Randomization and Blinding:

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

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

Dosage and Administration:

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

Copied below from the original protocol is the administration schedule:

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

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

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

Microbiologic Methods:

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

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

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

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

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

Efficacy and Safety evaluations:

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

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

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

Data Analysis:

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

EVALUABILITY CRITERIA:

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

Medical Officer's Comments:

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

Windows for Analysis:
(Copied from the electronic submission):

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

Analysis Windows

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

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

Primary and Secondary Efficacy Endpoints:

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

Sponsor-Defined Subject Bacteriological Response:

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

DEMOGRAPHICS:

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

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

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

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

Table 103.2
Subject Disposition, All Enrolled Patients

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

APPEARS THIS WAY
ON ORIGINAL

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

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

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

Table 103.3
Study Evaluation Groups/All Randomized Patients

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

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

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

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

Baseline Characteristics:

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

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

Concomitant Medications:

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

Protocol Deviations:

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

Exclusions from Evaluation:

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

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

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

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

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

Sponsor's Efficacy Analysis:

Bacteriologic Response:

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

Table A. Summary of Sponsor-Defined Subject Bacteriological Response Rates at the End of Treatment and at the End of Study (Bacteriologically Evaluable Subjects)

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

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

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

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

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

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

Sponsor-Defined Pathogen Eradication Rates:

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

Table B. Summary of Sponsor-Defined Pathogen Eradication Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens[a] (Bacteriologically Evaluable Subjects)

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

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

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

Table C. Summary of Sponsor-Defined Subject Bacteriological Response Rates at the End of Treatment and at the End of Study (Bacteriologically Evaluable Subjects With A Baseline Uropathogen $\geq 10^5$ CFU/mL)				
	Trovafloxacin 100 mg (N=30)	Trovafloxacin 100 mg BID (N=26)	Ciprofloxacin 250 mg BID (N=31)	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	30 (100%)	26 (100%)	31 (100%)	
Eradication	28 (93%)	23 (88%)	29 (94%)	
Persistence	2 (7%)	3 (12%)	2 (6%)	
Trova 100 mg vs. Trova 100 mg BID				(-10.3, 20.1)
Trova 100 mg vs. Ciprofloxacin				(-12.6, 12.6)
Trova 100 mg BID vs. Ciprofloxacin				(-20.1, 9.9)
End of Study:				
Number of Subjects Assessed	27 (100%)	25 (100%)	29 (100%)	
Eradication	20 (74%)	22 (88%)	24 (83%)	
Persistence	7 (26%)	3 (12%)	5 (17%)	
Trova 100 mg vs. Trova 100 mg BID				(-34.8, 6.9)
Trova 100 mg vs. Ciprofloxacin				(-30.2, 12.8)
Trova 100 mg BID vs. Ciprofloxacin				(-13.5, 24.0)
Ref.: Table 5.9				

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

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

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

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

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

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

Table D. Summary of Sponsor-Defined Pathogen Eradication Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Uropathogens ≥10 ^{5} CFU/mL[a]
(Bacteriologically Evaluable Subjects)

	Trovafloxacin 100 mg	Trovafloxacin 100 mg BID	Ciprofloxacin 250 mg BID	95% Confidence Intervals		
Pathogen	End of Treatment			Trova 100 mg vs. Trova 100 mg BID	Trova 100 mg vs. Cipro	Trova 100 mg BID vs. Cipro
E. coli	26/27 (96%)	20/21 (95%)	23/23 (100%)	-10.5, 12.6	-10.8, 3.4	-13.9, 4.3
	End of Study					
E. coli	18/24 (75%)	19/20 (95%)	20/22 (91%)	-39.8, -0.2	-37.0, 5.2	-11.3, 19.4

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

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

Superinfecting Pathogens and Colonizing Organisms:

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

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

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

Resistance:

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

Sponsor's Analysis of Clinical Response:

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

Table E. Summary of Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study (Clinically Evaluable Subjects)

	Trovafloxacin 100 mg (N=54)	Trovafloxacin 100 mg BID (N=50)	Ciprofloxacin 250 mg BID (N=49)	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	44 (100%)	42 (100%)	45 (100%)	
Success (Cure + Improvement)	42 (95%)	41 (98%)	41 (91%)	
Trova 100 mg vs. Trova 100 mg BID				(-9.9, 5.5)
Trova 100 mg vs. Ciprofloxacin				(-6.0, 14.7)
Trova 100 mg BID vs. Ciprofloxacin				(-3.0, 16.0)
Distribution of Clinical Response:				
Cure	37 (84%)	33 (79%)	39 (87%)	
Improvement	5 (11%)	8 (19%)	2 (4%)	
Failure	2 (5%)	1 (2%)	4 (9%)	
End of Study:				
Number of Subjects Assessed	46 (100%)	44 (100%)	44 (100%)	
Success (Cure + Improvement)	42 (91%)	41 (93%)	37 (84%)	
Trova 100 mg vs. Trova 100 mg BID				(-12.9, 9.2)
Trova 100 mg vs. Ciprofloxacin				(-6.3, 20.7)
Trova 100 mg BID vs. Ciprofloxacin				(-4.0, 22.2)
Distribution of Clinical Response:				
Cure	41 (89%)	40 (91%)	35 (80%)	
Improvement	1 (2%)	1 (2%)	2 (5%)	
Failure	2 (4%)	1 (2%)	4 (9%)	
Relapse	2 (4%)	2 (5%)	3 (7%)	
Ref.: Table 5.2.1				

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

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

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

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

Clinical Response by Baseline Pathogen:

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

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

Table F. Summary of Clinical Success Rates at the End of Treatment and at the End of Study For the Most Frequently Isolated Baseline Pathogens[a] (Clinically Evaluable Subjects)

	Trovafloxacin 100 mg (N=54)	Trovafloxacin 100 mg BID (N=50)	Ciprofloxacin 250 mg BID (N=49)	Trovafloxacin 100 mg (N=46)	Trovafloxacin 100 mg BID (N=44)	Ciprofloxacin 250 mg BID (N=44)
	Number of Subjects					
Pathogen	End of Treatment			End of Study		
E. coli	38/39 (97%)	34/35 (97%)	32/33 (97%)	35/38 (92%)	36/38 (95%)	31/33 (94%)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Medical Officer's Analysis of Efficacy:

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

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

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

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

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

Table 103.6
Bacteriologically Evaluable Population (as per the MO)

Bacteriologically Evaluable Population (Baseline Pathogen ≥ 10'5 CFU/mL)			
Reason for exclusion	**Trova 100/ day**	**Trova 100 bid**	**Cipro 250 bid**
	N= 221		
Total Randomized	N=72	N=74	N =75
No Baseline Pathogen	1	0	0
BSL count < 10'3	15	17	24
BSL count > 10'3 but < 10'5	13	14	10
Withdrawn because of insufficient R/x/ con. AB or no consent prior to EOT	13	17	10
Out of window for EOT	8	4	2
Total Evaluable at EOT	**22**	**22**	**29**
Total Evaluated at EOS	**20**	**21**	**27**

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

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

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

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

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

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

Table 103.8
Demographic Characteristics of the FDA Evaluable Population:

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

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

EFFICACY:

Table 103.9
Bacteriologic Efficacy by Patient (Per the MO)

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

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

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

Table 103.10
Bacteriologic Efficacy by Pathogen at EOT

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

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

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

Clinical Efficacy Analysis:

Table 103.11
Clinical Efficacy (FDA Bacteriologically Evaluable Population)

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

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

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

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

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

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

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

Trovafloxacin 100 bid (N=4):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf.Y /N	Reviewer Determination
50110206:	Persistent	Cure	Persistent	Not assessable	N	*Serratia marcescens Pers./Maxaquin R/x*, N
50420275:	Persistent	Cure	Eradicated	Not assessable	N	*Escherichia coli Pers., Enterobacter Erad/ Escherichia coli Erad EOS*, N
50050183:	Persistent	Improvement	Persistent	Relapse	N	*Klebsiella pneumoniae Pers. at EOT; R/x Keflex*, N
50030023:	Eradicated	Failure	Persistent	Failure	N	*Escherichia coli Erad. at EOT/Bactrim R/x, NG at 31 day*, N

Ciprofloxacin (N = 3):

50050181:	Persistent	Cure	Persistent	Improvement	N	*Pseudomonas aeruginosa Pers./ Noroxin*, N
50060027:	Persistent	Cure	Persistent	Not assessable	N	*Enterococcus faecalis Pers., Biaxin day 30, Escherichia coli Erad.*, N
50050198:	Eradicated	Failure	Eradicated	Failure	N	*Klebsiella pneumoniae Erad./ Escherichia coli day 35*, Superinfection Y

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

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

Clinical Relapses:

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

Trovafloxacin 100 (N = 1):

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

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

Bacterial Superinfections:

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

Trovafloxacin 100:

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

Trovafloxacin bid:

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

Ciprofloxacin:

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

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

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

Safety Analysis:

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

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

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

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

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

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

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

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

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

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

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

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

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

A breakdown of these 2 systems, revealed the following:

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

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

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

Table 103.16
Summary of Treatment-Related AEs by Body System

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

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

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

These events and patients are listed below:

Trovafloxacin 100 (N= 2):

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

- *5008053: dysmenorrhea, unrelated to treatment.*

Trovafloxacin bid (N = 7):

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

Ciprofloxacin bid (N=3):

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

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

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

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

Clinical Laboratory Abnormalities:

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

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

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

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

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

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

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

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

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

Patient #50030134 had a significant increase in SGOT. The SGPT in this patient also increased from These values normalized post-therapy This patient also had a urine protein No further information was available.

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

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

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

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

Reviewer's Conclusion:

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

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

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

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

Superinfection and relapse rates were comparable between all arms.

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

Study 154 - 116

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

List of Principal Investigators:

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

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

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

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

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

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

SCHEDULE OF STUDY VISITS AND PROCEDURES

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

abn= abnormal at previous visit or clinically significant adverse event

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

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

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

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

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

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

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

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

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

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

Protocol Amendments:

The protocol was amended on December 13, 1993 and on January 10, 1994 to reflect the following:

- to reflect monitoring procedures for subjects taking theophylline and warfarin.
- to reflect that overall clinical response was not to be determined by the Investigator at the time of discontinuation due to lack of efficacy.
- that bacteriological response was not to be determined by the sponsor at the time of discontinuation due to lack of efficacy
- that subjects who discontinued treatment for any reason were not to have been discontinued from the study, but rather followed to the last scheduled visit
- that the requirement for a final efficacy assessment and follow-up safety assessment in the event that an antibiotic was taken during the study period was deleted from the protocol.

STUDY POPULATION:

It was expected that a total of 540 subjects were to be enrolled in this study with 270 expected to be microbiologically evaluable. Approximately 30 sites were expected to participate which should have attempted to enrol at least 20 subjects each.

Medical Officer's Comment: *The inclusion and exclusion criteria were the same as those in study 103 with the exception that the lower age limit was lowered to age ≥ 16 at baseline. As noted by the MO previously, those patients who received only one dose of another antimicrobial prior to the study start and who had a microbiologically documented infection, were considered evaluable.*

Randomisation and Blinding:

The investigator assigned study numbers sequentially to the subjects as they were determined to be eligible for treatment. The study number was entered onto the patient's case report form and the patient received study medication with the corresponding number. Study medication was blinded by a double-dummy technique.

Study drug was in the form of tablets and was packaged in blister cards. The study drug administration schedule provided one of the following three dosage regimens of study drug, dependent on the random assignment:

Trovafloxacin:	100 mg daily (1 x 100 mg tablets) as a single dose in the morning for three days.
Trovafloxacin:	100 mg daily (1 x 100 mg tablets) as a single dose in the morning for seven days.
Norfloxacin:	800 mg daily in two equally divided doses (morning, evening) for three days.

The blister cards contained sufficient supplies for a 7-day course of treatment.

In order to maintain blinding, subjects were instructed to take the following tablets during each day of the 7 days of treatment:

	AM Administration	PM Administration
Trovafloxacin (100 mg/d x 3 days)	1-placebo for Norfloxacin x 3 days 1-trovafloxacin- 100 mg x first 3 days (1-placebo for trovafloxacin x last 4 days)	1-placebo for Norfloxacin x 3d
Trovafloxacin (100 mg/d x 7days)	1-placebo for Norfloxacin x 3 days 1-trovafloxacin - 100 mg x 7 days	1-placebo for Norfloxacin x 3d
Norfloxacin (800 mg/d x 3 days)	1-Norfloxacin 400 mg x 3 days 1-placebo for trovafloxacin x 7 days	1-Norfloxacin 400 mg x 3d

Patients were instructed to start with the AM dose on Day 1, even if it was not morning and to complete a full day of medication. The investigator was to have reviewed the labeling instructions with the patients, making clear the AM and PM doses. The patients were instructed to take their doses at least 1 hour before or 2 hours after a meal and that morning and evening dosing should be approximately 12 hours apart

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

Microbiologic Methods:

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

Criteria for determining susceptibility to the study drugs are summarized below:
(Copied from page 17 of the Study Report)

	Trovafloxacin		Norfloxacin	
	Zone size(mm)	MIC	Zone Size(mm)	MIC
Criteria	5µg disc	µg/ml	10 µg disc	µg/ml
Susceptible	≥15	≤2	≥17	≤4
Intermediate	11-14	4	13-16	5-15
Resistant	≤10	≥8	≤12	≥16

Clinical Response:

Clinical response was determined by the sponsor at visit 2 (EOT) and at Visit 3 (EOS). Response was based on a global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. This assessment was also to be based upon resolution or improvement of clinical and laboratory signs of infection as well as improvement in general condition.

All signs and symptoms were recorded on the CRFs at each visit and the severity of each was rated on the following scale: 0 = Absent, 1 = Mild, 2 = Moderate, and 3 = Severe.

The investigator classified the clinical response as cure; improvement or failure as defined previously in the MOR of study 103.

Medical Officer's Comment: *Notable is the use of a scoring system for severity of illness which was not used in study 103. As in 103 however, the sponsor made the ultimate determination of outcome.*

Bacteriological Response:

This was determined by the sponsor at the EOT and EOS and classified as eradication or persistence as defined previously in the MOR of study 103.

Safety Assessments:

All AEs were recorded on the CRFs and classified as described in the MOR of study 103.

Data Analysis:

Please refer to the MOR of study 103 for a review of the sponsor's subsets and their definitions.

Medical Officer's Comment*: As stated previously the MO's evaluable population consisted of only those patients with a baseline uropathogen ≥ 10'5 CFU/mL. Clinically evaluable subjects were a subset of this group.*

Evaluabiltiy Criteria:

The reader is referred to the introductory section of the MOR for a detailed analysis as well as to the MOR of study 103. The criteria and the MO's comments are the same.

Windows for analysis:

Medical Officer's Comment: *Please refer to the introduction to view the MO's determination of the analysis windows. For this study the lower boundary for the EOT window for analysis, (MO TOC), was set at study day 9 and greater for the patients on 3-day regimens and Day 13 and greater for the patients on 7-day regimens.*

Primary and Secondary endpoints for Efficacy and Definitions of Response

Please refer to of the MOR of study 103.