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 trovafloxcin, 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.

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

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

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 ≤4% in both treatment groups for individual laboratory parameters except urine white blood cells ≥6/HPF (6 subjects, 4%) in the trovafloxacin group, and urine red blood cells ≥6/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 x ULN) was two subjects (1%) in the trovafloxacin group. The percentage of subjects with clinically significant alanine aminotransferase (SGPT, >2.0 x 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 x ULN); one subject (<1%) in the clarithromycin group had a clinically significant total bilirubin value (>1.5 x 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 amoxycillin/clavulanate group were discontinued from treatment due to adverse events. Of these subjects, 13 in the trovafloxacin group and all in the amoxycillin/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

amoxycillin/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 amoxycillin/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 amoxycillin/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)	Amoxycillin/ 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

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)		Amoxycillin/ 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

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 neprhitis) 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.

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 ≥ 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

concurrence: 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/

Table of Contents/NDA 20 – 759:

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 cloace, 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®
Macrodantin®
Mandol®
Keftab®
Kefurox®
Kefzol®
Mefoxin®
Mezlin®
Monocid®
Monurol®
Nebcin®
Negram®
Netromycin®*
Omnipen®
Pipracil®
Primaxin®
Proloprim®*
Septra®
Rocephin®*
Seromycin®
Spectrobid®
Streptomycin®*
Suprax®

Tazicef®
Tazidime®
Ticar®
Timentin®
Trimpex®*
Zinacef®

* 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 cloace,* 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 glycuronide 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/mm'3 when unspun urine was examined in a counting chamber
- a positive pretreatment urine culture within 48 hours of enrollment , defined as ≥ 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 ≥ 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 ≥ 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 ≥ 10'5 CFU/mL should be adhered to.

Therefore, although the sponsor used ≥ 10'3 CFU/mL as a threshold for uncomplicated UTI and ≥ 10'4 CFU/mL for pyelonephritis, the MO adhered to current guidance and used ≥ 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 Evaluablity 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:

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 ≥ 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

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.*

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)

Table 6: Clinical Trials of Trovafloxacin in the Treatment of Urinary Tract Infection

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

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 mm 3 of unspun urine), bacteruria (≥10 3 CFU/mL for all subjects in protocol 154-116 and women in protocol 154-103; ≥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 ≥ 10'5 CFU/mL except for Staphylococcus saprophyticus where ≥ 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):

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 ≥ 103 CFU/mL for uncomplicated UTI studies

  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 ≥ 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 ≥ 10 '5CFU/mL:** all subjects in the bacteriologically evaluable subset with a baseline uropathogen of ≥ 10'5 CFU/mL.

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

Evaluability Criteria:

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ON ORIGINAL

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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ON ORIGINAL

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

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ON ORIGINAL

- 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.

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:

1. Eradication: Baseline pathogen absent from urine culture or reduced to≤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 (≥ 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 ≥ 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 ≥ 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 Scicor 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 ≥ 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 ≥ 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 ≥ 10'5 CFU/mL, present at a level ≥ 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.*

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 Gilderman, 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.

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

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.

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	

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 form 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 ≤ 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.*