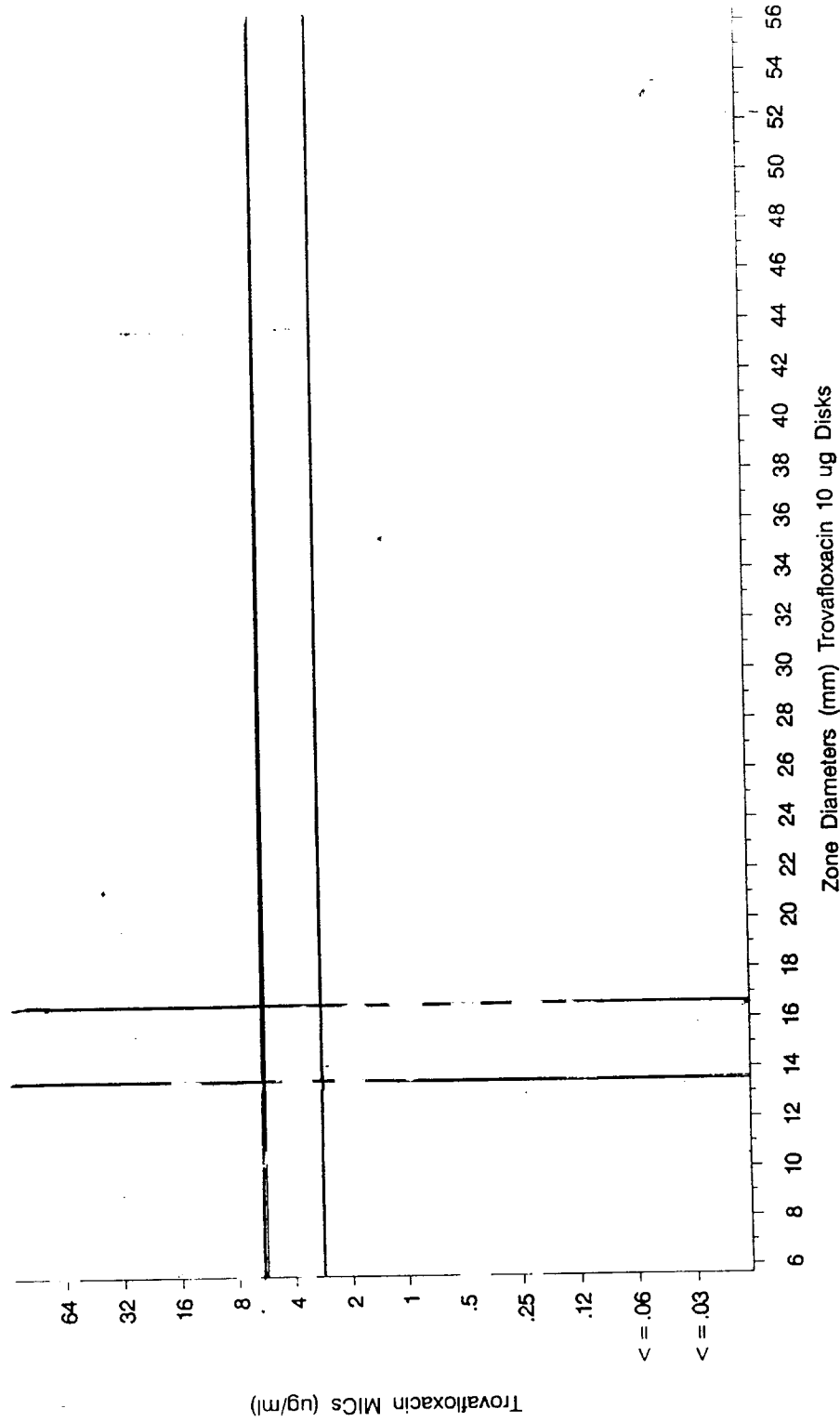
Very Major Errors = 3 (0.13% of Total or 2.94% of 67 Resistant Strains)
 Major Errors = 5 (0.22% of Total or 0.23% of 2175 Susceptible Strains)
 Minor Errors = 42 (1.84% of Total or 1.93% of 2175 Susceptible Strains)

Figure 25. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) Non - USA/Canada
 All Staph spp, all Enterococcal spp, all Enterobacteriaceae and all gram negative nonfermenters (n=1071)



Very Major Errors = 3 (0.28% of Total or 3.45% of 37 Resistant Strains)
 Major Errors = 3 (0.28% of Total or 0.29% of 1022 Susceptible Strains)
 Minor Errors = 13 (1.21% of Total or 1.27% of 1022 Susceptible Strains)

Figure 26. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)
 All Staph spp, all Enterococcal spps, all Enterobacteriaceae and all gram negative nonfermenters (n = 3353)



Very Major Errors = 6 (0.18% of Total or 3.10% of 104 Resistant Strains)
 Major Errors = 8 (0.24% of Total or 0.25% of 3197 Susceptible Strains)
 Minor Errors = 55 (1.64% of Total or 1.72% of 3197 Susceptible Strains)

V. CONCLUSIONS

Trovafloracin is a new antimicrobial of the fluoronaphthyridone class. Given its chemical structure and mechanism of action against bacterial DNA gyrase and topoisomerase IV, trovafloracin can be considered to be among the fluoroquinolone antimicrobial agents.

Trovafloracin has an elimination half-life in humans of around 10 to 12 hours, which suggests that it can be dosed once daily for some indications. The projected dose for serious infections is 200 to 300 mg once daily. Accumulation effects of multiple oral doses (1.3-fold) produce peak blood levels of between 2.1 and 4.1 $\mu\text{g/mL}$ for a 200 mg oral regimen of trovafloracin. Peak blood levels following multiple 300 mg intravenous doses of alatrofloracin range

Trovafloracin is 70% bound to human serum protein which is higher than that of other fluoroquinolones. *In vitro* studies with some enteric organisms show that addition of 70% human serum to susceptibility test medium raises the MICs of trovafloracin from 2 to 32-fold. This appears to have a minor effect on the activity of trovafloracin, however, since efficacy in mouse protection studies paralleled the *in vitro* potency of trovafloracin against challenge pathogens.

The elimination of trovafloracin is predominantly by the biliary route. Less than 10% of drug is recovered intact in the urine, resulting in peak urine levels of around 4.5 $\mu\text{g/mL}$ from 0-2 h following a 100 mg oral dose. Peak urine levels are around 18 $\mu\text{g/mL}$ following a 300 mg dose.

Unlike several other fluoroquinolones, trovafloracin appears to lack phototoxic activity and it does not interfere with the metabolism of theophylline. Coadministration of trovafloracin with food does not markedly affect the extent of absorption. Age or gender differences minimally impact the pharmacokinetic profile of trovafloracin.

Trovafloracin seems more active than ciprofloracin and ofloxacin and as active as sparfloracin against some Gram-positive organisms, and anaerobes. The published susceptibility studies focused on testing the activity of trovafloracin against *S. pneumoniae*, evaluating a number of penicillin-susceptible and -resistant isolates. The MIC range of trovafloracin against 1,867 penicillin-susceptible pneumococci from nineteen studies and the median MIC₉₀ was 0.125 $\mu\text{g/mL}$. This degree of activity was 16, 32, and 4-fold greater than that observed with ciprofloracin, ofloxacin, and sparfloracin, respectively. Trovafloracin is equally active against pneumococci that were penicillin-resistant. The MIC₉₀ range for trovafloracin against 498 penicillin-resistant isolates and the least susceptible strain had an MIC of 0.25 $\mu\text{g/mL}$. *In vitro* selection of resistance studies indicated that step-wise mutation in *grrA* (topoisomerase IV) and *gyrA* (DNA gyrase) are necessary to confer high-level resistance to ciprofloracin (MIC ≥ 64 $\mu\text{g/mL}$) in pneumococci. Trovafloracin is still quite active against the first-step mutants (MIC = 0.5 $\mu\text{g/mL}$), although it is not active against isolates with mutations in both genes (MIC = 8 $\mu\text{g/mL}$). Each step of mutation occurs at a low frequency of 1×10^{-9} . This low mutation frequency, coupled with the fact that resistance loci are not plasmid encoded, suggests that high-level resistance to trovafloracin may not be widespread in *S. pneumoniae*.

Trovafloracin is more active than ciprofloracin against staphylococci. Strains of MSSA have an MIC₉₀ range to trovafloracin, compared with values of 0.5 to 8.0 $\mu\text{g/mL}$

for ciprofloracin. Trovafloracin is also active against some of MRSA that are also resistant to ciprofloracin. The median MIC₉₀s against such isolates for trovafloracin, ciprofloracin, ofloxacin, and sparfloracin were 2.0, >16, 16, and 8 µg/mL, respectively. Clearly, while trovafloracin is active against some isolates of *S. aureus*, it is not predicted to be efficacious against isolates with MICs falling above the breakpoint of 1 µg/mL.

The activity of trovafloracin was evaluated against 574 isolates of vancomycin-susceptible *E. faecalis*. Trovafloracin had an MIC₉₀ range _____ compared with values of 1.0 to 32 µg/mL for ciprofloracin. Trovafloracin was inactive against vancomycin-resistant isolates of *E. faecalis* with an MIC₉₀ range _____ for 33 isolates. Neither trovafloracin nor ciprofloracin were very active against vancomycin-resistant isolates of *E. faecium*. The MIC₉₀ ranges for trovafloracin and ciprofloracin were _____ respectively for 285 such isolates.

In vitro trovafloracin is active against the group of pathogens that are associated with community acquired pneumonia. As described above, trovafloracin is more active than ciprofloracin, ofloxacin, and sparfloracin against pneumococci. Trovafloracin is as active as ciprofloracin, ofloxacin, and sparfloracin against isolates of *Haemophilus influenzae*, *M. catarrhalis*, *L. pneumophila*. Against *M. pneumoniae*, trovafloracin is slightly more active than ciprofloracin or ofloxacin and as active as sparfloracin _____. The available data suggest that trovafloracin like sparfloracin should provide broad coverage for community acquired pneumonia, particularly given its activity against pneumococci.

The spectrum of trovafloracin suggests that it might have clinical utility against nosocomial pneumonia pathogens given its improved *in vitro* activity against *S. pneumoniae*. Trovafloracin has activity against members of the *Enterobacteriaceae* that is comparable to that of ciprofloracin and sparfloracin. Median MIC₉₀ values of trovafloracin were ≤1 µg/mL against *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *M. morgani*. Ciprofloracin and sparfloracin had better activity than trovafloracin against *E. cloacae*. Median MIC₉₀s for trovafloracin for *P. aeruginosa*, *S. marcescens*, and *S. maltophilia* were 2.0, 2.5, and 2.0 µg/mL, respectively. The latter group of organisms is generally less susceptible to fluoroquinolones, and the activity observed for trovafloracin is similar to that of ciprofloracin and sparfloracin. Inspection of the data from several reports suggests that trovafloracin is inactive against pseudomonads that have already acquired resistance to ciprofloracin.

Trovafloracin possesses activity against one of the organisms associated with sexually transmitted disease. It was essentially equivalent in potency to ciprofloracin against 509 isolates of *N. gonorrhoeae*. However trovafloracin was inferior to sparfloracin against 70 isolates of *N. gonorrhoeae*.

Trovafloracin was active against 50 gonococci with reduced susceptibility to ciprofloracin (ciprofloracin MIC₉₀ = 1.0 µg/mL versus trovafloracin MIC₉₀ = 0.25 µg/mL).

Trovafloracin is active against the most commonly isolated bacteria in urinary tract infections and prostatitis. Given the limited levels of drug recovered in urine it remains to be seen whether adequate coverage will be achieved with less susceptible pathogens in complicated UTI and pyelonephritis.

A slight possible advantage of trovafloracin over ciprofloracin and ofloxacin involves its *in vitro* activity against anaerobes. The MIC₉₀ range of trovafloracin against 1,404 isolates of *B. fragilis*

from twelve studies was active than ciprofloracin against this species. At the median MIC₉₀ trovafloracin was 32 more active than ciprofloracin against this species. During clinical trials however, of 13 isolates of *Bacteroides* spp. only 9 (69%) were eradicated (no information on clinical outcome is available). This degree of eradication seems to be in contradiction with the *in vitro* data. This degree of difference in *in vitro* activity is less visible when one considers anaerobic species such as, *C. perfringens* (trova. MIC₉₀ of 0.25 verses cipro./oflox. MIC₉₀ of 0.5 µg/mL), *C. difficile* (trova. MIC₉₀ of 1.0 verses cipro./oflox. MIC₉₀ of 8.0 µg/mL), *Fusobacterium* spp. (trova. MIC₉₀ of 1.0 verses cipro. MIC₉₀ of 3 µg/mL), and peptostreptococci (trova. MIC₉₀ of 1.0 verses cipro. MIC₉₀ of 4.0 µg/mL). During clinical trials, there were no *C. difficile* or *C. perfringens* isolated and of 24 isolates of peptostreptococci 21 (88%) were eradicated (no information on clinical outcome is available).

The available data from Phase III trials indicate that using the MIC breakpoint of ≤ 1.0, 2.0, and ≥4 µg/mL for susceptible, intermediate and resistant respectively, of 1,954 isolates, 55 (2.8%) were resistant, 28 (1.4%) were intermediate and 1871 (95.8%) were susceptible to trovafloracin. As might be predicted, resistance was observed most frequently in isolates of enterococci, *P. aeruginosa*, and members of the *Enterobacteriaceae*. Few resistant isolates of *S. aureus*, *S. epidermidis*, and *S. haemolyticus*, Streptococci, and *Corynebacterium*, were also encountered.

VI. PACKAGE INSERT

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A. Isolates Approved

The following organisms may be placed in the label. The final decision on whether or not an organism should be in the clinical efficacy list will depend on the Medical Officer's final review of this product. If the clinical picture reveals that some of these genera/species are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise.

Trovafloracin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)

Staphylococcus aureus (methicillin-susceptible strains)

Staphylococcus epidermidis (methicillin-susceptible strains)

Streptococcus agalactiae

Streptococcus pneumoniae (penicillin-susceptible strains)

Streptococcus pyogenes

Viridans group streptococci

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Aerobic gram-negative microorganisms

Escherichia coli

Gardnerella vaginalis

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Moraxella catarrhalis

Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa

Anaerobic microorganisms

Bacteroides fragilis
Peptostreptococcus species
Prevotella species

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Other microorganisms

Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.** Trovafoxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of $\leq 1 \mu\text{g/mL}$ ($\leq 2 \mu\text{g/mL}$ for anaerobes) against most (90%) strains of the following microorganisms; however, the safety and effectiveness of trovafoxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic Gram-positive microorganisms

Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative microorganisms

Citrobacter freundii
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris

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Anaerobic microorganisms

Bacteroides distasonis
Bacteroides ovatus
Clostridium perfringens

Other microorganisms

Mycoplasma hominis
Ureaplasma urealyticum

B. Interpretive Criteria Established

The following MIC interpretive criteria should be used for testing non-fastidious aerobic organisms

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

OR (see addendum by Dr. Albert Sheldon)

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<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

The following zone diameter interpretive criteria should be used for testing non-fastidious aerobic organisms:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 18	Susceptible (S)
15-17	Intermediate (I)
≤ 14	Resistant (R)

OR (see addendum by Dr. Albert Sheldon)

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<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 17	Susceptible (S)
14-16	Intermediate (I)
≤ 13	Resistant (R)

The following MIC interpretive criteria should be used for testing *Haemophilus* spp.:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1.0	Susceptible (S)

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The following zone diameter interpretive criteria should be used for testing *Haemophilus* spp.:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 22	Susceptible (S)

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The following MIC interpretive criteria should be used for testing *Streptococcus* spp. including *Streptococcus pneumoniae*:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

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The following zone diameter interpretive criteria should be used for testing *Streptococcus* spp. including *Streptococcus pneumoniae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	Susceptible (S)
18-16	Intermediate (I)
≤ 15	Resistant (R)

The following MIC interpretive criteria should be used for testing *Neisseria gonorrhoeae*:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

The following zone diameter interpretive criteria should be used for testing *Neisseria gonorrhoeae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 37	Susceptible (S)
34-36	Intermediate (I)
≤ 33	Resistant (R)

The following MIC interpretive criteria should be used for testing anaerobic microorganisms:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

SPONSOR NOTIFICATION

The sponsor should be notified of the following:

- 1) The following organisms which the sponsor has placed in the first list (clinical efficacy list) must be deleted (see medical officers' reviews).

Aerobic gram-positive microorganisms:

Staphylococcus aureus (methicillin and cephalosporin-resistant strains)

Staphylococcus haemolyticus

Staphylococcus hominis

Staphylococcus simulans

Streptococcus anginosus

Streptococcus equisimilis

Streptococcus pneumoniae (penicillin-resistant strains)

Streptococcus species

Aerobic gram-negative microorganisms:

Enterobacter cloacae

Enterobacter species

Klebsiella oxytoca

Anaerobic microorganisms:

Bacteroides species

Bacteroides thetaiotaomicron

Corynebacterium species

Fusobacterium nucleatum

Fusobacterium species

Other microorganisms:

Gardnerella vaginalis

- 2) The following organisms which the sponsor has placed in the *in vitro* section of the label must be deleted:

Aerobic gram-positive microorganisms:

Bacillus cereus:

In addition to food poisoning, based on many reports and frequent and regular occurrence *Bacillus cereus* is now accepted to be associated with mild to severe, necrotic or gangrenous infected wounds. Even though the median MIC₉₀ is acceptable the number of the organisms tested are very few. This organism will not be allowed in the label.

Corynebacterium jeikeium

is the most common corynebacterial pathogen isolated in the clinical laboratory. It is associated with septicemia, endocarditis, skin and soft tissue infections, and occasionally, meningitis, peritonitis, and pneumonia, particularly in the compromised and previously treated host. The number of the isolates and the MIC₉₀ of 2.0 µg/mL is not acceptable. This organisms will not be allowed in the label.

Enterococcus faecium (Van-S)

Enterococcus faecium (Van-R)

Enterococci are involved most commonly in urinary tract infections and are implicated in 10% of all such infections. Intra abdominal or pelvic wound infections are the next commonly encountered infections. However, these wound cultures are frequently polymicrobial, and the role of enterococci in this setting remains controversial. Bacteremia is the third most common type of infection, and enterococci are the third leading cause of nosocomial bacteremia. Endocarditis is less common than bacteremia and enterococci is estimated to be the causative agent in 5-20% of bacterial endocarditis cases. *E. faecalis* is the most commonly encountered species in this setting, but various other species also have been implicated as causes of

endocarditis. The MIC₉₀ is above the susceptible breakpoint for both Van-R and Van-S *E. faecium*. This organism will not be allowed in the label

Staphylococcus saprophyticus is an important opportunistic pathogen in human urinary tract infections, especially in young, sexually active females. It has been proposed as an agent of nongonococcal urethritis in males and prostatitis. Although the median MIC₉₀ was 0.06 µg/mL, the number of the isolates are not sufficient to justify inclusion in the label. *Staphylococcus saprophyticus* will not be allowed in the label.

Aerobic gram-negative microorganisms:

Acinetobacter baumannii There are few isolates and the MIC₉₀ is >8.0 µg/mL. *Acinetobacter baumannii* will not be allowed in the label.

Alcaligenes faecalis There are few isolates and the MIC₉₀ is >8.0 µg/mL. *Alcaligenes faecalis* will not be allowed in the label

Alcaligenes xylosoxidans
subsp. *denitrificans* There are few isolates and the MIC₉₀ is 4.0 µg/mL. *Alcaligenes xylosoxidans* subsp. *denitrificans* will not be allowed in the label

Alcaligenes xylosoxidans
subsp. *xylosoxidans* There are few isolates and the MIC₉₀ is >8.0 µg/mL. *Alcaligenes xylosoxidans* subsp. *xylosoxidans* will not be allowed in the label

Bordetella bronchiseptica There are data on very few isolates and the MIC₉₀ is 1.0 µg/mL. *Bordetella bronchiseptica* will not be allowed in the label

Brevundimonas diminuta There are data on very few isolates and the MIC₉₀ is 8.0 µg/mL. *Brevundimonas diminuta* will not be allowed in the label

Burkholderia cepacia There are data on very few isolates and the MIC₉₀ is 4.0 µg/mL. *Burkholderia cepacia* will not be allowed in the label

Citrobacter diversus Less than 100 isolates were tested in a number of different centers. However, majority of the isolates were older than 5 years. Even though the median MIC₉₀ was 0.06 µg/mL and this organism may be associated with pneumonia, *Citrobacter diversus* will not be allowed into the label.

Neisseria meningitidis is an organism that is implicated in community -acquired pneumonia, urethritis, and most importantly in meningitis. Due to the seriousness of meningococcal meningitis and the associated public health issues, this organism will be listed

ONLY if the efficacy of a drug is studied and demonstrated in well controlled clinical trials. *Neisseria meningitidis* will not be allowed in the label.

Providencia rettgeri

There are not enough isolates tested and *Providencia rettgeri* will not be allowed into the label.

Providencia stuartii

There is not enough isolates tested and the median MIC₉₀ is 2.0 µg/mL. *Providencia stuartii* will not be allowed into the label.

P. fluorescens putida

There is not enough isolates tested and *Pseudomonas fluorescens putida* will not be allowed into the label.

Pseudomonas stutzeri

There is not enough isolates tested and *Pseudomonas stutzeri* will not be allowed into the label.

Salmonella enteritidis

There is not enough isolates tested and Infectious diarrhea is not an indication for trovafloxacin. *Salmonella enteritidis* will not be allowed into the label.

Salmonella typhi

There is not enough isolates tested and Infectious diarrhea is not an indication for trovafloxacin. *Salmonella typhi* will not be allowed into the label.

Salmonella spp.

Infectious diarrhea is not an indication for trovafloxacin. *Salmonella* spp. will not be allowed into the label.

Serratia marcescens

is an important cause of extraintestinal infections, having caused many nosocomial outbreaks associated with blood transfusions surgery, and the urinary tract. Most of the MIC₉₀s were above the susceptible breakpoint. *Serratia marcescens* will not be allowed in the label.

Shigella spp.

Infectious diarrhea is not an indication for trovafloxacin. *Shigella* spp. will not be allowed into the label.

Stenotrophomonas maltophilia

is ubiquitous in nature and has also been isolated from the hospital environment. It is the third most frequently isolated nonfermentative gram-negative rod in the clinical laboratory. Strains may be colonizers (e.g., in cystic fibrosis) or infecting agents. Septicemia (often associated with intravenous catheters), pneumonia, and wound infections have been reported. Most of the isolates tested are not recent isolates and the MICs were greater than the susceptible breakpoint. The two recent studies with 50 and 30 isolates each reported the MIC₉₀ to be >8.0 µg/mL and 4.0 µg/mL respectively. *Stenotrophomonas maltophilia* will not be allowed into the label.

Vibrio cholerae There is not enough isolates tested and *Vibrio cholerae* will not be allowed into the label.

Yersinia enterocolitica Infectious diarrhea is not an indication for trovafoxacin and there is not enough isolates tested therefore, *Yersinia enterocolitica* will not be allowed into the label.

Anaerobic microorganisms:

Bacteroides uniformis

Bacteroides uniformis as a member of *Bacteroides fragilis* group is recovered from most intra-abdominal infections and may occur in infections at other sites. The MIC₉₀ of 46 recent isolates was 4.0 µg/mL. *Bacteroides uniformis* will not be allowed in the label.

Clostridium difficile

Clostridium difficile is the major cause of antibiotic-associated diarrhea and pseudomembranous colitis. There were less than 100 isolates tested and the one U.K. study with one third of the isolates, reported the MIC₉₀ to be 4.0 µg/mL. *Clostridium difficile* will not be allowed in the label.

Clostridium ramosum

There is not enough isolates tested and *Clostridium ramosum* will not be allowed into the label.

Fusobacterium mortiferum

There is no *in vitro* data presented in the NDA to support the inclusion of this organism. *Fusobacterium mortiferum* will not be allowed in the label.

Fusobacterium nucleatum

There is only 12 isolates that may be considered as "recent" isolates. The reported MIC₉₀ was 0.5 µg/mL. There is not enough *in vitro* data presented to justify the inclusion of *Fusobacterium nucleatum* in the label. *Fusobacterium nucleatum* will not be allowed in the label.

Prevotella bivia

Only data for 62 isolates could be found in the NDA. One study with the majority of the isolates reported the MIC₉₀ to be 2.0 µg/mL. *Prevotella bivia* will not be allowed in the label.

Prevotella intermedia

Only data for 13 isolates could be found in the NDA. There is not enough *in vitro* data presented to justify the inclusion of *Prevotella intermedia* in the label. *Prevotella intermedia* will not be allowed

Prevotella melaninogenica

Only data for 11 isolates could be found in the NDA. There is not enough *in vitro* data presented to justify the inclusion of *Prevotella melaninogenica* in the label. *Prevotella melaninogenica* will not be allowed

Other microorganisms:

Legionella dumoffii

Legionella micdadei
Legionella longbeacheae
Legionella maltophilia??

There were no *in vitro* data presented in the NDA in support of inclusion of *Legionella dumoffii*, *Legionella micdadei*, *Legionella longbeacheae*, or *Legionella maltophili??*. These organisms will not be allowed in the label.

Toxoplasma gondii

There were no *in vitro* data presented in the NDA to support the inclusion of *Toxoplasma gondii* in the label. *Toxoplasma gondii* will not be allowed in the label.

3) Reword the "Microbiology" section to read exactly as indicated bellow.

Trovafoxacin is a fluoronaphthyridone related to the fluoroquinolones with *in vitro* activity against a wide range of gram-negative and gram-positive aerobic, and anaerobic microorganisms. The bactericidal action of trovafoxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. Mechanism of action of fluoroquinolones including trovafoxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between trovafoxacin and the mentioned classes of antibiotics. The overall results obtained from *in vitro* synergy studies, testing combinations of trovafoxacin with beta-lactams and aminoglycosides, indicate that synergy is strain specific and not commonly encountered. This agrees with results obtained previously with other fluoroquinolones. Resistance to trovafoxacin *in vitro* develops slowly via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to trovafoxacin *in vitro* occurs at a general frequency of between Although cross-resistance has been observed between trovafoxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to trovafoxacin.

Trovafoxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes
Viridans group streptococci

Aerobic gram-negative microorganisms

Escherichia coli
Gardnerella vaginalis
Haemophilus influenzae

Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa

Anaerobic microorganisms
Bacteroides fragilis
Peptostreptococcus species
Prevotella species

Other microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown.

Trovafoxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 2 $\mu\text{g/mL}$ against most (90%) strains of the following microorganisms; however, the safety and effectiveness of trovafoxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative microorganisms
Citrobacter freundii
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris

Anaerobic microorganisms
Bacteroides distasonis
Bacteroides ovatus
Clostridium perfringens

Other microorganisms
Mycoplasma hominis
Ureaplasma urealyticum

NOTE: *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* complex organisms are commonly resistant to trovafoxacin.

NOTE: The activity of trovafoxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum*. (See WARNINGS.)

Susceptibility Tests:

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trovafoxacin powder. The MIC values should be interpreted according to the following criteria:

For testing non-fastidious aerobic organisms

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

For testing *Haemophilus* spp.^a:

<u>MIC (µg/mL)</u>	<u>Interpretation^b</u>
≤ 1.0	Susceptible (S)

^a These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)¹

^b The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*^c:

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<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

^c These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.

For testing *Neisseria gonorrhoeae*^d:

<u>MIC ($\mu\text{g}/\text{mL}$)</u>	<u>Interpretation</u>
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

- ^d These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement¹.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trovafloxacin powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC Range ($\mu\text{g}/\text{mL}$)</u>
<i>Escherichia coli</i> ATCC 25922	0.004-0.016
<i>S. aureus</i> ATCC 29213	0.008-0.03
<i>P. aeruginosa</i> ATCC 27853	0.25-2.0
<i>E. faecalis</i> ATCC 29212	0.06-0.25
<i>Haemophilus influenzae</i> ^e ATCC 49247	0.004-0.016
<i>S. pneumoniae</i> ^f ATCC 49619	0.06-0.25
<i>N. gonorrhoeae</i> ^g ATCC 49226	0.004-0.016

- ^e This quality control range is applicable to only *H. influenzae* ATCC 49247

- ^f This quality control range is applicable to only *S. pneumoniae* ATCC 49619

- ^g This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 μg trovafloxacin to test the susceptibility of microorganisms to trovafloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10- μ g trovafoxacin disk should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing non-fastidious aerobic organisms:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 17	Susceptible (S)
14-16	Intermediate (I)
≤ 13	Resistant (R)

For testing *Haemophilus* spp.^h:

<u>Zone Diameter (mm)</u>	<u>Interpretationⁱ</u>
≥ 22	Susceptible (S)

^h These zone diameter standards are applicable only to tests with *Haemophilus* spp

ⁱ The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*^j:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 19	Susceptible (S)
18-16	Intermediate (I)
≤ 15	Resistant (R)

^j These zone diameter standards only apply to tests performed

For testing *Neisseria gonorrhoeae*^k:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 37	Susceptible (S)
34-36	Intermediate (I)
≤ 33	Resistant (R)

^k These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement² incubated in 5% CO₂.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trovafoxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 10- μ g trovafoxacin disk should provide the following zone diameters in these laboratory quality control strains:

<u>Microorganism</u>	<u>Zone Diameter Range (mm)</u>
<i>Escherichia coli</i> ATCC 25922	29-36
<i>S. aureus</i> ATCC 25923	29-35
<i>P. aeruginosa</i> ATCC 27853	21-27
<i>Haemophilus influenzae</i> ^l ATCC 49247	32-39
<i>S. pneumoniae</i> ^m ATCC 49619	25-32
<i>N. gonorrhoeae</i> ⁿ ATCC 49226	42-55

^l This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247

^m This quality control range is applicable only to tests performed by disk diffusion

ⁿ This quality control range is only applicable to tests performed by disk diffusion

Anaerobic techniques: For anaerobic bacteria, the susceptibility to trovafoxacin as MICs can be determined by standardized test methods³. The MIC values obtained should be interpreted according to the following criteria:

<u>MIC (μg/mL)</u>	<u>Interpretation</u>
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized trovafoxacin powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC^p (μg/mL)</u>
<i>Bacteroides fragilis</i> ATCC 25285	0.125-0.5
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	0.25-1.0
<i>Eubacterium lentum</i> ATCC 43055	0.25-1.0

^p These quality control ranges were derived from tests performed

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101. Dubois, J., St.-Pierre, C. (1996). An *in vitro* susceptibility study of trovafoxacin against *Legionella* spp. Abstract E75, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 15-18.
102. Dalvie, D., Khosla, N., Vincent, J. (1995). Metabolism of a new quinolone antibiotic, CP-99,219, in humans. In *Proceedings of the Fourth International Society of Study of Xenobiotics (ISSX) Meeting, Seattle, Washington*. Abstract 126, p. 126. International Society of Study of Xenobiotics.
103. Hopkins, S., Williams, D., Dunne, M., Marinovich, L., Edeline, M., Utt, E., Dutse, A. (1996). A randomized, controlled trial of oral or i.v. trovafoxacin versus ceftriaxone in the treatment of epidemic meningococcal meningitis. 36th International Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 15-18.

105. Jenkins, S.G. (1996). *In vitro* synergy between trovafloxacin and ampicillin-sulbactam against bacterial pathogens. Abstract E82 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept. 15-18.
106. Visalli, M.A., Bajaksouzian, S., Jacobs, M.R., Appelbaum, P.C. (1996). Activity of trovafloxacin, alone and in combination with other agents, against gram-negative non-fermentative rods, compared with other quinolone and non-quinolone agents. *Antimicrob. Agents Chemother.* (submitted).

APPEARS THIS WAY
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NFD 590/Fogain

**REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

JUL 3 1997

JUL 3 1997

Microbiologist's Review #1 of NDA 20-760
June 30, 1997

A. 1. APPLICATION NUMBER: 20-760

APPLICANT: Pfizer Inc.
Central Research Division
Eastern Point Road
Groton, CT 06340

APPROVED THIS WAY
JUL 1 1997

2. PRODUCT NAMES: Trovan Injection (alatrofloxacin mesylate injection)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A sterile solution of 20.6 ml (in a 20 ml vial), 40.9 ml (in a 40 ml vial), and 61.2 ml (in a 60 ml vial) at 5 mg/ml of alatrofloxacin mesylate. It is administered intravenously.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Trovan is indicated for the treatment of bacterial infections in adults 18 years of age and older, and for the treatment of epidemic meningococcal meningitis in children 3 months to 16 years using a 3 mg/ml daily dose.

B. 1. DATE OF INITIAL SUBMISSION: December 27, 1996

2. AMENDMENT:

3. RELATED DOCUMENTS: NDA 20-759

4. ASSIGNED FOR REVIEW: February 13, 1997

APPROVED THIS WAY
FEB 13 1997

5. DATE OF CONSULT REQUEST: January 29, 1997

C. REMARKS:

Trovan is a synthetic, broad-spectrum antibacterial agent. Alatrofloxacin (bis-alanyl derivative of trovafloxacin) is the parenterally-administered

It is to be manufactured by Pfizer in Brooklyn, New York.

Alatrofloxacin mesylate injection

The product. Alatrofloxacin mesylate injection of the drug

to the drug product.

D. CONCLUSIONS:

APPROVED FOR RELEASE
ON 06/30/97

The submission is recommended for approval with regard to microbiology. However, the validation for the should be submitted as part of the post-approval commitment.

/S/

6/30/97

**Brenda Uratani, Ph.D.
Review Microbiologist**

/S/

7/3/97

cc:

- NDA 20-760
- HFD-520/ Div. File
- HFD-805/ Uratani
- HFD-520/CSO/ P. Fogarty
- HFD-520/Chemist/ B.V. Shetty
- drafted by: Brenda Uratani, 6/30/97
- R/D initialed by P. Cooney, 6/30/97

APPROVED FOR RELEASE
ON 06/30/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20759/20760

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: (i) 20-759
(ii) 20-760

Submission Date: December 27, 1996

Drug Products & Dosage Forms (i) Trovafloxacin Mesylate (CP-99,219) Tablets
TROVAN® 100 and 200 mg Oral Tablets
(ii) Alatrofloxacin Mesylate (CP-116,517) Injection
TROVAN® 100, 200, and 300 mg IV Solution

Sponsor: Pfizer Central Research
Groton, CT

Type of Submission: NME
Category: 1S

OCPB Reviewer: Philip M. Colangelo, Pharm.D., Ph.D.
OCPB Log-In Date: January 7, 1997

I. BACKGROUND

Trovafloxacin and alatrofloxacin are synthetic fluoronaphthyridone antibiotics which are similar in structure and mechanism of action to the fluoroquinolone class of antibiotics. Trovafloxacin is being developed as an immediate release oral film coated tablet and alatrofloxacin as the intravenous (iv) solution. Alatrofloxacin is the bis-alanyl iv form of trovafloxacin and was formulated as such because of solubility problems with trovafloxacin. Alatrofloxacin is by circulating to trovafloxacin *in vivo* following iv infusion. Both products will be marketed in the United States under the tradename TROVAN® and will be available as 100 and 200 mg tablets and 100, 200, and 300 mg solution for iv infusion following dilution. In addition to the U.S., the sponsor also plans to market both formulations in Europe, Canada, and several other countries throughout the world in 1997.

II. INDICATIONS and DOSAGES

TROVAN® is being developed for the treatment of a variety of infectious diseases caused by several classes of bacterial pathogens, including certain drug-resistant strains (e.g., *Strep. pneumoniae*, *Staph. aureus*). The proposed oral doses are 100 to 200 mg given once per day and the iv doses range from 200 to 300 mg per day in adults 18 years of age and older.

The proposed indications and dosages are listed below. Since several of the indications were studied using TROVAN® iv followed by the tablets, it was agreed upon by the Agency that the sponsor could combine the two NDA's into one integrated submission and that the Agency would review them simultaneously.

DOSAGE GUIDELINES		
INFECTION*/LOCATION AND TYPE	DAILY UNIT DOSE AND ROUTE OF ADMINISTRATION	TOTAL DURATION
Nosocomial Pneumonia	300 mg I.V. followed by 200 mg oral	10-14 days
Community Acquired Pneumonia	200 mg oral or 200 mg I.V. followed by 200 mg oral	7-14 days
Acute Bacterial Exacerbation of Chronic Bronchitis	100 mg oral	7-10 days
Acute Sinusitis	200 mg oral	10 days
Complicated Intra-Abdominal Infections, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Gynecologic and Pelvic Infections, Complicated, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Surgical Prophylaxis - Elective Colorectal Surgery	200 mg I.V. or oral	Single dose
Surgical Prophylaxis - Elective Abdominal and Vaginal Hysterectomy	200 mg I.V. or oral	Single dose
Skin and Skin Structure Infections, Uncomplicated	100 mg Oral	7-10 days
Skin and Skin Structure Infections, Complicated, including diabetic foot infections	200 mg oral or 200 mg I.V. followed by 200 mg oral	10-14 days
Uncomplicated Urinary Tract Infections (cystitis)	100 mg oral	3 days
Bacterial Prostatitis	200 mg oral	28 days
Acute, Uncomplicated Gonorrhea	100 mg oral	Single Dose
Non-Gonococcal Urethritis/ and Cervicitis	200 mg oral	5 days
Pelvic Inflammatory Disease	200 mg oral or 200 mg I.V. followed by 200 mg oral	14 days

* due to the designated pathogens

III. HUMAN PK/BIOAVAILABILITY SYNOPSIS

Item 6: Human Pharmacokinetics and Bioavailability was comprised of 50 volumes containing data from 46 Phase I PK studies of trovafloxacin tablets and alatrofloxacin iv infusion. Of these 46 total studies, data from at least 32 studies were incorporated into the proposed labeling, and thus, the majority of these 32 studies were reviewed. All sections of the submission, except for the CMC section (Items 3 and 4), were provided by the sponsor as an electronic submission and was accessed from the reviewers' personal computers. This includes the entire contents of Item 6 and the raw serum drug

concentration-time and PK data for selected studies from Item 6 which were requested by the reviewer to be provided by the sponsor. Item 6 was also provided for review as a paper copy.

A synopsis of the basic pharmacokinetic characteristics of both compounds is as follows:

Tablet Absorption: T_{max} was 1-2 hrs; absolute bioavailability of trovafloxacin 100 mg tablets was 88%; oral availability not effected by food (high-fat breakfast) at 200 mg dose.

Alatrofloxacin Hydrolysis: hydrolyzed by plasma esterases; plasma alatrofloxacin concentrations are non-quantifiable within 5-10 minutes after the end of a 60 minute infusion.

Distribution: trovafloxacin volume of distribution (V_{d_{ss}}) after iv alatrofloxacin was ; distributes well into tissues/fluids, including lung, gynecologic, prostate tissues, blister fluid.

Metabolism: Phase II conjugation, i.e., glucuronidation (major), sulfation (minor), N-acetylation (major); minimal oxidative metabolism; N-acetyl trovafloxacin has some microbiological activity.

Excretion/Elimination: total recovery of trovafloxacin was 86% (63% from feces, 23% from urine); excretion of unmetabolized trovafloxacin was primarily via feces (~40%) and/or bile; minor renal elimination (<10%); elimination T_{1/2} 10-12 hrs.

Single Dose PK - Trovafloxacin: dose proportional PK from 30 to 1000 mg (solution or oral suspension), and from 100 to 200 mg (tablets)

Single Dose PK - Alatrofloxacin IV: dose proportional PK from 100 to 300 mg

Multiple Dose/Steady-State PK: linear and stationary PK; C_{ss} attained by 3rd daily dose; C_{min_{ss}} 0.4-0.6 ug/mL.

	<u>C_{max_{ss}} (ug/mL)</u>	<u>AUC_{ss} (ug.hr/mL)</u>
100 mg PO	~1.5	~12
200 mg PO	~3.0	~30
200 mg IV	~3.0	~30
300 mg IV	~4.0	~45

Special Populations:

Hepatic Impairment (mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) chronic cirrhosis) - systemic exposure (i.e., AUC) increased and T_{1/2} prolonged after repeated 100 mg (mild) and 200 mg (moderate) doses vs matched controls.

Renal Impairment, including dialysis - no significant effect on trovafloxacin PK; dialysis did not appreciably remove trovafloxacin from serum.

Age - no significant effect on trovafloxacin PK.

Gender - females show increases in systemic exposure (i.e., AUC) of ~16% and C_{max} of ~40% after repeated 200 mg doses; the increases can be attributed to the lower body weights of females.

Drug Interactions:

No significant effect of trovafloxacin on the PK of caffeine, digoxin, warfarin (including PT, INR, and APTT as pharmacodynamic measures), cyclosporine, and theophylline all at steady-state.

No significant effect of omeprazole, calcium carbonate (TUMS®), or cimetidine on trovafloxacin PK.

Significant reduction in oral availability of trovafloxacin by Maalox TC (i.e., Al/Mg antacid), sucralfate, and ferrous sulfate, presumably mainly through complexation with trovafloxacin. Morphine iv also significantly reduces trovafloxacin oral availability, presumably through opiate-induced reduction in gastric motility and/or gastric emptying.

There were no population pharmacokinetics analyses or pharmacodynamic analyses (i.e., relation (and/or correlation) of trovafloxacin levels in tissues/fluids of infection or other PK parameters with the MIC₉₀ of the associated pathogens) included in the submission.

The bioequivalence between the proposed commercial formulation for the trovafloxacin mesylate tablet (100 mg) and the Phase III clinical trials tablet (100 mg) was demonstrated. There was no need to establish bioequivalence between the proposed commercial formulation for the 200 mg tablet and the Phase III 100 mg clinical trials tablet since both 100 mg and 200 mg tablet strengths were manufactured from a

IV. RECOMMENDATION

The information for Item 6: Human Pharmacokinetics and Bioavailability of NDA 20-759 / 20-760 for trovafloxacin mesylate tablets / alatrofloxacin mesylate intravenous solution has been reviewed and was found to be acceptable and adequate to support approval of both oral and iv formulations.

V. COMMENTS FOR THE SPONSOR

1. Study 154-024 (PET study) - the study report was classified as "interim" by the sponsor, i.e., with respect to the data for the 19 subjects enrolled at this clinical site (study dates 11/95-5/6/96). However, the interpretation of this is not clear, i.e., whether there will be more data generated from this site, or whether the data already generated and reported is in final form. Another concern is that no information regarding the formulation/manufacture, purity, etc. of the iv trovafloxacin was provided with the study report. It is recommended that the sponsor provide further clarification of the term "interim" for this study report, and also provide additional formulation information for trovafloxacin iv. The Agency will provide a full review of this study following submission of the final study report by the sponsor.

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trovafloxacin mesylate tablets.

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APPEARS THIS WAY
ON ORIGINAL

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

/S/

RD/FT signed by Funmi Ajayi, Ph.D (Acting TL) _____
Briefing (12/8/97) Attendees: F. Ajayi, J. Lazor, P. Marroum, J. Collins, J. Hunt, J.
Jenkins, B. Leissa

cc:

Div. File: NDA 20-759; 20-760
HFD-590 (B. Leissa, TL/MO; P. Coyne, MO)
HFD-590 (P. Fogarty, PM/CSO)

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HFD-340 (Viswanathan)
HFD-205 (FOI)
HFD-880 (Division File)
HFD-880 (F. Ajayi; P. Colangelo)
CDR (Barbara Murphy)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020759/020760

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

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Central Research

BM
ORIG

December 11, 1997

Department of Clinical Research

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



CONFIDENTIAL/TRADE SECRET
INFORMATION SUBJECT TO 18-USE-1905
AND TO WHICH ALL CLAIMS OF PRIVILEGE
AND CONFIDENTIALITY ARE ASSERTED IN
BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Handwritten notes: "New" and "12/15/97" with a signature.

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)

Serial No. 079

NDA-20-760 - TROVAN® I.V. (Alatrofloracin Mesylate Injection)

Serial No. 076 *(Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to the following teleconferences: an October 8, 1997 teleconference with Drs. Dan Davis and Regina Alivisatos, Medical Reviewers; an October 30, 1997 teleconference with Dr. Alivisatos and Dr. Brad Leissa, Medical Team Leader; and a November 11, 1997 teleconference with Dr. Leissa.

On October 8, 1997, Dr. Alivisatos asked if patients in study #154-144* of a lower socioeconomic status were harder to treat (Query #331). In response to this request Dr. Luke informed Dr. Alivisatos that patients of a lower socioeconomic status typically delayed seeking medical attention, placing them at risk for infection. In support of this answer, an August 1994 New England Journal of Medicine article was sent by facsimile on October 20, 1997. It is now being formally submitted to complete our records (Enclosure #1).

In support of our Nosocomial Pneumonia indication, on October 30, 1997 Dr. Alivisatos requested additional information substantiating the lack of direct association between Apache scores and severity of Nosocomial pneumonia (Query #385A). A draft response to this request was provided by facsimile on November 7, 1997. It is now being formally submitted to complete our records (Enclosure #2).

On November 10, 1997, Dr. Leissa asked Pfizer to justify the claim of TROVAN being equivalent to Ciprofloracin for Nosocomial Pneumonia in light of the current labeling (Query #396). Dr. Leissa also asked Pfizer to please explain the conclusion previously stated that TROVAN is superior to the comparator (Query #397). A draft response to these requests was provided by Email and facsimile on December 4, 1997. It too is now being formally submitted to complete our records (Enclosure #3).

A desk copy of this cover letter is being provided to Pauline Fogarty, Project Manager.

Dr. Goldberger, Director
NDA-20-759
NDA-20-760

2

December 11, 1997

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Bullock for:

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

*154-144- entitled "A Randomized, Double-Blind, Multicenter Trial Assessing the Safety and Efficacy of Intravenous Alatrofloxacin (CP-116,517) Followed by Oral Trovafloxacin (CP-99,219) Compared with Intravenous Cefoxitin Followed by Oral Amoxicillin/Clavulanic Acid for the Treatment of Acute PeM_c Infections."

lab
Enclosures
Desk Copy: Ms. P. Fogarty (cover letter)

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Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 411 4100

ORIGINAL



Central Research

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01/12/97

December 11, 1997



Department of Clinical Research

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunology
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

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FURTHER DISSEMINATION MAY ONLY BE
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Handwritten: NDA 20-759

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN[®] Tablets (Trovafloracin Mesylate)
Serial No. 78

NDA-20-760³ - TROVAN[®] I.V. (Alatrofloracin Mesylate Injection)
Serial No. 75 *(Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION



Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a November 26, 1997 facsimile from Dr. Philip Coyne, Medical Reviewer.

On November 26, 1997, Dr. Coyne requested a table of subjects that contained combinations of dizziness, nausea, or headache by treatment relatedness for each oral dose level, all multi-dose oral and IV-to-Oral regimens for the comparative Phase 2/3 trials (Query #418). A draft response to this request was provided by facsimile on December 2, 1997. It is now being formally submitted to complete our records.

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Bulkinitch for:

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab
Enclosure
Desk Copy: Ms. P. Fogarty (cover letter)

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Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

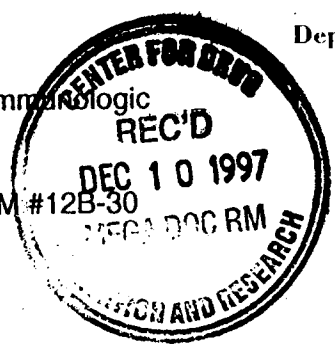


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ORIG AMENDMENT
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Central Research

December 9, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



Department of Clinical Research
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Nci 12/15/97
[Redacted]

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN[®] Tablets (Trovafoxacin Mesylate)
Serial No. 074

NDA-20-760 TROVAN[®] I.V. (Alatrofoxacin Mesylate Injection)
Serial No. 071 (*Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996.
Reference is also made to an October 10, 1997 teleconference with Dr. Regina Alivisatos,
Medical Reviewer.

On October 10 Dr. Alivisatos requested hard copies of radiology reports for certain patients in
study #154-113* (Query #325). On October 17 radiology reports were forwarded to Dr.
Alivisatos' attention via Federal Express for the following patients:

51110083	65430540
51110108	65430809
51120277	51110106
51210230	51150122
51880004	51180069
54090358	52110782
54100363	53860247
54830113	54830116
54830115	54830254
55080613	55100609
55460090	55110619
55460091	55130622
65430538	56280117

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These radiology reports are now being formally submitted to complete our records (Enclosure #1).

The last radiology report for patient 54090345 was provided by facsimile on December 5, 1997. It too is now being formally submitted to complete our records (Enclosure #2).

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

December 9, 1997

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Linda Bullonitch for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab

Enclosures

Desk Copy: Ms. P. Fogarty (cover letter)

*154-113: entitled "A Randomized, Multicenter, Double-Blind, Double-Dummy Trial Comparing Intravenous Alatrofloxacin (CP-116,517) Followed by Oral Trovafloxacin (CP-99,219) with Intravenous Ciprofloxacin Followed by Oral Ciprofloxacin for the Treatment of Nosocomial Pneumonia."

APPEARS THIS WAY ON ORIGINAL

/s/

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100



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ORIG AMENDMENT
ORIGINAL

Central Research

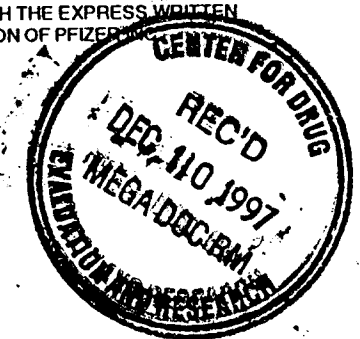
December 9, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Department of Clinical Research

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MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER

Handwritten initials and date: *Wai*, *12/15/97*



Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 075

~~NDA-20-750~~ TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 072 (*Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996, and our submission of our draft package insert. Reference is also made to our teleconference of November 6, 1997 and an Email message on that same day from Dr. Brad Leissa, Medical Team Leader.

Dr. Leissa had requested a reanalysis of results from our complicated UTI program, including only those non-pyelonephritis patients infected with either *E. coli* or *K. pneumoniae* (Query #388) and to provide a revised labeling statement that highlights the efficacy in patients infected with these two organisms and restricting use to patients in whom the infecting organism is known prior to initiating treatment (Query #389).

Responses to Queries #388 and #389 are enclosed (**Enclosures #1 and #2**, respectively). The questions are bolded, followed by the replies in italics, or in the case of tables, in normal type.

Six desk copies of this submission are being provided to Ms. Fogarty for distribution to Medical Reviewers, Drs. Alivisatos and Leissa, Statistical Reviewers, Dr. Silliman and Jiang, and Dr. Goldberger.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Ronald I. Trust
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

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rit
Enclosures
Desk Copies (6): Ms. P. Fogarty

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Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

BM
ORIG AMENDMENT

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Central Research



December 9, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Department of Clinical Research

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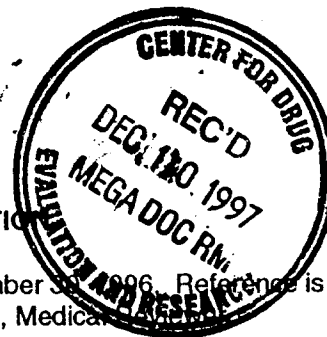
Handwritten: 12/15/97
Handwritten: [Signature]
[Redacted]

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 077

NDA-20-760* TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 074 (*Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION



Reference is made to our pending New Drug Applications, submitted December 3, 1996. Reference is also made to an October 16, 1997 teleconference with Dr. Regina Alivisatos, Medical Director.

On October 16, 1997, Dr. Alivisatos requested any information available regarding the *in vitro* effects of trovafloxacin antagonism with aztreonam (Query #365). In response to this request, an abstract was forwarded to Dr. Alivisatos' attention by facsimile on October 21, 1997. It is now being formally submitted to our NDAs to complete our records.

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Handwritten: [Signature]
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab
Enclosure
Desk Copy: Ms. P. Fogarty (Cover letter)

BB

ORIG AMENDMENT

ORIGINAL



Central Research

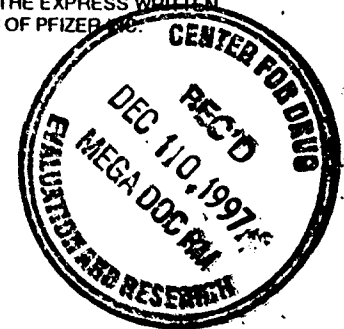
December 9, 1997

Department of Clinical Research

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
INFORMATION SUBJECT TO 18- USC-1905
AND TO WHICH ALL CLAIMS OF PRIVILEGE
AND CONFIDENTIALITY ARE ASSERTED IN
BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
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PERMISSION OF PFIZER INC.

Handwritten signature and date: N. Trust 12/15/97



Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 076

NDA-20-760 TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 073 (*Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to November 24, and November 26, 1997 teleconferences with Dr. Philip Colangelo, Biopharmaceutics Reviewer.

On November 24, 1997, Dr. Colangelo requested literature references for PET study #154-024* (Query #414). These references were forwarded to his attention by facsimile on November 25 and 26, 1997. They are now being formally submitted to complete our records (Enclosure #1).

On November 26, 1997, Dr. Colangelo requested revised tissue levels from study #154-024 (Query #415) as well as dissolution data on the stability batches (Query #416). A table providing revised tissue levels from this study was forwarded to Dr. Colangelo's attention via facsimile on December 3, 1997. It is now being formally submitted to complete our records (Enclosure #2). Our response to the request for dissolution data on the stability batches was also provided by facsimile on December 3, 1997. It is also being formally submitted (Enclosure #3).

A desk copy of this submission is being provided to Dr. Colangelo. A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Ronald I. Trust
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab
Enclosures
Desk Copies:

Dr. P. Colangelo (Complete)
Ms. P. Fogarty (Cover letter)

APPEARS THIS WAY ON ORIGINAL

*154-024- entitled "The Pharmacokinetics and Tissue Distribution Of [¹⁸F]-Trovafloracin ([¹⁸F]-CP-99,219) in Man Utilizing Positron Emission Tomography (PET)."

CONFIDENTIAL

BW

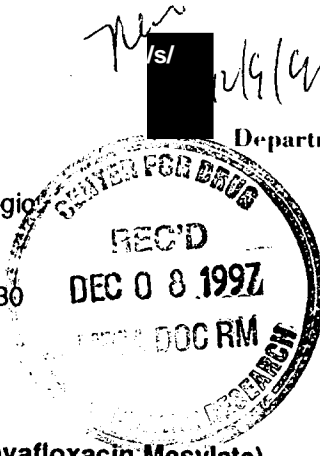


ORIGINAL

Central Research

December 5, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



Department of Clinical Research

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FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN[®] Tablets (Trovafloracin Mesylate)
Serial No. 73

~~NDA-20-760~~ TROVAN[®] I.V. (Alatrofloracin Mesylate Injection)
Serial No. 70 (*Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION- COMMUNITY ACQUIRED PNEUMONIA

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to our November 14, 1997 telecon with the Division to discuss the Community Acquired Pneumonia (CAP) and Acute Exacerbation of Chronic Bronchitis (AECB) indications.

Prior to the meeting a table that combined organisms from all CAP studies to show Pfizer's total organism count for this indication was provided to Dr. Coyne by facsimile. This table is now being formally submitted to complete our records (Enclosure #1).

During this telecon Dr. Coyne requested new tables for subjects infected with either *C. pneumoniae*, *L. pneumophila*, or *S. aureus* that showed the incidence of these organisms when each was the sole pathogen or when they were co-pathogens. Dr. Coyne also requested the bacteriologic eradication rate for these pathogens as well as *M. catarrhalis* and *K. pneumoniae* (Query #400). A response to this request was provided by facsimile on November 17, 1997. It is now being formally submitted to our NDAs to complete our records (Enclosure #2).

A desk copy of this submission is being provided to Dr. Coyne. A desk copy of the cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Donald I. Trust
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab
Enclosures
Desk Copies: Dr. P. Coyne (Complete)
Ms. P. Fogarty (Cover Letter)

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100



BM
ORIG AMENDMENT

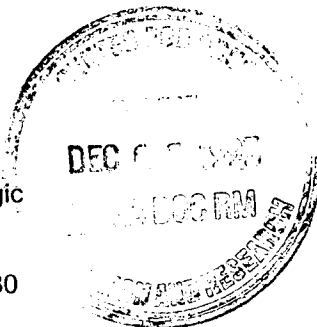
Central Research

ORIGINAL

Department of Clinical Research

December 4, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



APPE 12/4/97

CONFIDENTIAL/TRADE SECRET
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AND TO WHICH ALL CLAIMS OF
PRIVILEGE AND CONFIDENTIALITY ARE
ASSERTED IN BOTH STATUTORY AND
COMMON LAW. FURTHER
DISSEMINATION MAY ONLY BE MADE
WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 072
NDA-20-760 - TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 069

RESPONSE TO FDA REQUEST FOR INFORMATION- ADVERSE REACTION OF DIZZINESS

Reference is made to our pending New Drug Applications, submitted December 30, 1996, and our submission of our draft package insert. Reference is also made to an Email message on October 24, 1997 from Dr. Brad Leissa, Medical Team Leader.

Dr. Leissa had requested a response to a series of ten questions addressing the adverse reaction of dizziness that has been associated with the use of Trovan (Query #369).

The enclosed response is provided in two parts. Part A (Enclosures 1 to 10) contains a direct response to each of the Division's questions. Each question is repeated in bold type, followed by Pfizer's response. For most of the questions, a table or figure was requested. The relevant tables or figures have been inserted following the brief comments for each question, if applicable. Part B (Enclosure #11) contains a discussion of our conclusions about dizziness associated with Trovan use, and draws from examination of our clinical data.

Draft copies of this submission was provided by facsimile on November 26, 1997 and by desk copies on December 2, 1997. This formal submission differs from the draft submission in the following ways: administrative edits were made to our response to Question #6; administrative edits were made to Enclosure #11, Part B, Section 2; administrative edits were made to Enclosure #11, Part B, Section 3.

Please note that Enclosure #11 contains data from study #154-046*. This study was not filed in our original NDAs. This information should be considered preliminary because analysis of this Phase I study is still in progress.

Desk copies of this submission are being provided to Ms. Fogarty for distribution to the Medical Reviewers, Statistical Reviewers and Dr. Goldberger.

Dr. Goldberger, Director
NDA-20-759
NDA-20-760

2

December 4, 1997

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991.
Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Linda Bulkowitch for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab/rit
Enclosures
Desk Copies (12): Ms. P. Fogarty

154-046: Phase I, Double Blind, Parallel, Placebo Controlled Pilot Study to Assess the Safety, Toleration and Pharmacokinetics of Oral Trovafloxacin Administration as a Single Dose and in Divided Doses to Healthy Male Subjects.

APPEARS THIS WAY ON ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

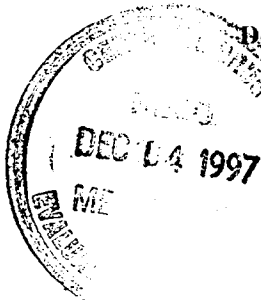


BM
ORIG AMENDMENT
ORIGINAL

Central Research

December 3, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



Department of Clinical Research
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Nov 2/9/97



Dear Doctor Goldberger:

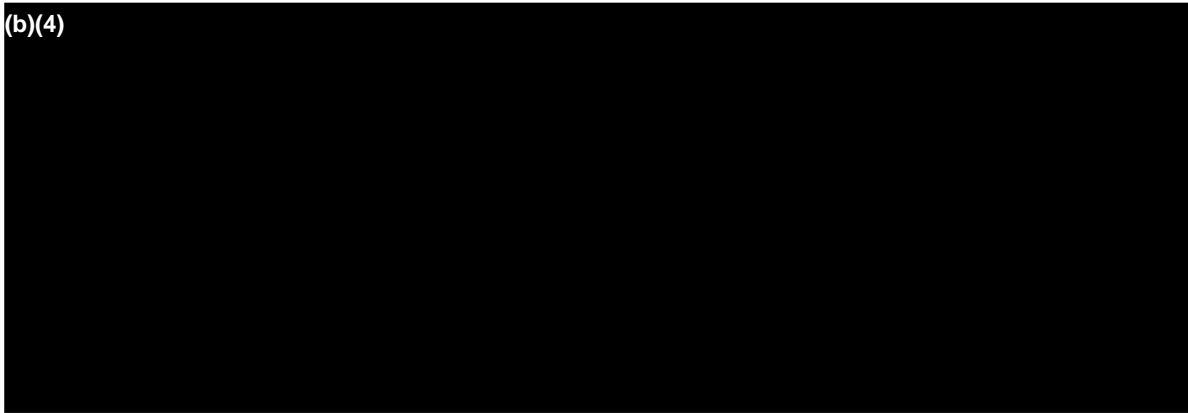
RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 070

~~NDA-20-760~~ TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 068 (*Cover letter only)

CLINICAL INFORMATION AMENDMENT

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to our November 14, 1997 telecon with the Division to discuss the Community Acquired Pneumonia (CAP) and Acute Exacerbation of Chronic Bronchitis (AECB) indications.

(b)(4)



A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager and Dr. Coyne.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

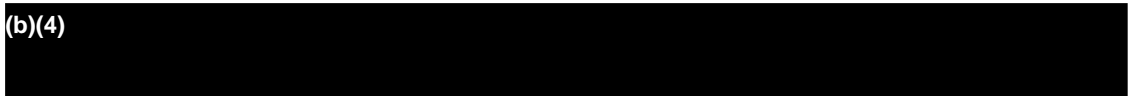


Sincerely yours,

Linda Bullock for:

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

(b)(4)



lab

Enclosure

Desk Copies (cover letter): Ms. P. Fogarty and Dr. P. Coyne

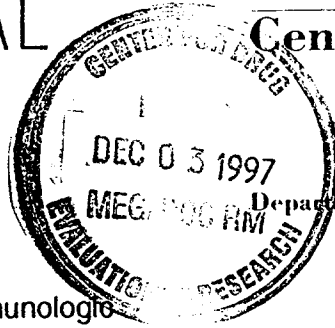
Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

BI

ORIG AMENDMENT



ORIGINAL



Central Research

December 2, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunology
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Department of Clinical Research

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PERMISSION OF PFIZER INC.

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafoxacin Mesylate)

Serial No. 67

NDA-20-760 TROVAN® I.V. (Alatrofoxacin Mesylate Injection)

Serial No. 66 *(Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Na
[Redacted] *12/9/97*

Reference is made to our pending New Drug Applications, submitted December 30, 1996.
Reference is also made to an October 24, 1997 telecon with Dr. Sousan Altaie, Microbiology
Reviewer.

Dr. Altaie had requested scattergrams on clinical microbiology data (Query #370). These
scattergrams were faxed to her attention on October 28, 1997. They are now being formally
submitted to complete our records.

A desk copy of this complete submission is being provided to Dr. Altaie. A desk copy of this
cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860)
441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Bullock

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

lab
Enclosure
Desk Copy: Dr. S. Altaie (complete)
Ms. P. Fogarty (cover letter)



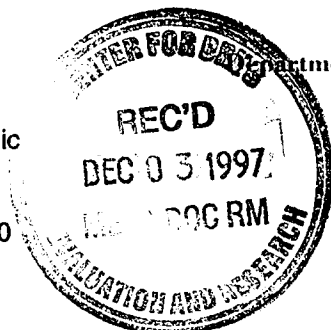
BM
ORIG AMENDMENT

ORIGINAL

Central Research

December 2, 1997

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



Department of Clinical Research

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BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovaflaxacin Mesylate)
Serial No. 068

~~NDA-20-760-~~ TROVAN® I.V. (Alatrofloxacacin Mesylate Injection)
Serial No. 067 (*Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION- NON-GONOCOCCAL CERVICITIS
AND URETHRITIS

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a May 13, May 19, May 21, May 22, June 4, and June 11, 1997 teleconferences with Dr. M. Makhene, Medical Reviewer.

On May 13, 1997, Dr. Makhene had requested assistance in preparing tables and listings to aid in her review of protocol #154-123*. Dr. Makhene requested the following (Query 146A):

- Preliminary listings of concomitant medication information to assist her in choosing drugs of interest to be included in subsequent patient listings. In response to this request, the tables were delivered on May 15, 1997:
 - ◆ "Indication" for Concomitant Antibiotics (Table NMED.1).
 - ◆ Reasons for concomitant antibiotics during study (Table NMED.2).
 - ◆ Con Meds by therapeutic class (Table NMED.3).
 - ◆ Con Meds by therapeutic class and prepared term (NMED.4).
- These tables are enclosed (Enclosure #1).
- Tables summarizing the number of patients randomized/treated/sponsor evaluable by center. In response to this request, Tables DM.1 and DM.2 were faxed to Dr. Makhene's attention on May 19, 1997. These tables are enclosed (Enclosure #2).
- Listing of reasons for non-evaluability. In response to this request, Dr. Makhene was referred to Table I of Appendix III of the study report.
- Listing of "relevant" concomitant medications for non-evaluable patients. This request was subsequent to Dr. Makhene's request for a preliminary listing of concomitant medication (Enclosure #1). In response to this request, Table DM.4 was provided by facsimile on May 22, 1997. This table is enclosed (Enclosure #3).
- Subject listing of day of assessment for first follow-up (EOT) with nominal window of day 8 to day 16. In response to this request, Tables DM.3.a and DM.3.b were faxed to Dr. Makhene's attention on May 19, 1997. These tables are enclosed (Enclosure #4).
- A listing of patients receiving ceftriaxone (as per protocol criteria) in order to allow assessment of "susceptibility pattern" and a listing of patients with unprotected sexual contact during study. In response to these request, Tables DM.5 and DM.6 were provided to Dr. Makhene by facsimile on May 22, 1997. These tables are enclosed (Enclosure #5).



new B/9/97

December 2, 1997

- Summaries of patients with co-infections (i.e., chlamydia with GC) by site and gender along with outcomes for the sponsor's evaluable analysis. In response to this request, Dr. Makhene was referred to Tables 5.1.1 through 5.4.4 in the study report.

On June 4, 1997 and June 11, 1997 Dr. Makhene requested that the listing of patients with unprotected sexual contact (Table DM.6) be modified to display information only for bacteriologically evaluable patients and display the bacteriological response at the end of the study. In response to this request, Table DM.7 was faxed to Dr. Makhene's attention on June 4, 1997 (Enclosure #6, Query #146B and Query #192).

She also requested a listing of post baseline positive Chyamydia cultures. In response to these requests, Table DM.8 was forwarded to Dr. Makhene's attention on June 19, 1997. This table is enclosed (Enclosure #7, (Queries #170 and #191).

On June 11, 1997 Dr. Makhene requested that electronic files be provided for the following of the above mentioned tables (Query #171):

- Subject Counts by Center (Table DM.1)
- Subject Counts [Randomized vs. Sponsor Evaluable] by Center (Table DM.2)
- Listing of Patients with Unprotected Sexual Exposure (Table DM.6)

A "draft" diskette was forwarded to Dr. Makhene's attention on June 23, 1997. A QA'd diskette containing these files is currently being submitted to complete our records (Enclosure #8). This diskette has been scanned and is free of viruses.

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager. If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991.

Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

APPEARS THIS WAY ON ORIGINAL

Linda Bulkowitch for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

*154-123- "A Randomized, Multicenter, Double-Blind, Double-Dummy Comparative Study of Trovafloxacin (CP-99,219) and Doxycycline for the Treatment of Uncomplicated Chlamydial Urethritis/Cervicitis" most recently amended on March 20, 1995 (b)(4)

lab

Enclosures

Desk Copy: Ms. P. Fogarty (Cover letter only)

NEW CORRESP

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100



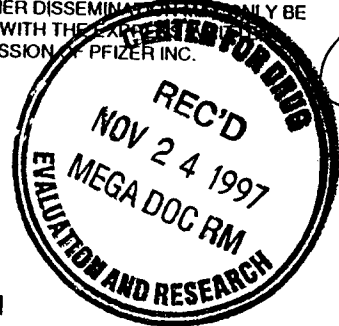
Central Research

November 21, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

New
12/14/97
[Redacted]

Department of Clinical Research
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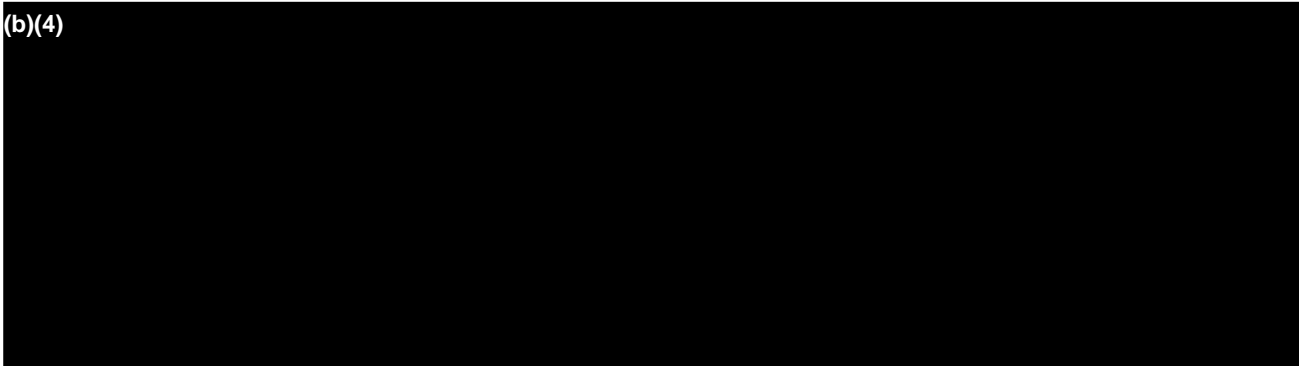
[Handwritten signature]

Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 64
NDA-20-760 - TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 63 (*Cover letter only)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a November 10, 1997 Email message and a November 11, 1997 telecon with Dr. Philip Coyne, Medical Officer.

(b)(4)



A desk copy of this submission is being provided to Dr. Coyne. A desk copy of the cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Ronald I. Trust

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

lab/rit

Enclosures

Desk Copies: Dr. P. Coyne (Complete)
Ms. P. Fogarty (Cover Letter)

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100



Central Research

October 29, 1997

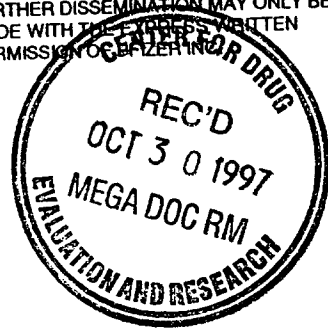
BB
ORIG AMENDMENT

Department of Clinical Research

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Handwritten signature/initials

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Dear Doctor Goldberger:

RE: NDA-20-759 - TROVAN® Tablets (Trovafloracin Mesylate)

Serial No. 059

~~NDA-20-760 - TROVAN® I.V. (Alatrofloracin Mesylate Injection)~~

Serial No. 058 *(Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996.
Reference is also made to an October 7, 1997 telecon with Dr. Philip Colangelo,
Biopharmaceutics Reviewer.

Dr. Colangelo had requested dissolution data for the tablet ~~(b)(4)~~.
(b)(4) A response to this request was provided by facsimile on October 14, 1997. It is
now being formally submitted to complete our records.

A desk copy of this cover letter is being provided to Ms. Fogarty. A desk copy of this complete
submission is being provided to Dr. Colangelo.

If you have any questions regarding this submission, please contact the undersigned at (860)
441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

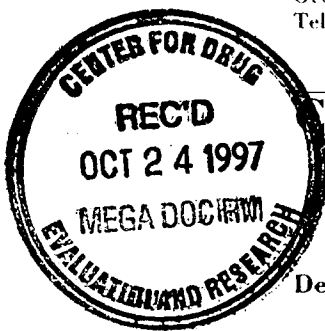
Sincerely yours,

Handwritten signature of Ronald I. Trust

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab
Enclosures
Desk Copy: Ms. P. Fogarty (Cover letter only)
Dr. P. Colangelo (Complete)

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100



Central Research

BM

October 23, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Department of Clinical Research

msi 10/24/97

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Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 58
NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 57 *(Cover letter only)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a September 29, 1997 teleconference with Dr. Brad Leissa, Team Leader and his request that Pfizer reanalyze our efficacy results for TROVAN studies in which Dr. Fiddes participated (Query #308).

Dr. Fiddes participated in four TROVAN studies: studies #154-103**, #154-116^, #154-109^ and #154-114°. Modified efficacy tables for these studies were forwarded by Federal Express to Ms. Fogarty's attention on October 13, 1997. Electronic copies of these tables were provided to Dr. Leissa on October 14, 1997 (Query #342).

A review of these tables suggests that removal of the efficacy results from Dr. Fiddes' center will not affect the overall conclusions from these studies.

A desk copy of this cover letter is being provided to Ms. Fogarty and Dr. Leissa.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Bulkinitch for:

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

** study #154-103, entitled, "A Randomized, Double-Blind, Multicenter Trial Comparing 7 Days of Oral Therapy with Trovafloracin (CP-99,219) (100 mg or 200 mg Daily) or Ciprofloracin Hydrochloride (500 mg Daily) for the Treatment of Uncomplicated Urinary Tract Infections."

Mark Goldberger, Director
NDA-20-759
NDA-20-760

2

October 23, 1997

^study #154-116, entitled, "A Randomized, Double-Blind, Multicenter Trial Comparing 3 Days and 7 Days of Oral Therapy with Trovafloxacin (CP-99,219) (100 mg Daily) and 3 Days Therapy with Norfloxacin (400 mg BID) for the Treatment of Uncomplicated Acute Urinary Tract Infections."

^study #154-109, entitled, "A Randomized, Double-Blind, Multicenter Trial Comparing 7 Days of Oral Therapy with Trovafloxacin (CP-99,219) (100 mg Daily) and Clarithromycin (500 mg BID) for the Treatment of Acute Exacerbation of Chronic Bronchitis."

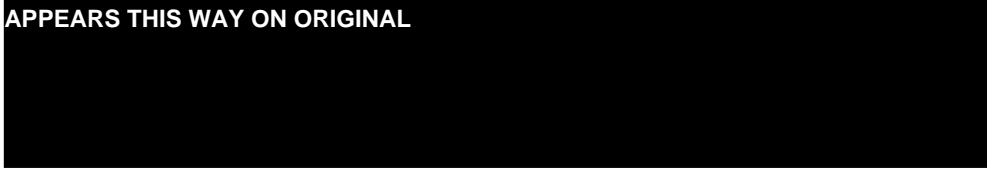
*study #154-114, entitled, "An Open, Noncomparative, Multi-Center Trial Designed to Assess the Efficacy and Safety of 10 Days Oral Therapy with Trovafloxacin (CP-99,219) (200 mg Once Daily) for the Treatment of Acute Sinusitis."

lab

Enclosures

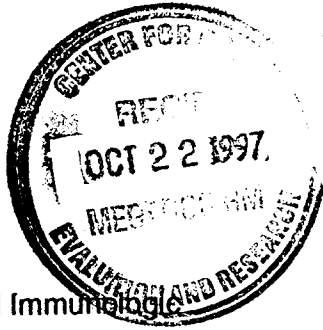
Desk Copies: Ms. P. Fogarty (Cover letter only)
Dr. B. Leissa (Cover letter only)

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Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

BB
~~NEW COURTESY~~
ORIG AMENDMENT



Central Research

Department of Clinical Research

October 21, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunology
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
INFORMATION SUBJECT TO 18-USE-1905
AND TO WHICH ALL CLAIMS OF PRIVILEGE
AND CONFIDENTIALITY ARE ASSERTED IN
BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

[Handwritten signature]
[Handwritten initials]

Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 56
NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 55 *(Cover letter only)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996.
Reference is also made to September 8 and 11, 1997 Email messages received from Dr. Philip Colangelo, Biopharmaceutics Reviewer. Reference is also made to a September 15, 1997 teleconference between Pfizer and Dr. Colangelo.

Dr. Colangelo had requested formulation details for the investigational formulations used in studies #154-028**, #154-042 (b)(4) A response to this request was provided by facsimile on October 3, 1997. It is now being formally submitted to complete our records (Enclosure #1).

(b)(4)

On September 4, 1997, Dr. B.V. Shetty, Chemistry Reviewer, asked for information on the alatrofloracin (TROVAN IV) formulation (Queries #273-280).

A response (normal type) to these questions (bold type) was provided by facsimile on October 3, 1997. It is now being formally submitted to complete our records (Enclosure #2).

A desk copy of this cover letter is being provided to Ms. Fogarty. Desk copies of this complete submission are being provided to Drs. Colangelo and Shetty.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Linda Bultman

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II

Dr. Goldberger, Director
NDA-20-759
NDA-20-760

2

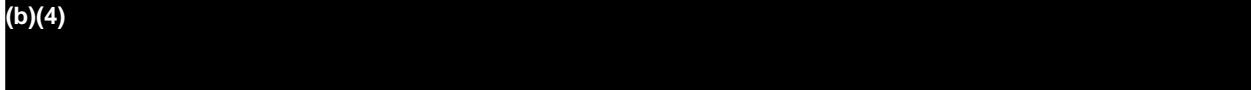
October 21, 1997

Regulatory Affairs Department

** study #154-028, entitled, "An Open, 3-Period, 3-Treatment, Randomized Crossover Evaluation of the Bioavailability of Trovafloxacin (CP-99,219) Administered as an Oral Suspension (OS) in a Fasted and Fed State Relative to the Tablet Formulation in Healthy Subjects."

^study #154-042, entitled, "Phase I, Open-Labeled, Cross-Over, Bioequivalence Study of the Proposed Commercial Table of Trovafloxacin (CP-99,219) Relative to the Phase III Tablet in Healthy Subjects."

(b)(4)

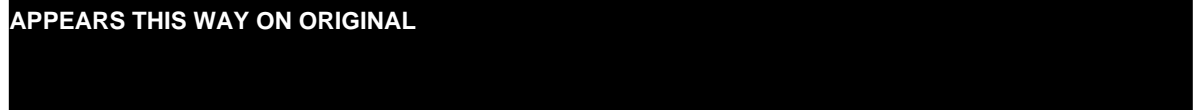


lab

Enclosures

Desk Copy: Ms. P. Fogarty (Cover letter only)
Dr. P. Colangelo (Complete)
Dr. B.V. Shetty (Complete)

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NC
NEW CORRESP

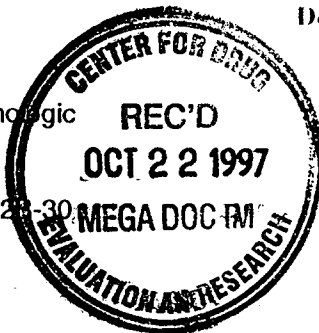


Central Research

October 21, 1997

Department of Clinical Research

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #128-30
5600 Fishers Lane
Rockville, MD 20857



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[Handwritten signature]
[Redacted box]

Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovaflloxacin Mesylate)
Serial No. 057

NDA-20-760* TROVAN® I.V. (Alatroflloxacin Mesylate Injection)
Serial No. 056 *(Cover letter only)

GENERAL CORRESPONDENCE

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a September 26, 1997 teleconference with Dr. Regina Alivisatos, Medical Reviewer.

Dr. Alivisatos had requested a list of #154-113* investigator sites that had enrolled patients. A list was provided by Email on September 26, 1997 (Query #307). This list is now being formally submitted to our NDAs to complete our records (Enclosure #1).

Pfizer has taken the initiative to also provide a list of investigator sites that enrolled patients for study #154-137**. This list was provided to Dr. Alivisatos via Email on October 6, 1997. It is being formally submitted to our file to complete our records (Enclosure #2).

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Linda Bulkowitch

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

*154-113- entitled "A Randomized, Multicenter, Double-Blind, Double-Dummy Trial Comparing Intravenous Alatroflloxacin (CP-116,517) Followed by Oral Trovaflloxacin (CP-99,219) with Intravenous Ciproflloxacin Followed by Oral Ciproflloxacin for the Treatment of Nosocomial Pneumonia."

**154-137- entitled "A Randomized Multicenter Open Trial Comparing Intravenous Alatroflloxacin (CP-116,517) Followed by Oral Trovaflloxacin (CP-99,219) with Intravenous Ceftazidime Followed by Oral Ciproflloxacin with Optional Gentamycin and Vancomycin for the Treatment of Nosocomial Pneumonia."

lab
Enclosure

ORIGINAL



Central Research

Department of Clinical Research

October 9, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products HFD-590
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

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Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 52

RESPONSE TO FDA REQUEST FOR INFORMATION- CHEMISTRY, MANUFACTURING
& CONTROLS

Reference is made to our pending New Drug Application, NDA-20-759, submitted December 30, 1996.
Reference is also made to Trovan Tablet Chemistry, Manufacturing and Controls questions received
August 13, 1997 from Dr. B.V. Shetty, Chemistry Reviewer (Queries #258-264).

Enclosed are Pfizer's responses to these questions. Each question is repeated and followed by our
response.

A desk copy of this submission is being provided to Dr. Shetty. A desk copy of this cover letter is being
provided to Ms. Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991.
Please include this information in our files for NDA-20-759.

Sincerely yours,

Linda Bullonitch

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

lab

Enclosure

Desk Copy: Ms. P. Fogarty (Cover letter only)
Dr. B. V. Shetty (Complete)

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

ORIGINAL



Central Research

September 25, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Department of Clinical Research

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Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)

Serial No. 51

~~NDA-20-760~~ TROVAN® I.V. (Alatrofloracin Mesylate Injection)

Serial No. 52 *(Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a teleconference on September 15, 1997 between Dr. Mamodikoe Makhene, Medical Reviewer and Dr. Raymond B. Johnson, Mr. Michael Zelasky, and Ms. Ann Dohmann of Pfizer.

During the September 15 teleconference we discussed two papers which addressed the low percentage of endocervical cultures with *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in patients with pelvic inflammatory disease. Dr. Makhene requested a copy of these papers (Query #293).

On September 16 these papers were forwarded to Dr. Makhene's attention via Federal Express. They are now being formally submitted to complete our records.

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

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lab
Enclosures
Desk Copy: Ms. P. Fogarty (Cover letter only)

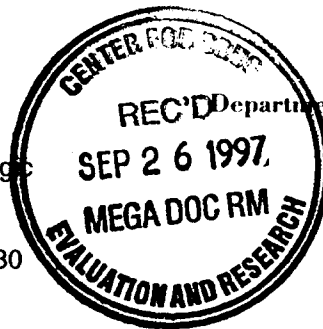
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Central Research

September 25, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857



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PERMISSION OF PFIZER INC.

Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovaflaxacin Mesylate)
Serial No. 51

NDA-20-760*- TROVAN® I.V. (Alatroflaxacin Mesylate Injection)
Serial No. 52 *(Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a teleconference on September 15, 1997 between Dr. Mamodikoe Makhene, Medical Reviewer and Dr. Raymond B. Johnson, Mr. Michael Zelasky, and Ms. Ann Dohmann of Pfizer.

During the September 15 teleconference we discussed two papers which addressed the low percentage of endocervical cultures with *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in patients with pelvic inflammatory disease. Dr. Makhene requested a copy of these papers (Query #293).

On September 16 these papers were forwarded to Dr. Makhene's attention via Federal Express. They are now being formally submitted to complete our records.

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager.

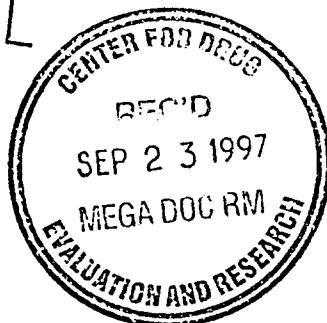
If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

lab
Enclosures
Desk Copy: Ms. P. Fogarty (Cover letter only)

61
ORIG AMENDMENT
ORIGINAL



Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

Central Research

Department of Clinical Research

September 22, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
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Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)

Serial No. 49

NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)

Serial No. 50 *(Cover letter only)

RESPONSE TO FDA REQUEST FOR INFORMATION- MICROBIOLOGY

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to our August 28, 1997 submission to our pending New Drug Applications. Reference is also made to teleconferences and Email, on August 5 and 19, 1997, between Dr. Soutan Altaie, Microbiology Reviewer and Ms. Ann Dohmann of Pfizer.

On August 5, Dr. Altaie requested the following:

APPEARS THIS WAY ON ORIGINAL

- Scattergrams for clinical microbiology data for TROVAN (Query #244, Enclosure #1).
- Redo the clinical microbiology tables in Section 7, taking into account only those patients from whom the following four parameters were determined: MIC, zone, clinical response and bacteriological response (Query #243, Enclosure #2).
- Prepare scattergrams of all in vitro microbiology data (in house and published) (Query #245)

On August 19, Dr. Altaie requested that Pfizer provide further breakdowns of scattergram plots to show U.S. and Non-U.S. clinical isolates (Query #266, also provided in Enclosure #1).

A draft response to queries 243, 244 and 266 was forwarded to Dr. Altaie's attention via Federal Express on August 29, 1997. This response is now being formally submitted to complete our records. Please note that a more detailed explanation of the content of this submission is included in the enclosed memo.

The response to query #245 was already formally submitted on August 28, 1997.

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager. If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Bulkonitch for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

lab
Enclosures
Desk Copy: Ms. P. Fogarty (Cover letter only)

MC
NEW CORRESP

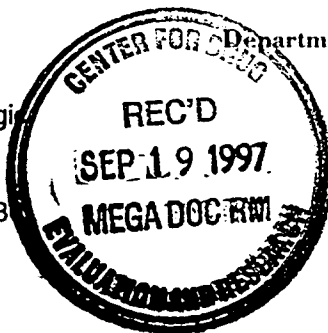


ORIGINAL

Central Research

September 18, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunology
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATTN: DOCUMENT CONTROL ROOM #12B-3
5600 Fishers Lane
Rockville, MD 20857



Department of Clinical Research

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Handwritten signature and date: 9/19/97

Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
Serial No. 47
NDA-20-760- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
Serial No. 48 *(Cover letter only)
GENERAL CORRESPONDENCE

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to our August 11, 1997 meeting with the Division (b)(4)

We are, herewith, submitting the slides that were presented by Michael DeBari, Pfizer Clinical Systems, and Linda Bulkovitch, Pfizer Regulatory Affairs. (Enclosure #1).

As requested, a revised table listing encrypted Email user names, titles and Email addresses (RRT List) was forwarded to Dr. Leissa's attention via encrypted Email on August 18, 1997. It is currently being submitted to complete our records (Enclosure #2). Also requested was the enclosed updated query tracking chart (Enclosure #3).

A desk copy of this submission is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

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lab
Enclosures
Desk Copy: Ms. P. Fogarty (Complete)

NC
NEW CORRESP



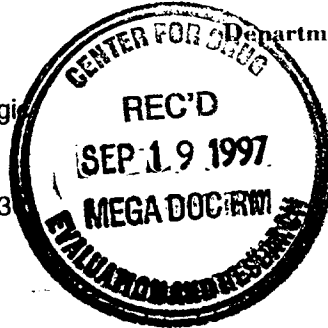
ORIGINAL

Central Research

si/ [redacted]
10/1/97
NAT

September 18, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-3
5600 Fishers Lane
Rockville, MD 20857



Department of Clinical Research

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Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovfloxacin Mesylate)

(b)(4)

NDA-20-760*- TROVAN® I.V. (Alatrofloxacin Mesylate Injection)

(b)(4)

GENERAL CORRESPONDENCE

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to our August 11, 1997 meeting with the Division (b)(4)

We are, herewith, submitting the slides that were presented by Michael DeBari, Pfizer Clinical Systems, and Linda Bulkovitch, Pfizer Regulatory Affairs (Enclosure #1).

As requested, a revised table listing encrypted Email user names, titles and Email addresses (RRT List) was forwarded to Dr. Leissa's attention via encrypted Email on August 18, 1997. It is currently being submitted to complete our records (Enclosure #2). Also requested was the enclosed updated query tracking chart (Enclosure #3).

A desk copy of this submission is being provided to Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

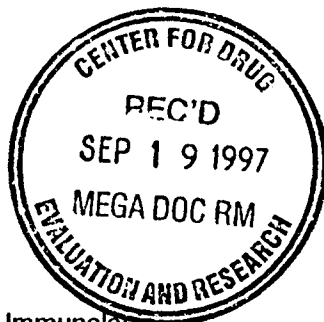
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL [redacted]

lab
Enclosures
Desk Copy: Ms. P. Fogarty (Complete)

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

ORIGINAL



Central Research

BM
ORIG AMENDME

September 18, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

Department of Clinical Research
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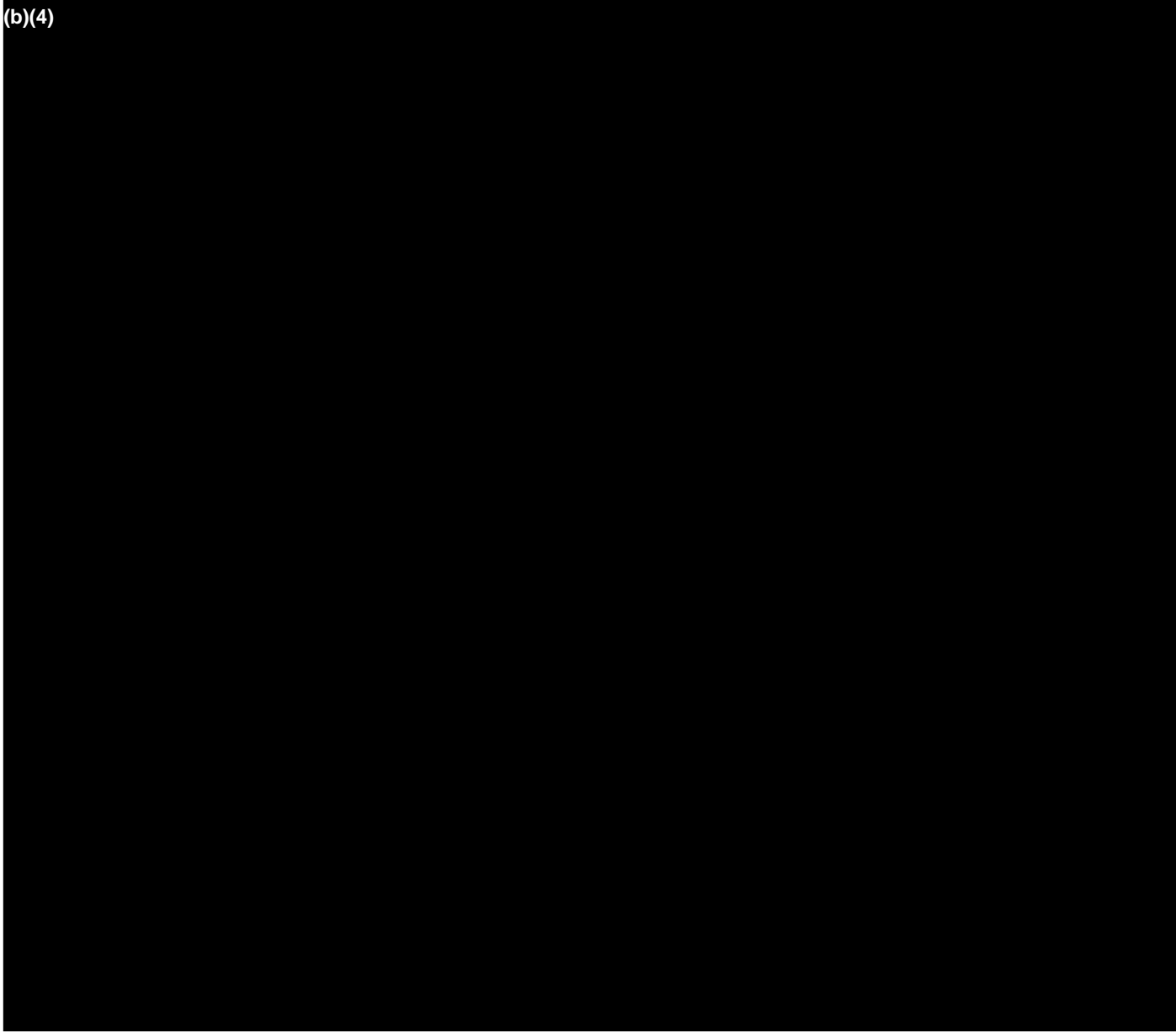
Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovfloxacin Mesylate)

(b)(4)

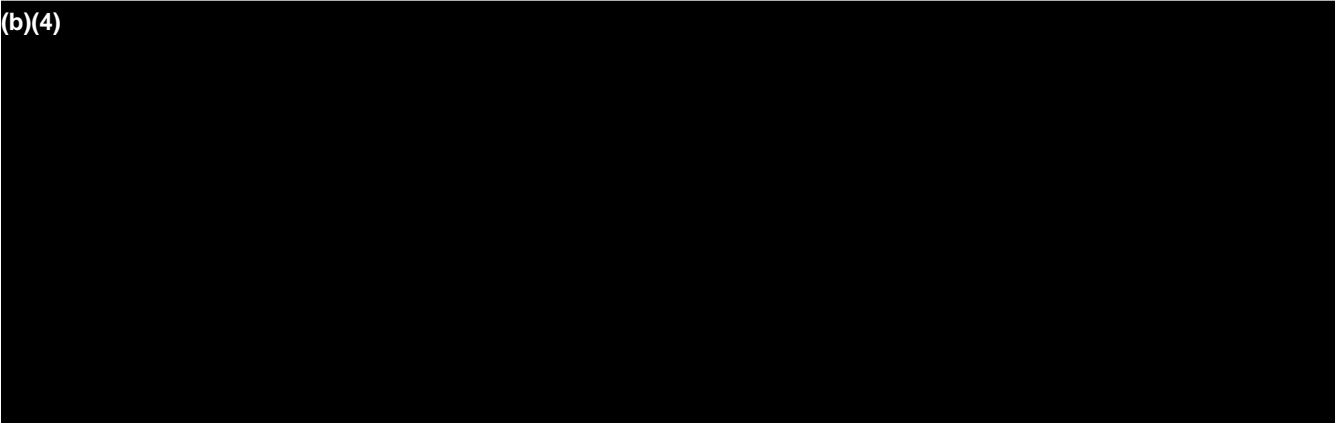
NDA-20-760*- TROVAN® I.V. (Alatrofloxacin Mesylate Injection)

(b)(4)



September 18, 1997

(b)(4)



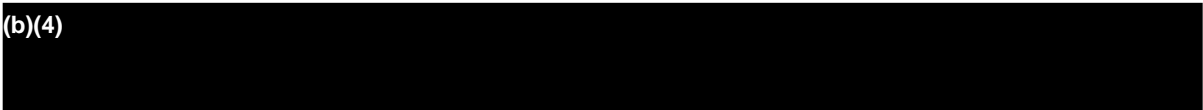
A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager and to Dr. Alivisatos.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Buckwiler for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

(b)(4)



lab

Enclosures

Desk Copy (Cover Letter): Ms. P. Fogarty
Dr. R. Alivisatos

APPEARS THIS WAY ON ORIGINAL



Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

ORIGINAL



Central Research

BUY
ORIG AMENDMENT

August 26, 1997

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic
Drug Products (HFD-590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

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Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
**INFORMATION AMENDMENT - CLINICAL
ELECTRONIC SUBMISSION UPDATE**

ms/ [redacted]
9/14/97

Reference is made to our pending New Drug Applications submitted on December 30, 1996. Reference is also made to our August 8, 1997 teleconference with Dr. Brad Leissa, Medical Team Leader and Ms. Pauline Fogarty, Project Manager, and to our August 15, 1997 submission that outlined corrections in clinical tables that need to be made to our pending New Drug Applications and Four Month Safety Update.

Provided herewith are hard copy corrected pages of the tables affected in our New Drug Applications and our Four Month Safety Update. These pages are being submitted to update the archival copy of the NDAs. The following are enclosed:

- A listing of the affected tables (**Enclosure #1**), depicting the page(s) within each table that was affected, followed by the corrected pages in yellow for ease of differentiation (**Enclosure #2**). Please note that the affected Appendix V study report listings are only being provided in the Esub, as per our original submission.
- A listing of additional corrections to complete or replace other sections of the NDAs in which either a table had been omitted or the incorrect table was placed in the NDAs (**Enclosure #3**), followed by the correct pages in yellow for ease of differentiation (**Enclosure #4**).
- A listing of case report forms that should have been included in the PDF versions of the update to the New Drug Applications (**Enclosure #5**). Please note that none of these additional CRFs (3) were for patients who prematurely discontinued from the trial for an adverse event.

Please note that each of these listings were previously provided in our August 15, 1997 submission.

Reference is also made to the FDA Form 483 which was prepared at the conclusion of FDA's inspection and cited certain discrepancies between source documents and information captured in the Case Report Forms for meningitis study #154-149. The relevant corrections in data, referred to as "Errata," were provided to the Office of Compliance as part of our response to the 483 which addresses these observations. This was also provided in our August 15, 1997 submission.

In regards to the Esub amendment, arrangements to deliver the (b)(4) [redacted] will be made in the near future. The Esub Update will contain electronic files of all enclosures, the Errata and the additional PDF Case Report Forms.

August 26, 1997

Please note that none of the files from the original (b)(4) will be overwritten by this (b)(4) update. The corrected tables will be listed first (with the corrected pages noted), followed by the table in error. Please also note that where many errors occurred in one section of the application (e.g., Appendix V of the study reports), a separate list will be used to outline the pages in a table that were changed. A separate table listing the corrected pages will therefore be used for studies #154-134, #154-101, #154-128, #154-132, #154-139, #154-140, #154-119, and #154-125.

As agreed with Ms. Fogarty, the hard copy archive will be corrected on Thursday, September 4, 1997.

As stated previously, none of the errors noted have any impact on the safety and efficacy conclusions presented in our NDAs.

A desk copy of this cover letter is being provided to Ms. Fogarty.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Bulkonitch for:

Ronald I. Trust, Ph.D., MBA
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

lab

Enclosures

Desk Copy: Ms. P. Fogarty (Cover letter only)

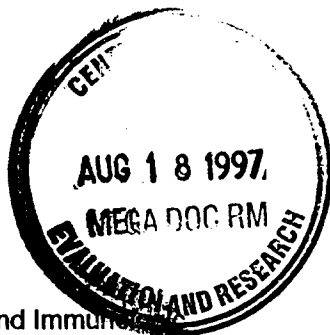
Serial No. 43 NDA-20,759

44 NDA-20,760 *(Cover letter only)

APPEARS THIS WAY ON ORIGINAL

BM
ORIG AMENDMENT
ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100



Central Research

August 15, 1997

Department of Clinical Research

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunology
Drug Products (HFD-590)
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
INFORMATION SUBJECT TO 18-USE-1905
AND TO WHICH ALL CLAIMS OF PRIVILEGE
AND CONFIDENTIALITY ARE ASSERTED IN
BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Goldberger:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
INFORMATION AMENDMENT - CLINICAL
ELECTRONIC SUBMISSION UPDATE

Reference is made to our pending New Drug Applications submitted on December 30, 1996. Reference is also made to our August 8, 1997 teleconference with Dr. Brad Leissa, Medical Team Leader and Ms. Pauline Fogarty, Project Manager.

As you are aware, the Office of Compliance has recently completed GMP, clinical investigator and, most recently, a sponsor/monitor inspection at our facility (b)(4)

The recently completed clinical inspection (b)(4) facility also included a clinical investigator (b)(4)

The FDA Form 483 which was prepared at the conclusion of this inspection cites certain discrepancies between source documents and information captured in the Case Report Forms for this meningitis study. The relevant corrections in data, referred to as "Errata," was provided to the Office of Compliance as part of our response to the 483 which addresses these observations. A copy of this Errata is provided in Enclosure #1.

Upon examination of (b)(4) files, we recently noted that on rare occasions (less than 5% of all tables in the NDA), blank lines were inadvertently substituted for lines of text in portions of tables (typically one to three lines, or occasionally, more in a few very large tables). This occurred during the ASCII → PDF conversion steps. We have identified a particular characteristic contained in the files in which these blank lines appeared. We then scanned our entire NDA and subsequently identified 333 tables in our original application and 11 tables in our 4-month Safety Update with this characteristic. Approximately 50% of these blank lines appeared in areas of the table that do not contain data (e.g., table header, lines separating header from body of table, or footer).

Enclosure #2 provides a listing of these tables and depicts the page(s) within each table that was affected. As discussed with Dr. Leissa and Ms. Fogarty, corrected pages for these tables will be provided for both the archive (b)(4)

August 15, 1997

We will also be making additional corrections to complete or replace other sections of the Esub in which we have found additional errors. A list of the affected tables is provided in **Enclosure #3**.

Additional case report forms that should have been included will be provided in the upcoming update. A list of these case report forms is enclosed (**Enclosure #4**). (b)(4)

We believe that none of the errors noted have contributed to incorrect conclusions regarding the safety or efficacy of Trovan. Arrangements to deliver this amendment will be made in the near future.

Desk copies of this submission are being provided to Ms. Fogarty for distribution to all seven Medical Reviewers (Drs. R. Albrecht, R. Alivisatos, P. Coyne, D. Davis, B. Leissa, M. Makhene and R. Roca), herself, and Dr. Philip Colangelo, Pharmacological Reviewer.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,



Ronald I. Trust, Ph.D., MBA
Associate Director II
Regulatory Affairs Department

lab

Enclosures

Desk Copies (9 complete): Ms. P. Fogarty

Serial No. 42 NDA-20,759

43 NDA-20,760 *(Cover letter only)

APPEARS THIS WAY ON ORIGINAL

DUPLICATE

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100



Central Research

SU
NDA ORIG AMENDMENT

Department of Clinical Research

April 28, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
INFORMATION SUBJECT TO 18-USC-1905
AND TO WHICH ALL CLAIMS OF PRIVILEGE
AND CONFIDENTIALITY ARE ASSERTED IN
BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Feigal:

RE: NDA-20-759 - TROVAN® TABLETS (TROVAFLOXACIN MESYLATE)
NDA-20-760* - TROVAN® I.V. (ALATROFLOXACIN MESYLATE INJECTION)
FOUR MONTH SAFETY UPDATE

Reference is made to our pending New Drug Applications, NDA-20-759 and NDA-20-760 submitted December 30, 1996. Reference is also made to a January 28, 1997 teleconference with the Division and to our February 4, 1997 Four Month Safety Update proposal. On February 7, 1997 the Division agreed with this proposal.

Pursuant to 314.50 vi(b), we are submitting a Four Month Safety Update for the above referenced NDAs. As stated in the proposal, Pfizer is submitting Case Report Forms (CRFs) for safety discontinuations and serious adverse events. Please note that the CRFs are being provided electronically and all other information is being provided both hardcopy and electronically as in the original submission. Please also note that there are no new data for I.V.-only studies. Therefore, only oral treatment, which also includes I.V.-to-oral data, has been updated.

A desk copy of this submission is being provided to Dr. Philip Coyne, Primary Medical Reviewer and a cover letter to Ms. Pauline Fogarty, Project Manager. If you have any questions or need any additional information, please contact the undersigned at (860) 441-6991.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ MAIL ☐ IMPROV
CSO INITIALS

Sincerely yours,

Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

isl
2/29/97

law

Enclosures

Desk Copies: Dr. Philip Coyne (Complete)
Ms. Pauline Fogarty (Cover Letter)

Serial No. 30 NDA-20-759

30 NDA-20-760 *(Cover letter only)



ORIGINAL

Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

1



Central Research

NEW CORRESPONDENCE

Department of Clinical Research

April 25, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug
Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
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FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Feigal:

RE: NDA-20-759- TROVAN[®] Tablets (Trovafloracin Mesylate)
NDA-20-760*- TROVAN[®] I.V. (Alatrofloracin Mesylate Injection)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a March 18, 1997 discussion with Dr. Brad Leissa, Medical Team Leader.

Dr. Leissa had requested that Pfizer provide a revised contact list to include Dr. David Luke as the contact for the surgical studies (query #73). A revised contact list was forwarded to Dr. Leissa's attention via facsimile on March 19, 1997. In the interim, this list has been revised again to add Ms. Kristi Helmbold's pager number, Mr. Michael DeBari, Pfizer Email Contact, Dr. Daphne Lin, Biostatistics Reviewer, Dr. David Feigal, Acting Director and Kjeld Molvig, Division Systems Support.

A revised list is being submitted to our NDAs to complete our records. A desk copy of this submission is being provided to Dr. Leissa, Dr. Philip Coyne, Primary Medical Reviewer and Ms. Pauline Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information in our files for NDA-20-759 and NDA-20-760.

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ M.A.L.
☐ MERAQ	
CSO INITIALS	DATE

ISI [Redacted] *[Signature]*

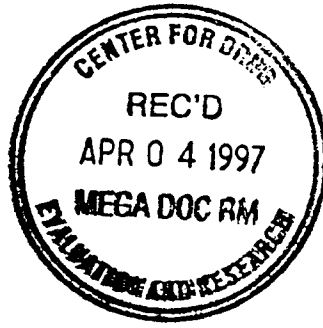
Sincerely yours,

Linda Wypocki for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

law
Enclosure
Desk Copy: Ms. P. Fogarty
Dr. P. Coyne
Dr. B. Leissa
Serial No.: 29 NDA-20-759
29 NDA-20-760 *(Cover letter only)





Central Research

BC
ORIG AMENDMENT

Department of Clinical Research

April 3, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug
Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
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FURTHER DISSEMINATION MAY ONLY BE
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PERMISSION OF PFIZER INC.

Dear Doctor Feigal:

RE: ~~NDA-20-759~~ TROVAN® Tablets (Trovafloracin Mesylate)
~~NDA-20-760~~ TROVAN® I.V. (Alatrofloracin Mesylate Injection)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996.

(b)(4)
[Redacted]
(b)(4)
[Redacted]

A desk copy of this submission is being provided to Dr. B.V. Shetty, Chemistry Reviewer and a copy of this cover letter is being provided to Ms. Fogarty, Project Manager.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information for our file for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL
[Redacted]

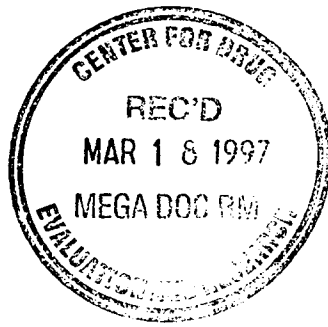
Sincerely yours,

Linda Wysocki for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

law
Enclosures
Desk Copies: Dr. B.V. Shetty (Complete)
Ms. Pauline Fogarty (Cover Letter)
Serial No.: 23 NDA-20-759
23 NDA-20-760 *Cover letter only

REVIEWS COMPLETED
CSO ACTION:
 LETTER N.A.I. MEMO
CSO INITIALS /s/ [Redacted] DATE 4/1/97

ORIGINAL



Central Research

Department of Clinical Research

March 17, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug
Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
INFORMATION SUBJECT TO 18-USE-1905
AND TO WHICH ALL CLAIMS OF PRIVILEGE
AND CONFIDENTIALITY ARE ASSERTED IN
BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Feigal:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our pending New Drug Applications, submitted December 30, 1996.
Reference is also made to a February 19, 1997 discussion with Ms. Pauline Fogarty, Project
Manager. Ms Fogarty had indicated that the Environmental Safety Officer, Ms. Nancy Sager,
had completed her review and had a few comments.

Enclosed are Ms. Sager's questions followed by our responses (Queries #48 and #49). A
desk copy of this submission is being provided to Ms. Sager, Ms. Fogarty and Dr. B.V. Shetty,
Chemistry Reviewer. If you have any questions regarding this submission, please contact the
undersigned at (860) 441-6991.

Please include this information for our files for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

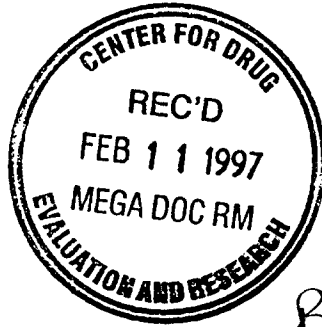
Sincerely yours,
Linda Wypocki for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

- law
- Enclosures
- Desk Copies (3): Ms. Nancy Sager (Complete)
- Ms. Pauline Fogarty (Complete)
- Dr. B.V. Shetty (Complete)
- Serial No.: 20 NDA-20-759
- 20 NDA-20-760 *Cover letter only

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ M.A.I. ☐ MEMO
CSO INITIALS <i>ls/</i> [Redacted] DATE 3/19/97

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100



#1
Central Research

Department of Clinical Research

February 10, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug
Products

BC
NDA ORIG AMENDMENT

Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
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FURTHER DISSEMINATION MAY ONLY BE
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Dear Doctor Feigal:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
INFORMATION AMENDMENT- CHEMISTRY, MANUFACTURING AND CONTROL
GENERAL CORRESPONDENCE

Pursuant to 21 CFR 312.31, we are submitting an amendment to NDA-20-759 and NDA-20-760.
Reference is made to our December 30, 1996 submission of NDA-20-759 and NDA-20-760. Reference
is also made to our January 15, 1997 teleconference with Dr. B.V. Shetty, Chemistry Reviewer.

We are currently submitting information on manufacturing and testing sites in preparation for the pre-
approval inspections for trovafloracin mesylate and trovafloracin mesylate tablets (100 and 200 mg)
(Enclosure #1) and alatrofloracin mesylate and alatrofloracin mesylate injection (b)(4)
as trovafloracin/vial (Enclosure #2). This information was previously provided by facsimile on January
23, 1997.

A desk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager. If you have
any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please
include this information for our files for NDA-20-759 and NDA-20-760.

Sincerely yours,

Linda Wypack for:
Ronald I. Trust, Ph.D.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

law

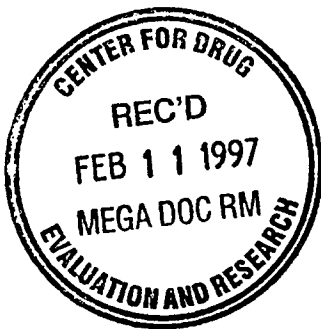
Desk Copy: Ms. Pauline Fogarty (Cover letter only)
Serial No. 11NDA-20-759
11NDA-20-760 (*Cover letter only)

REVIEWS COMPLETED
CSO ACTION:
 LETTER N.A.I. MEMO
CSO INITIALS */sl* [redacted] *1/19/97* DATE

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

#1



Central Research

Department of Clinical Research

February 10, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESPONDENCE

CONFIDENTIAL/TRADE SECRET
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FURTHER DISSEMINATION MAY ONLY BE
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APPEARS THIS WAY ON ORIGINAL

Dear Doctor Feigal:

RE: NDA-20-759- TROVAN® Tablets (Trovafoxacin Mesylate)
NDA-20-760* - TROVAN® I.V. (Alatrofoxacin Mesylate Injection)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to our December 30, 1996 submission of NDA-20-759 and NDA-20-760. Reference is also made to our December 6, 1996 meeting with the Division and our January 15, 1997 teleconference with Ms. Pauline Fogarty, Project Manager.

The Division had requested a list of Pfizer counterparts the Division reviewers can contact directly for minor clarifications. Enclosed is a chart listing the names, phone numbers, facsimile numbers and Email addresses for both the Division reviewers and their Pfizer counterparts. A desk copy of this submission is being provided to Ms. Fogarty and Dr. Philip Coyne, Primary Medical Reviewer.

Queries #10 and #20 have been completed with the submission of this information. If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information for our file for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Linda Wypocki for:
Ronald I. Trust, Ph.D.
Associate Director II
Regulatory Affairs Department

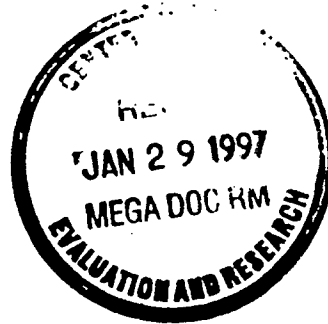
law

Desk Copies: Ms. Pauline Fogarty
Dr. Philip Coyne
Serial No. 10 NDA-20-759
10 NDA-20-760 (*Cover letter only)

REVIEWS COMPLETED
CSO ACTION: LETTER N.A.I. MEMO
CSO INITIALS */s/* [redacted] DATE 2/19/97

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100



Central Research

Department of Clinical Research

January 28, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
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FURTHER DISSEMINATION MAY ONLY BE
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PERMISSION OF PFIZER INC.

BM
NDA ORIG AMENDMENT

Dear Doctor Feigal:

RE: NDA-20-759 - TROVAN® TABLETS (TROVAFLOXACIN MESYLATE)
NDA-20-760* - TROVAN® I.V. (ALATROFLOXACIN MESYLATE INJECTION)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to teleconferences with Dr. Matthew Thomas, Division of Scientific Investigations on September 4 and December 6 and 9, 1996. Reference is also made to our pending NDA submissions of December 30, 1996.

To assist Dr. Thomas in preparing for clinical study site inspections, he has requested the following information:

- A list of site locations and number of subjects enrolled for each pivotal study, by site.
- A table showing overall subject randomization, treatment with study drug, evaluability and completion status, including those evaluated for adverse events and discontinuations.
- A copy of the study report synopsis for each pivotal study.

In response to these requests we are providing the following:

- A copy of the cover letter to the NDAs, including all attachments (Enclosure #1). Please note that Attachment #6 contains a table outlining all pivotal studies by indication along with the basic study design of each.
- For each pivotal study we are providing the following (Enclosure #2):
 - A table outlining sites that randomized subjects, separated by country.
 - The study report synopsis.
 - The following tables from each study report:
 - Table 1.1 "Subject Disposition"
 - Table 1.2 "Study Evaluation Groups: Randomized Subjects"

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS <i>/s/</i> DATE 2/3/97

January 28, 1997

- Table 1.3 "Number of Subjects Enrolled by Center: Randomized Subjects"

Please note that the pivotal study information provided in Enclosure #2 is presented in the order of Attachment #6 to the cover letter. We hope that this information provides sufficient information to help Dr. Thomas prepare for the site inspections.

Dr. Thomas also requested evaluability, discontinuation and safety information by site. We will be analyzing our data using these analysis parameters and will provide this information at a later date.

In addition, we will also be providing a list of study sites that were audited during the conduct of the studies. Please note that we did not exclude any clinical information from analysis as a result of any audit findings.

Enclosed is our Query Tracking Chart that describes the status of our NDA queries to date (Enclosure #3). Queries with completed responses have been shaded. We have designated Dr. Thomas' request as Queries #1 and #2.

A desk copy of this submission is being provided to Dr. Thomas and a copy of this cover letter is being provided to Ms. Pauline Fogarty, CSO. If you have any questions or need any additional information, please contact the undersigned at (860) 441-6991.

Sincerely yours,

Linda Wypochi for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director II
Regulatory Affairs Department

APPEARS THIS WAY ON ORIGINAL

law

Enclosures

Desk Copies: Dr. Matthew Thomas (Complete)
Ms. Pauline Fogarty (Cover Letter)

Serial No. 5 NDA-20-759
5 NDA-20-760 (Cover letter only)

APPEARS THIS WAY ON ORIGINAL

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS
DATE



Central Research

BT
NDA ORIG AMENDMENT

Department of Clinical Research

January 20, 1997

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug
Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

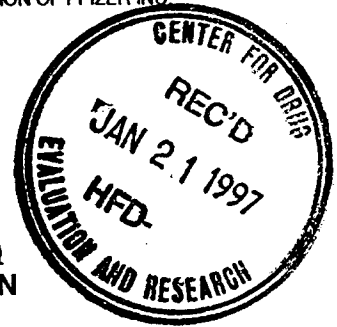
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FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

noted
SI

3/14/97

Dear Doctor Feigal:

RE: NDA-20-759- TROVAN® Tablets (Trovafloracin Mesylate)
NDA-20-760*- TROVAN® I.V. (Alatrofloracin Mesylate Injection)
RESPONSE TO FDA REQUEST FOR INFORMATION



Reference is made to our pending New Drug Applications, submitted December 30, 1996. Reference is also made to a December 30, 1996 discussion with Dr. Terry Peters, Pharmacology Reviewer and her request that Pfizer provide "raw data" of histopathology information, by animal, for studies of 3 months duration or greater, if not available in the study reports.

In response to her request please note that there were three studies of 3 months duration or greater, that study reports for these studies have been submitted to (b)(4) NDA-20-759, and NDA-20-760 and that the histopathology data can be found in a study report appendix. For ease of review, we are providing (b)(4) and page references for the studies:

- Study 93-783-16: entitled "CP-99,219-27 6 Month Gavage Study In Beagle Dogs @ 7.5, 15, (7.5 bid), and 50 (25 bid) mg/kg" (b)(4) Individual pathology data begins on page 144.
- Study 93-783-17: entitled "CP-99,219-27 6 Month Oral Gavage Study In Sprague-Dawley Rats @ 25, 75, and 200 (100 bid) mg/kg" (b)(4) Individual pathology data begins on page 194.
- Study 94-783-23: entitled " CP-99,219-27 Six Month Oral Gavage Reversibility Study In Beagle Dogs @ 50 (25 BID) mg/kg/day" (b)(4) Individual pathology data begins on page 84 (this is liver data only).

Dr. David Feigal, Acting Director
NDA-20-759
NDA-20-760

2

January 20, 1997

Desk copies of this submission are being provided to Ms. Pauline Fogarty, CSO and to Dr. Peters. Please note that this query is query #4 on our enclosed tracking chart. All completed queries are shaded for ease of review.

If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information for our file for NDA-20-759 and NDA-20-760.

Sincerely yours,

APPEARS THIS WAY ON ORIGINAL

Linda Wypocki for:
Ronald I. Trust, Ph.D., M.B.A.
Associate Director I
Regulatory Affairs Department

law

Enclosures

Desk Copies (2): Ms. Pauline Fogarty
Dr. Terry Peters

Serial No.: 4 NDA-20-759
4 NDA-20-760 *Cover letter only

APPEARS THIS WAY ON ORIGINAL

ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100



#1
Central Research

January 20, 1997

NEW CORRESPONDENCE

Department of Clinical Research

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug
Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, MD 20857

CONFIDENTIAL/TRADE SECRET
INFORMATION SUBJECT TO 18-USE-1905
AND TO WHICH ALL CLAIMS OF PRIVILEGE
AND CONFIDENTIALITY ARE ASSERTED IN
BOTH STATUTORY AND COMMON LAW.
FURTHER DISSEMINATION MAY ONLY BE
MADE WITH THE EXPRESS WRITTEN
PERMISSION OF PFIZER INC.

Dear Doctor Feigal:

RE: NDA-20-759- TROVAN® Tablets (Trovafoxacin Mesylate)
NDA-20-760*- TROVAN® I.V. (Alatrofoxacin Mesylate Injection)
RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made our December 30, 1996 submission of NDA-20-759 and NDA-20-760. Reference is also made to a December 20, 1996 discussion with Ms. Pauline Fogarty, Project Manager and our discussion regarding training the NDA reviewers on use of the Esub.

Enclosed please find a revised list of suggested reviewers to receive Esub training. This list supersedes the list provided to Ms. Addie Evans, CSO Support by facsimile on December 30, 1996. This request is Query #3. Enclosed is an updated tracking chart containing all queries received to date. Completed queries have been shaded for ease of review.

Arrangements have been made to provide training on use of the Esub for Dr. Philip Coyne (completed on January 6, 1997) and with other DAIDP staff (completed on January 14, 1997). We appreciate the opportunity to provide this orientation for electronic review of our Applications.

A desk copy of this submission is being provided to Ms. Fogarty. If you have any questions regarding this submission, please contact the undersigned at (860) 441-6991. Please include this information for our file for NDA-20-759 and NDA-20-760.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Linda Wypochi for:
Ronald I. Trust, Ph.D.
Associate Director I
Regulatory Affairs Department

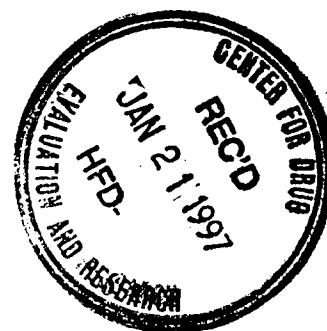
law

Desk Copy: Ms. Pauline Fogarty

Serial No. 3 NDA-20-759

3 NDA-20-760 (*Cover letter only)

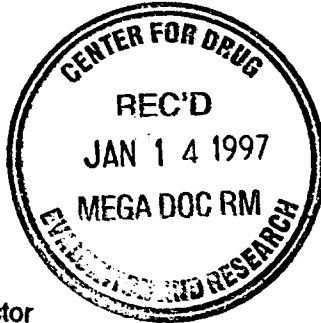
REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☒ N.A.I.
☐ MEMO	
CSO INITIALS	DATE
[Redacted]	1/22/97



ORIGINAL

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 203 441 4100

NDA 20-760



Central Research

January 13, 1997

Department of Clinical Research

David Feigal, M.D., Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD #520
Office of Drug Evaluation IV
ATT: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
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BT

NDA ORIG AMENDMENT

Dear Doctor Feigal:

RE: NDA-20-759 - TROVAN® Tablets (TROVAFLOXACIN MESYLATE)
NDA-20-760 - TROVAN® I.V. (Altrofloxacin Mesylate)

(b)(4)

Reference is made to our pending New Drug Applications for TROVAN® Tablets and TROVAN® I.V., submitted on December 20, 1996. Pursuant to 21 CFR 312.30 and 314.60 we are submitting, in triplicate, and in duplicate respectively, an amendment to our investigational New Drug Application for TROVAN® Tablets, Oral and an amendment to our New Drug Application for TROVAN® Tablets and TROVAN® I.V.

We are enclosing the following preclinical report conducted by the Department of Drug Safety Evaluation, Pfizer Central Research, Groton, Connecticut:

Study No. 96-783-32- *In Vitro* Cytogenetic Photomutagenicity Studies

In order to be consistent with our IND process, we will submit all Information Amendments for Pharmacology and Toxicology and Clinical Data to NDA-20-759, with cross-reference with NDA-20-760. If you have any questions, please contact the undersigned at (860) 441-6991.

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,

Ronald I. Trust, Ph.D., M.B.A.
Associate Director I
Regulatory Affairs Department

law

Enclosure

Serial No. 265
002
002

(b)(4)
NDA-20-759
NDA-20-760 *(Cover Letter Only)

REVISIONS COMPLETED

CSO ACTION	DATE
☐ LETTER	
☒ MEMO	
CSO INITIALS	DATE

/s/ [Redacted]