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 Number (%) of Subjects		Doxycycline 100 mg BID Number (%) of Subjects		95% CI
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	Trovafloxacin (200 mg) E	P	Total Eradicated	Doxycycline (100 mg b. i. d.) E	P	NA	Total Eradicated	95% CI
MALE									
C. trachomatis	URETHRA	86	10	86/96	96	1	0	96/97	(- 15.8, -3.0)
N. gonorrheae/ 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. gonorrheae/ 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. gonorrheae/ 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

Trovafloxacin

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 3. 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)

	Trovafloxacin 200 mg qd	Doxycycline 100 mg BID	95% CI
	Number (%) of Subjects		
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	Trovafloxacin (200 mg) E	P	Total Eradicated	Doxycycline (100 mg b. i. d.) E	P	Total Eradicated
MALE							
C. trachomatis	URETHRA	76	5	76/81(94%)	88	1	88/89(99%)
N. gonorrheae/ C. trachomatis	URETHRA	3	1	¾	5	0	5/5
FEMALE							
C. trachomatis	URETHRA/ CERVIX	140	5	140/145(97%)	111	4	111/115(97%)
N. gonorrheae/ C. trachomatis	CERVIX	4	1	4/5	7	1	7/8

APPEARS THIS WAY ON ORIGINAL

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	Doxycycline 100 mg BID	95% CI
	Number (%) of Subjects		
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:

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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. APPEARS THIS WAY ON ORIGINAL

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. APPEARS THIS WAY ON ORIGINAL

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. gonorrheae.* APPEARS THIS WAY ON ORIGINAL

1. Anorectal cultures were necessary only if the male subject's history indicated rectal sexual exposure.
2. In females who lacked cervices (e.g. those who have undergone hysterectomy), the urethra was cultured. APPEARS THIS WAY ON ORIGINAL

Patients with Gram stain evidence of gonococcal urethritis and/or cervicitis received a single 125 mg IM dose of ceftriaxone. APPEARS THIS WAY ON ORIGINAL

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									
	Baseline Day							Post-treatment Follow-ups (5-9 d)[a]	(12-18 d)	(25-35 d)
	1	2	3	4	5	6	7	1 week	2 weeks	4 weeks
Treatment										
Groups 1,3, 4[b]	X	X	X	X	X	X	X			
Group 2[c]	X	X	X	X	X					
History and Physical	X									
Assessments										
Clinical	X							X	X	X
Laboratory										
1. FTA or RPR	X									
2. Hematology	X							X	X	
abn[d]										
3. Serum Chemistry	X							X	X	abn
4. Urinalysis	X							X	X	abn
5. Gram stain[e]	X									
6. Cultures for *C. trachomatis*	X							X	X	X
7. Cultures for *N. gonorrhoeae*	X							X	X	X
8. Pregnancy Test[f]	X									
Adverse Events								X	X	X

[a]Window for follow-up visit

[b]Group 1 - 200 mg qd x 7 days; Group 3 - 100 mg qd x 7 days; Group 4 - 50 mg qd x 7 days

[c]Group 2 - 200 mg qd x 5 days

[d]Only for clinically significant abnormalities present at previous visit

[e]Where feasible (i.e., presence of urethral or cervical discharge)

[f]For women of childbearing potential

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BEST POSSIBLE

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

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

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:

CRITERIA	MIC* (ug/ml)
SUSCEPTIBILITY	≤2
INTERMEDIATE	4
RESISTANT	≥8

APPEARS THIS WAY ON ORIGINAL

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

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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

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.

[redacted]

STATISTICAL CONSIDERATIONS

The methods of analysis were those used in study 123.

[redacted]

PROTOCOL DEVIATIONS

No significant protocol deviations were noted during this study.

[redacted]

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

[redacted]

PATIENT ENROLLMENT AND DISPOSITION

Table 105.1 (from study report)

Table B. Summary of Study Evaluation Groups for Males and Females
Randomized Subjects

	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 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

[redacted]

BEST POSSIBLE

Demographics

Table 105.2 Demographic Characteristics for Treated Subjects
(applicant's table 2.1.1)

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	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
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.

APPEARS THIS WAY ON ORIGINAL

EFFICACY [BEST POSSIBLE]

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
Trovafloxacin 200 mg Daily for 7 Days							
Females							
5068-2004	*C. trachomatis*[a]	7	BL EOS	ND ND	Persistent	Persistent	Cure
Trovafloxacin 100 mg Daily for 7 Days							
Males							
5069-1225	*C. trachomatis*[b]	7	BL EOS	ND ND	Persistent	Persistent	Cure
Females							
5068-2201†	*C. trachomatis*[a]	7	BL EOS	0.031 ND	Persistent	Persistent	Cure
Trovafloxacin 50 mg Daily for 7 Days							
Males							
5068-1304	*C. trachomatis*[b]	7	BL EOS	0.063 ND	Persistent	Persistent	Cure
Females							
5068-2308	*C. trachomatis*[a, b]	7	BL EOS	0.25 ND	Eradication	Eradication	Failure
5069-2332	*C. trachomatis*[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

[APPEARS THIS WAY ON ORIGINAL]

Medical reviewer's comments:
The two female subjects (50682308, 50692332) in group 4, Trovafloxacin 50mg for 7 days, were bacteriologic failures.

[APPEARS THIS WAY ON ORIGINAL]

Table 105.4 Sponsor Defined Subject Bacteriological Response. By Gender for Bacteriologically Evaluable Subjects
(applicant's table 5.1.1) [APPEARS THIS WAY ON ORIGINAL]

	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	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%.

APPEARS THIS WAY ON ORIGINAL

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

APPEARS THIS WAY ON ORIGINAL

Medical Reviewer's comments:
This table should also show two failures at the lowest dose of trovafloxacin instead of the one currently indicated.

APPEARS THIS WAY ON ORIGINAL

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

BEST POSSIBLE

BEST POSSIBLE

Table 105.7 Summary of the Number and Percentage of Subjects with Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin (200 mg x 7 Days) (N= 31)	Trovafloxacin (200 mg x 5 Days) (N= 34)	Trovafloxacin (100 mg x 7 Days) (N= 28)	Trovafloxacin (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 trovafloxacin 200 mg x 7 days group, 18% in the trovafloxacin 200 mg x 5 days group, 21% in the trovafloxacin 100 mg x 7 days group, and 14% in the trovafloxacin 50 mg x 7 days group.

Clinically significant post-baseline abnormalities were observed for 20% (4/20) of subjects in the trovafloxacin 200 mg x 7 days group, 12% (2/17) of subjects in the trovafloxacin 200 mg x 5 days group, 22% (2/9) of subjects in the trovafloxacin 100 mg x 7 days group, and 6% (1/17) of subjects in the trovafloxacin 50 mg x 7 days group.

APPEARS THIS WAY ON ORIGINAL

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)

	Trovafloxacin 200 mg x 7 Days (N=31)	Trovafloxacin 200 mg x 5 Days (N=34)	Trovafloxacin 100 mg x 7 Days (N=28)	Trovafloxacin 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 1	5 5	2 1	0 0
GASTROINTESTINAL SYSTEM Nausea	1 1	3 2	1 1	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

APPEARS THIS WAY ON ORIGINAL

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.

APPEARS THIS WAY ON ORIGINAL

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.

APPEARS THIS WAY ON ORIGINAL

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.

APPEARS THIS WAY ON ORIGINAL

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.

APPEARS THIS WAY ON ORIGINAL

/s/

Mamodikoe K. Makhene, M.D.

APPEARS THIS WAY ON ORIGINAL

cc:

IND (b)(4)
IND
NDA 20-759
HFD-590/ Deputy Div Director/Albrecht
HFD-590/Medical TL/Leissa /s/
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

concurrence only:
HFD-590/Division Director/Goldberge /s/

APPEARS THIS WAY ON ORIGINAL

NOV 4 1998

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 microbiologicaly 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/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	*E. coli* *Gr. D. Strept* *Lactobacillus* *C. perfringens* *B. fragilis* *Fusobacterium*	*E. coli* *Lactobacillus*	*E. coli* *Gr. D. Strept* *Lactobacillus*

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 MIC_{90}s 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 (+)		
S. agalactiae		0.25
S. aureus (MSSA + MRSA)		2.0
viridans group streptococci		0.25
E. faecalis (vanc S)		2.0
E. faecalis (vanc R)		8.0
E. faecium (vanc S)		2.0
E. faecium (vanc R)		8.0
Gram (-)		
Acinetobacter baumanii		>8
C. freundii		0.375
E. coli		0.06
E. cloacae		1.6
K. pneumoniae		0.12
M. morganii		0.5
Proteus mirabilis (indole -)		0.5
Proteus vulgaris (indole +)		0.5
Providencia stuartii		2.0
P. aeruginosa		2.0
STRICT ANAEROBES		
B. fragilis group		1.0
B. fragilis		0.5
B. thetaiotaomicron		1.0
B ovatus		2.0
B. distasonsis		1.0
B. vulgatus		4.0
B. uniformis		4.0
Prevotella spp.		1.0
P. bivia		1.0
P. intermedia		1.0
P. melaninogenica		1.5
C. perfringens		0.25
Peptostreptococcus spp.		1.0
Fusobacterium spp.		1.0
F. nucleatum		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 MIC_{90} 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 P. Aeruginosa
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/mm^3, 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:

	CP-99,219[1]	Imipenem-cilastatin[2]		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

[1]tentative criteria based on projections from pharmacokinetic data and *in vitro* susceptibility testing
[2]NCCLS 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 ≥ 12,500 cells/mm^3], 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".

APPEARS THIS WAY
ON ORIGINAL

Bacteriologic Response

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.