DEMOGRAPHICS:

560 subjects were enrolled at 34 centers. 15 centers were in the US and the remainder were in Europe including the Netherlands, France, Germany and Sweden.

Of the enrolled subjects, 18 were withdrawn prior to randomization because they did not meet the study criteria. There were 182 subjects randomized to the trovafloxacin 3-day regimen, 182 to the trovafloxacin 7-day regimen, and 178 to the norfloxacin 3-day regimen. All randomized patients received study drug.

6 trovafloxacin 3-day, 9 trovafloxacin 7-day, and 6 norfloxacin subjects were withdrawn from treatment. Of these 3, 3 and 2 respectively, completed the study and thus a total of 176 trovafloxacin 3-day, 173 trovafloxacin 7-day, and 172 norfloxacin randomized subjects completed treatment.

Copied and modified below is the sponsor's table 1.3 from the Esub:

Table 116.1:

Number of Subjects Enrolled By Center: All Randomized Patients (As per the Sponsor, Modified by MO)

			Trovafloxacin				Trovafloxacin				Norfloxacin			
			100 mg x 3 days				100 mg x 7 days.				400 mg b. i. d. x 3 days			
Center	Total Randomized N = 542	(100%)	Randomized N = 182 (33.5%)	(33.5%)	Treated N= 182		Randomized N = 182 (33.5 %)		Treated N=182 (33.5 %)		Randomized N = 178 (32.8%)		Treated N= 178 (33.9%)	
5003 *	35	6.4	12	6.5	12	6.5	11	6.0	11	6.0	12	6.7	12	6.7
5005*	54	9.9	18	9.8	18	9.8	18	9.0	18	9.0	18	10.1	18	10.1
5011 *	18	3.3	6	3.2	6	3.2	6	3.2	6	3.2	6	3.3	6	3.3
5013 *	27	4.9	10	5.4	10	5.4	9	4.9	9	4.9	8	4.4	8	4.4
5041 *	27	4.9	9	4.9	9	4.9	9	4.9	9	4.9	9	5.0	9	5.0
5138 *	14	2.5	4	0.7	4	0.7	5	2.7	5	2.7	5	2.8	5	2.8
5492 *	48	8.8	16	8.7	16	8.7	16	8.0	16	8.0	16	8.9	16	8.9
5630 *	13	2.3	4	0.7	4	0.7	5	2.7	5	2.7	4	2.2	4	2.2
5632 *	28	5.1	9	4.9	9	4.9	9	4.9	9	4.9	10	5.6	10	5.6
5633 *	7	1.2	2	1.0	2	1.0	3	1.6	3	1.6	2	1.1	2	1.1
5635 *	8	1.4	2	1.0	2	1.0	3	1.6	3	1.6	3	1.6	3	1.6
5636 *	8	1.4	3	1.6	3	1.6	2	1.0	2	1.0	3	1.6	3	1.6
5637 *	10	1.8	4	0.7	4	0.7	2	1.0	2	1.0	4	2.2	4	2.2
5681 *	54	9.9	18	9.8	18	9.8	18	9.0	18	9.0	18	10.1	18	10.1
5733 *	29	5.3	10	5.4	10	5.4	9	4.9	9	4.9	10	5.6	10	5.6
5783	18	3.3	6	3.2	6	3.2	6	3.2	6	3.2	6	3.3	6	3.3
5784	17	3.1	6	3.2	6	3.2	6	3.2	6	3.2	5	2.8	5	2.8
5785	6	1.1	2	1.0	2	1.0	2	1.0	2	1.0	2	1.1	2	1.1
5786	6	1.1	2	1.0	2	1.0	2	1.0	2	1.0	2	1.1	2	1.1
5787	19	3.5	6	3.2	6	3.2	6	3.2	6	3.2	7	3.9	7	3.9
5792	2	0.3	0	0	0	0	2	1.0	2	1.0	0	0	0	0
5794	13	2.3	4	0.7	4	0.7	5	2.7	5	2.7	4	2.2	4	2.2
5797	2	0.3	1	0.5	1	0.5	1	0.5	1	0.5	0	0	0	0
5798	7	1.2	2	1.0	2	1.0	3	1.6	3	1.6	2	1.1	2	1.1
5799	5	1.4	2	1.0	2	1.0	2	1.0	2	1.0	1	0.5	1	0.5
5801	12	2.2	4	0.7	4	0.7	4	2.1	4	2.1	4	2.2	4	2.2
5802	10	1.8	4	0.7	4	0.7	3	1.6	3	1.6	3	1.6	3	1.6
5803	4	0.7	2	1.0	2	0.7	1	0.5	1	0.5	1	0.5	1	0.5
5804	24	4.4	8	4.3	8	4.3	8	4.3	8	4.3	8	4.4	8	4.4
5821	17	3.1	6	3.2	6	3.2	6	3.2	6	3.2	5	2.8	5	2.8

* denotes US centers

Medical Officer's Comment: *It appeared as if the patients were randomized equally between treatment arms and centers. No center had greater than 10% of the total patients. 340 patients or 70.1% were enrolled at US centers.*

Table 116.2:
Subject Disposition, All Enrolled Patients (As per the Sponsor)

		Trovafloxacin 100 mg x 3 days	Trovafloxacin 100 mg x 7 days	Norfloxacin 400 mg bid x 7 days
Subjects with Signed Consent	560			
Withdrawn Prior to Randomization	0			
Randomized		182	182	178
Randomized, But Not Treated		0	0	0
All Treated Subjects		182 (100%)	182(100%)	178 (100%)
Withdrawn During Treatment		6 (3%)	9 (5%)	6 (3%)
Completed Treatment		178 (97%)	173 (95%)	172 (97%)
Withdrawn During Follow- up		6 (3%)	6 (3%)	4 (2%)
Completed Study		173 (95%)	170 (93%)	170 (96%)
Completed Treatment and Study		170(93%)	167(92%)	168 (94%)
Withdrawn During Treatment and Study		3 (2%)	6 (3%)	4 (2%)

Medical Officer's Comment: From *116. 2 it is apparent that as stated above, 3 trovafloxacin 3-day patients, 6 trovafloxacin 7-day patients, and 4 norfloxacin patients did not complete the study, thus 173, 170, and 170 subjects per arm respectively, completed the study.*

Copied below, from page 25 of the study report is the sponsor's analysis of these patients:

One-hundred forty-seven (147) trovafloxacin 3-day, 152 trovafloxacin 7-day, and 130, norfloxacin subjects were included in the bacteriological intent-to-treat analyses and 182 trovafloxacin 3-day, 182 trovafloxacin 7-day, and 178 norfloxacin subjects were included in the clinical intent-to-treat analyses. All treated subjects were included in the analysis of adverse events (182, trovafloxacin 3-day; 182 trovafloxacin 7-day; and 178, norfloxacin).

One hundred seventy-nine (179) subjects with on-treatment laboratory evaluations were included in the analysis of laboratory data (17,trovafloxacin 3-day; 154 trovafloxacin 7-day; and 8, norfloxacin). The difference in the number of subjects analyzed for laboratory data among the three treatment groups is due to the standard method of laboratory data collection which was to have been during the study or within 7 days of the last dose.

Medical Officer's Comment: *The difference in the numbers of patients analyzed for laboratory data is because 2 arms of the study had a duration of 3 days as opposed to the one 7 day arm*

Copied below is the sponsor's table 1.2 (Modified by MO)

Table 116.3:

Study Evaluation Groups/All Randomized Patients (As per the Sponsor, Modified by MO

	Trovafloxacin 100 mg x 3 days	Trovafloxacin 100 mg x 7 days	Norfloxacin 400 mg bid x 7 days
All Randomized Subjects	182 (100%)	182 (100%)	178 (100%)
All Treated Subjects	182 (100%)	182 (100%)	178 (100%)
Subjects with Low Baseline Colony Count or No Pyuria	32 (18%)	27 (15%)	44 (25%)
Subjects with Inappropriate Baseline Diagnosis	3 (2%)	3 (2%)	4 (2%)
Bacteriologically Intent- to- Treat Subjects	147 (81%)	152 (84%)	130 (73%)
Bacteriologically Evaluable Subjects	143 (79%)	142 (78%)	125 (70%)
Bacteriologically Not Evaluable Subjects	4 (2%)	10 (5%)	5 (3%)
No post- baseline cultures	3 (2%)	7 (4%)	3 (2%)
Insufficient Therapy Concomitant Antibiotic Therapy	1 (< 1%) 1 (< 1%)	4 (2%) 3 (2%)	3 (2%) 1 (< 1%)
Bacteriologically Evaluable at End of Study Visit	128 (70%)	118 (65%)	109 (61%)
Act. Evaluable w/ Baseline uropathy. >10** 5 cfu/ ml	120 (66%)	113 (62%)	106 (60%)
Act. Evaluable w/ Baseline Uropathy. >10** 5 cfu/ ml at EOS	108 (59%)	98 (54%)	94 (53%)
Clinically Intent- to- Treat Subjects	182 (100%)	182 (100%)	178 (100%)
Clinically Evaluable Subjects	144 (79%)	144 (79%)	125 (70%)
Clinically Not Evaluable Subjects	3 (2%)	8 (4%)	5 (3%)
No post baseline assessment	1 (< 1%)	5 (3%)	1 (< 1%)
Insufficient Therapy	1 (<1%)	5 (3%)	3 (2%)
No post baseline assessment in window	2 (1%)	4 (2%)	3 (2%)
Concomitant Antibiotic Therapy	1 (< 1%)	3 (2%)	1 (< 1%)
Clinically Evaluable at End of Study Visit	133 (73%)	127 (70%)	114 (64%)
Analyzed for Safety			
Adverse Events	182 (100%)	182 (100%)	178 (100%)
Laboratory Data	17 (9%)	154 (85%)	8 (4%)

Medical Officer's Comment: *The MO determined that the MO's evaluable population would be compromised of only those subjects with a baseline culture with ≥ 10'5 CFU/mL. From table 116.3, it appeared as if this group was compromised of 120 trovafloxacin 3-day, 113 trovafloxacin 7-day, and 109 norfloxacin patients per arm respectively, or approximately 60% of the randomized population.*

The MO independently reviewed the CRFs and patient profiles on all patients who were withdrawn from the study and agreed with the sponsor's determination of unevaluability.

The sponsor provided 4 tables of the patients who were withdrawn for the study (4.2 and 4.3.2) and 2 for those who discontinued treatment (4.1 and 4.3.1)

There were 29 patients (9 trovafloxacin 3-day, 12 trovafloxacin 7-day, and 8 norfloxacin) who discontinued from the study. Of the 9 trovafloxacin 3-day patients, 3 did not complete therapy. The respective numbers for the two other treatment arms were 6 and 4. The MO reviewed all of the case report forms and found NO inconsistencies. Most common was that these patients did not follow-up after therapy and therefore could not be evaluated. Other causes for withdrawal included immediate allergic reactions and GI side effects.

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

Baseline Characteristics:

Copied below from page 26 of the study report is the sponsor's text regarding baseline characteristics.

All randomized subjects were females. The three treatment groups were comparable with respect to age, race, and weight. Similar results were observed in the bacteriologically evaluable group.

The mean age for subjects in the trovafloxacin 3-day, trovafloxacin 7-day, and norfloxacin groups was 39.8, 38.8 and 39.8 years, respectively.

The median duration since onset of UTI was 3.0 days for both bacteriologically evaluable and intent-to-treat subjects in all treatment groups.

There were no marked differences among subjects in the three treatment groups with respect to physical examination findings at baseline.

Study Drug Administration:

The median duration of treatment was 3 days for the 3-day patients and 7 days for the 7-day patients.

Concomitant Medications:

During the study, 29 patients in the trovafloxacin 3-day group, 21 in the trovafloxacin 7-day and 28 in the norfloxacin group received concomitant antimicrobials for:

- inadequate response 20, 9 and 22 respectively.
- adverse event 2, 1 and 0
- other illnesses 7, 11 and 6.

The MO reviewed the tables provided by the sponsor as well as the CRFs for these patients and determined that in ALL cases of insufficient response, the failures were carried forward.

Protocol Deviations:

There were 19 deviations, none of which affected evaluability.

Evaluable Population:
(Copied from page 28 of the study report):

Of the randomized subjects, 35 trovafloxacin 3-day subjects, 30 trovafloxacin 7-day subjects and 48 norfloxacin subjects had no baseline urinary pathogen, or low colony counts or no evidence of pyuria and were excluded from the bacteriological intent-to-treat and evaluable analyses. Thus, 147 trovafloxacin 3-day, 152 trovafloxacin 7-day and 130, norfloxacin subjects were included in the bacteriologic intent-to-treat analysis.

Of the bacteriological intent-to-treat subjects, four subjects in the trovafloxacin 3-day group, 10 subjects in the trovafloxacin 7-day group and 5 subjects in the norfloxacin group were not bacteriologically evaluable; thus, 143 trovafloxacin 3-day, 142 trovafloxacin 7-day, and 125 norfloxacin subjects were bacteriologically evaluable.

The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline cultures in evaluable windows (3, trovafloxacin 3-day; 7, trovafloxacin 7-day and 3, norfloxacin). Other reasons were insufficient therapy and concomitant antibiotic therapy.

All randomized subjects were assumed to have uncomplicated UTI and were, therefore, included in the clinical intent-to-treat analysis (182, trovafloxacin 3-day; 182,trovafloxacin 7-day and 178, norfloxacin).

Of the bacteriological intent-to-treat subjects, 16 subjects were not included in the clinically evaluable analysis. Thus, 144 trovafloxacin 3-day, 144 trovafloxacin 7-day, and 125, norfloxacin subjects were clinically evaluable.

The most common reason for exclusion from clinical evaluability was no post-baseline clinical assessment (1,trovafloxacin 3-day; 5, trovafloxacin 7-day and 1, norfloxacin), no post-baseline assessment in evaluable analysis window (2, trovafloxacin 3-day; 5, trovafloxacin 7-day and 3, norfloxacin), insufficient therapy (1, trovafloxacin 3-day; 4, trovafloxacin 7-day and 3, norfloxacin) and concomitant antibiotic therapy (1, trovafloxacin 3-day; 3, trovafloxacin 7-day and 1, norfloxacin).

Sponsor's Efficacy Analysis:

Bacteriological Response:
(Copied below is the sponsor's text from pages 29 and 30 of the study report):

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined subject bacteriological eradication rates at the end of treatment supported equivalence of both trovafloxacin regimens versus norfloxacin (trovafloxacin 3-day, 86% versus norfloxacin, 88% [95% CI: -9.7, 6.5] and trovafloxacin 7-day, 93% versus norfloxacin, 88% [95% CI: -2.1, 12.2]).

Sponsor-defined subject bacteriological eradication rates were comparable among the trovafloxacin 3-day (74%), trovafloxacin 7-day (84%), and norfloxacin (73%) groups at the end of study.

A summary of sponsor-defined bacteriological response rates for bacteriologically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in the following table.

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

	Trovafloxacin 100 mg/day 3 Days (N=143)	Trovafloxacin 100 mg/day 7 Days (N=142)	Norfloxacin 400 mg BID 3 Days (N=125)	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	139 (100%)	142 (100%)	124 (100%)	
Eradication	120 (86%)	132 (93%)	109 (88%)	
Persistence	19 (14%)	10 (7%)	15 (12%)	
Trova 3 days vs. Trova 7 days				(-13.7, 0.5)
Trova 3 days vs. Norfloxacin				(-9.7, 6.5)
Trova 7 days vs. Norfloxacin				(-2.1, 12.2)
End of Study:				
Number of Subjects Assessed	128 (100%)	118 (100%)	109 (100%)	
Eradication	95 (74%)	99 (84%)	80 (73%)	
Persistence	33 (26%)	19 (16%)	29 (27%)	
Trova 3 days vs. Trova 7 days				(-19.7, 0.4)
Trova 3 days vs. Norfloxacin				(-10.4, 12.1)
Trova 7 days vs. Norfloxacin				(-0.1, 21.1)

Medical Officer's Comment: *From sponsor's table C which includes all bacteriologically evaluable patients, (≥ 10'3 CFU/mL at baseline), it was apparent that there was equivalence between the 3-day treatment arms and that the 7-day regimen was equivalent to the norfloxacin arm.*

Sponsor-Defined Pathogen Eradication Rates:
(Copied below is the sponsor's text and Table B from pages 30 and 31 of the study report):

Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates were comparable among the three treatment groups for the most frequently isolated baseline pathogen (*Escherichia coli*), at both the end of treatment and the end of study.

A summary of sponsor- defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in the following table.

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

	Trovafloxacin 100 mg/day 3 Days	Trovafloxacin 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days	95% Confidence Intervals		
Pathogen	End of Treatment			Trova 3 days vs. Trova 7 days	Trova 3 days vs. Norfloxacin	Trova 7 days vs. Norfloxacin
E. coli	105/114 (92%)	103/108 (95%)	87/97 (90%)	-9.6, 3.1	-5.4, 10.2	-1.6, 12.9
E. faecalis	3/10	4/6	4/6	ND	ND	ND
	End of Study					
E. coli	85/105 (81%)	74/89 (83%)	62/84 (74%)	-13.0, 8.6	-4.9, 19.2	-2.9, 21.5
E. faecalis	1/9	3/5	3/6	ND	ND	ND

Trova=trovafloxacin; ND=not done.
a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when the denominator is ≥15.
Ref.: Table 5.5.1

Medical Officer's Comment: *The sponsor has provided a list of all pathogens and their eradication rates in Appendix 1, Table 5.5.1. This table has been reproduced by the MO below:*

Table 116.4:
Table of Sponsor-Defined Pathogen Eradication Rates at the EOT (Modified by MO)
(Table includes all relevant sponsor-evaluable isolates)

Pathogen	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
Escherichia coli	114	105	92	108	103	95	97	87	90
Enterococcus faecalis	10	3	30	6	4	67	6	4	67
Proteus mirabilis	8	7	88	5	5	100	4	4	100
Citrobacter freundii	2	1	50	-	-	-	-	-	-
Pseudomonas aeruginosa	1	1	100	1	0	0	-	-	-
Pseudomonas fluorescens	-	-	-	1	1	100	-	-	-
Staphylococcus haemolyticus	4	3	75	3	2	67	1	1	100
Citrobacter diversus	-	-	-	-	-	-	2	2	100
Staphylococcus aureus	2	2	100	1	1	100	4	3	75
Enterobacter aerogenes	1	1	100	1	1	100	-	-	-
Enterobacter agglomerans	-	-	-	1	1	100	-	-	-
Enterobacter cloacae	3	2	67	2	2	100	1	1	100
Morganella morganii.	1	1	100	1	1	100	1	1	100
Klebsiella oxytoca	-	-	-	1	1	100	1	1	100
Klebsiella pneumoniae	3	2	67	6	5	83	5	3	60
Total	**146**	**128**	**87.6**	**137**	**127**	**92.7**	**122**	**107**	**87.7**

***Medical Officer's Comment**: There was equivalence between the 3 arms at EOT and EOS for Escherichia coli, the most frequently isolated pathogen. A distant second isolate, Enterococcus faecalis, appeared to be much less sensitive to the trovafloxacin 3-day regimen with eradication rates of 30% or less as compared to the 3-day norfloxacin or the 7-day trovafloxacin (60% or greater). A statistical analysis was not provided. Additionally, although the numbers are few, the trovafloxacin 3-day regimen appeared less effective against other Gram (-) organisms as compared to the 7-day regimen.*

Overall, there was numerical equivalence between the 3-day regimens and superiority of the 7-day compared to both.

Bacteriologically Evaluable Subjects with a Baseline Uropathogen of ≥ 10'5 CFU/mL:
(Copied below is the sponsor's text and Table C):

Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor- defined subject bacteriological eradication rates supported equivalence of trovafloxacin 7-day versus norfloxacin at the end of treatment (trovafloxacin 7-days 93% versus norfloxacin 90% [95% CI: -4.1, 10.9]).

Sponsor-defined subject bacteriological eradication rates were comparable among the trovafloxacin 3-day (75%), trovafloxacin 7-day (83%), and norfloxacin (74%) groups at the end of study.

A summary of sponsor- defined bacteriologic response rates for bacteriologically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in the following table.

Table C. Summary of Sponsor-Defined Subject Bacteriologic Response Rates at the End of Treatment and at the End of Study (Bacteriologically Evaluable Subjects With A Baseline Uropathogen ≥10^5 CFU/ML)

	Trovafloxacin 100 mg/day 3 Days (N=120)	Trovafloxacin 100 mg/day 7 Days (N=113)	Norfloxacin 400 mg BID 3 Days (N=106)	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	116 (100%)	113 (100%)	105 (100%)	
Eradication	101 (87%)	105 (93%)	94 (90%)	
Persistence	15 (13%)	8 (7%)	11 (10%)	
Trova 3 days vs. Trova 7 days				(-13.6, 1.9)
Trova 3 days vs. Norfloxacin				(-10.9, 6.0)
Trova 7 days vs. Norfloxacin				(-4.1, 10.9)
End of Study:				
Number of Subjects Assessed	108 (100%)	98 (100%)	94 (100%)	
Eradication	81 (75%)	81 (83%)	70 (74%)	
Persistence	27 (25%)	17 (17%)	24 (26%)	
Trova 3 days vs. Trova 7 days				(-18.7, 3.4)
Trova 3 days vs. Norfloxacin				(-11.5, 12.5)
Trova 7 days vs. Norfloxacin				(-3.4, 19.8)

Trova=trovafloxacin; CI=confidence interval
Ref.: Table 5.9

Medical Officer's Comment: *In this population of patients which can be corresponds to that of the MO, the 3-day trovafloxacin regimen was NOT EQUIVALENT to the 7-day trovafloxacin regimen, however it was equivalent to the comparator, (norfloxacin), at the EOT which was the MO's TOC. The MO requested comment from the FDA statistical reviewer, Dr. Jiang.*

Dr. Jiang provided a statistical analysis which revealed equivalence between the trovafloxacin 3-day arm, (sponsor's requested dose), and the comparator, norfloxacin. Specifically, for trovafloxacin 3-day vs. norfloxacin, the lower bound of the C.I. is -11.8% and the upper is 6,9% with CCF.

Sponsor-Defined Pathogen Eradication Rates for Baseline Pathogens ≥ 10'5 CFU/mL:
(Copied from pages 32 and 33 of the study report are the sponsor's text and Table D)

Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates for baseline isolates of *Escherichia coli* ≥ 10' 5 cfu/ mL were comparable among the three treatment groups at both the end of treatment and the end of study.

A summary of sponsor- defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline uropathogen ≥ 10' 5 cfu/ mL is presented for bacteriologically evaluable subjects in the following table.

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/day 3 Days	Trovafloxacin 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days	95% Confidence Intervals		
Pathogen	End of Treatment			Trova 3 days vs. Trova 7 days	Trova 3 days vs. Norfloxacin	Trova 7 days vs. Norfloxacin
E. coli	88/96 (92%)	85/90 (94%)	75/81 (93%)	-10.1, 4.5	-8.9, 7.0	-5.6, 9.3
End of Study						
E. coli	73/90 (81%)	64/77 (83%)	54/72 (75%)	-13.6, 9.6	-6.8, 19.0	-4.9, 21.2

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

Medical Officer's Comment: *The sponsor has provided a list of all pathogens and their eradication rates in, Table 5.10. This table was reproduced and modified by the MO below:*

Table 116.5:
Table of Sponsor-Defined Pathogen Eradication Rates at the EOT (Modified by MO)
(Table includes all relevant sponsor-evaluable uropathogens ≥ 10'5 at baseline)

	Trova 3-day			Trova 7-day			Norflox 3-day		
Pathogen	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
Escherichia coli	96	88	92	90	85	94	81	75	93
Enterococcus faecalis	5	1	20	3	2	67	5	3	60
Proteus mirabilis	8	7	88	4	4	100	4	4	100
Pseudomonas aeruginosa	1	1	100	1	0	0	0	0	0
Pseudomonas fluorescens	-	-	-	1	1	100	-	-	-
Staphylococcus aureus	2	2	100	-	-	-	3	2	66.6
Enterobacter aerogenes	1	1	100	1	1	100	-	-	-
Enterobacter cloacae	2	1	50	1	1	100	1	1	100
Morganella morganii.	-	-	-	-	-	-	1	1	100
Klebsiella oxytoca	-	-	-	1	1	100	1	1	100
Klebsiella pneumoniae	3	2	67	5	4	80	5	3	60
Total	**118**	**103**	**87.2**	**107**	**99**	**92.5**	**101**	**89**	**88.1**

Medical Officer's Comment*: The MO provided a similar table of the eradication rates of the above isolates at the EOS.*

Table 116.6:
Table of Sponsor-Defined Pathogen Eradication Rates at the EOS (Modified by MO)
(Table includes all relevant sponsor-evaluable uropathogens ≥ 10'5 at baseline)

Pathogen	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
Escherichia coli	90	73	81	77	64	83	72	54	75
Enterococcus faecalis	5	1	20	2	0	0	-	-	-
Proteus mirabilis	7	5	71	4	4	100	3	2	67
Pseudomonas aeruginosa	1	1	100	1	0	0	-	-	-
Pseudomonas fluorescens	-	-	-	1	1	100	-	-	-
Staphylococcus aureus	1	1	100	-	-	-	3	2	67
Enterobacter aerogenes	1	1	100	-	-	-	1	1	100
Enterobacter cloacae	2	1	50	1	1	100	1	1	100
Klebsiella oxytoca	-	-	-	1	1	100	-	-	-
Klebsiella pneumoniae	3	2	67	5	3	60	5	3	60
Total	**110**	**85**	**77.2**	**92**	**74**	**80.4**	**85**	**63**	**74.1**

***Medical Officer's Comment**: The MO points out that all of the above pathogen eradication tables apply only to those isolates which could be construed as uropathogens, thus excluding organisms thought to be contaminants.*

The MO was unclear as to why the sponsor elected to present eradication rates for the EOT and EOS separately. When queried, the sponsor stated that both timepoints were evaluable as TOCs and thus the EOS tabulations applied only to those patients who followed up at that point. Additionally, changes in numerators and denominators are explained by the ability for a patient to have been assessed at either the EOT or the EOS.

Equivalence was shown between the trovafloxacin 3-day regimen and norfloxacin treatment arm for Escherichia coli at the EOT. Additionally, bacteriologically, the 3-day regimen appeared comparable to the other arms for other Gram (-) organisms. There were however, too few isolates to draw any firm conclusions. The FDA Statistical Reviewer, Dr. Jiang confirmed that there was equivalence between the trovafloxacin 3-day arm and the norfloxacin 3-day regimen.

Superinfecting Pathogens and Colonizing Organisms:
(Copied below is the sponsor's text from page 33 of the study report. This information refers to the clinically ITT population (182, 182, 178):

Superinfecting organisms were isolated from 22 subjects (12%) in the trovafloxacin 3-day group (*Escherichia coli* [seven isolates], *Klebsiella pneumoniae* [three isolates], *Staphylococcus haemolyticus* [three isolates], *Enterococcus faecalis* [two isolates], *Proteus mirabilis* [two isolates], and one isolate each of *Acinetobacter* spp., *Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae, Pseudomonas fluorescens, Lecleria adecarboxylata*, and *Citrobacter freundii*), from 16 subjects (9%) in the trovafloxacin 7-daygroup (*Staphylococcus haemolyticus* [four isolates], *Staphylococcus epidermidis* [three isolates], *Enterococcus faecalis* [three isolates], *Escherichia coli* [two isolates], and one isolate each of *Proteus mirabilis, Acinetobacter calcoaceticus V. lwoffi, Acinetobacter* spp., *Coryenbacterium* spp., *Enterobacter cloacae, Klebsiella pneumoniae., Morganella morganii, Providencia spp., Pseudomonas putida*, and *Staphylococcus saprophyticus*), and 20 subjects (11%) in the norfloxacin group (*Escherichia coli* [seven isolates], *Enterococcus faecalis* [four isolates] ,*Staphylococcus haemolyticus* [four isolates],

Staphylococcus epidermidis [four isolates], *Enterobacter cloacae* [two isolates], *Klebsiella oxytoca* [two isolates], *Klebsiella pneumoniae* [two isolates] , and one isolate each of *Acinetobacter calcoaceticus v. anitratus, Corynebaterium spp., Staphylococcus saprophyticus,* and *Staphylococcus* spp.).

Colonizing organisms were isolated from 36 subjects (20%) in the trovafloxacin 3-day group, 35 subjects (19%) in the trovafloxacin 7-day group, and 37 subjects (21%) in the norfloxacin group.

Medical Officer's Comment*: The most frequently isolated superinfecting pathogen was Escherichia coli followed by Enterococcus faecalis. Interestingly, Group B Streptococcus was the most frequent colonizer. These results seem to be in accord with the overall eradication rates and possibly the fact that the patient population was composed mostly of women.*

Clinical Response:
(Copied from pages 35 and 36 of the study report are the sponsor's analysis and Table E)

Sponsor-defined clinical success rates (cure + improvement) were comparable among the trovafloxacin
3-day group, the trovafloxacin 7-day group, and the norfloxacin group at the end of treatment (97%, 97%, and 92%, respectively).

Sponsor-defined clinical success rates at the end of study were comparable for the trovafloxacin 3-day group and the norfloxacin group at the end of study (86% and 82%, respectively). A higher clinical success rate was noted in the trovafloxacin 7-day group compared to the norfloxacin group at the end of study (91% and 82%, respectively).

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

	Trovafloxacin 100 mg/day 3 Days (N=144)	Trovafloxacin 100 mg/day 7 Days (N=144)	Norfloxacin 400 mg BID 3 Days (N=125)	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	140 (100%)	144 (100%)	125 (100%)	
Success (Cure + Improvement)	136 (97%)	140 (97%)	115 (92%)	
Trova 3 days vs. Trova 7 days				(-3.9, 3.8)
Trova 3 days vs. Norfloxacin				(-0.4, 10.6)
Trova 7 days vs. Norfloxacin				(-0.2, 10.7)
Distribution of Clinical Response:				
Cure	106 (76%)	123 (85%)	98 (78%)	
Improvement	30 (21%)	17 (12%)	17 (14%)	
Failure	4 (3%)	4 (3%)	10 (8%)	
End of Study:				
Number of Subjects Assessed	133 (100%)	127 (100%)	114 (100%)	
Success (Cure + Improvement)	114 (86%)	115 (91%)	93 (82%)	
Trova 3 days vs. Trova 7 days				(-12.7, 3.0)
Trova 3 days vs. Norfloxacin				(-5.1, 13.4)
Trova 7 days vs. Norfloxacin				(0.2, 17.7)
Distribution of Clinical Response:				
Cure	109 (82%)	111 (87%)	91 (80%)	
Improvement	5 (4%)	4 (3%)	2 (2%)	
Failure	4 (3%)	4 (3%)	10 (9%)	
Relapse	15 (11%)	8 (6%)	11 (10%)	

Trova=trovafloxacin; CI=confidence interval
Ref.: Table 5.2.1

Medical Officer's Comment: *The MO agreed with the sponsor's analysis of clinical response.*

Summary of the Differences between the Investigator and Sponsor-Defined Clinical Response at the EOT and EOS:

The sponsor provided multiple tables both in the study report as well as in the appendices. These were reviewed as well as the CRFs when necessary.

The MO noted the following:

- *Overall the sponsor's determination was more conservative.*
- *In all cases, those patients who received an alternative antimicrobial during follow-up were classified as failures by the sponsor and carried forward.*
- *The MO can provide a list of these patients, however, in all cases the MO agreed with the sponsor and therefore the data is accepted as presented.*

Clinical Response by Baseline Pathogen:

Copied from page 39 of the study report:

Among clinically evaluable subjects with *Escherichia coli* isolated at baseline, sponsor-defined clinical success rates (cure + improvement) at the end of treatment were 97% in the trovafloxacin 3-day group, 98% in the trovafloxacin 7-day group, and 91% in the norfloxacin group.

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in the following table.

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

	Trovafloxacin 100 mg/day 3 Days	Trovafloxacin 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days	Trovafloxacin 100 mg/day 3 Days	Trovafloxacin 100 mg/day 7 Days	Norfloxacin 400 mg BID 3 Days
	Number and Percentage (%) of Subjects					
Pathogen	End of Treatment			End of Study		
E. coli	111/115 (97%)	108/110 (98%)	88/97 (91%)	98/109 (90%)	90/98 (92%)	71/87 (82%)

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

Medical Officer's Comment: *The MO agreed with the sponsor's analysis.*

Signs and Symptoms:

Overall the percentage of patients with moderate to severe signs and symptoms at baseline was comparable among the 3 groups (dysuria: trovafloxacin 3-day: 76%, trovafloxacin 7-day: 72%, and norfloxacin: 72%, urgency 85%, 81%, and 75% respectively, suprapubic pain: 37%, 41%, and 44% respectively, frequency 86%, 84%, and 78% respectively, flank pain and CVA tenderness 1%: all arms.

In all treatment groups there was improvement from baseline to the EOT and then to the EOS and there were no significant differences between the arms.

Analysis of Sponsor-Defined Patients with a Bacteriologic Response of Persistence and a Clinical Response of Failure/Relapse:

35 trovafloxacin 3-day patients had a bacteriologic response of persistence. Of these, 14 received additional antimicrobial therapy.

For the 7-day trovafloxacin arm, these numbers were 23 and 9 and for the norfloxacin arm: 31 and 16.

The remaining 21 trovafloxacin 3-day, 14 trovafloxacin 7-day, and 15 norfloxacin patients did not receive additional therapy and were classified as clinical cures or improvements at the EOT.

27 of the 35 trovafloxacin 3-day patients with persistence had cultures that showed *Escherichia coli*, *Enterococcus faecalis*, and *Proteus mirabilis*. The respective numbers for the trovafloxacin 7-day arm were 17 *Escherichia coli* and for the norfloxacin arm 21 *Escherichia coli*.

Medical Officer's Comment: *There was no table to accompany this information, a review of these patients revealed that Escherichia coli was the predominant isolate found in all groups which is compatible with this organism being the predominant isolate.*

Of theses isolates only 1 Proteus mirabilis from the trovafloxacin 3-day arm and 1 Pseudomonas aeruginosa from the 7-day arm were resistant at baseline with MICs of 8. 1 Enterococcus faecalis from the norfloxacin arm was intermediate to norfloxacin at baseline with an MIC of 8.

Clinical Failures:
(Copied below from page 43 of the study report is the sponsor's analysis of the clinical failures)

Four trovafloxacin 3-day subjects, four trovafloxacin 7-day subjects, and 10 norfloxacin subjects were clinical failures at both the end of treatment and the end of study. All subjects were designated as clinical failures after completing their respective treatment regimens. With the exception of Subject 5681- 0289 in the norfloxacin group, all subjects designated as clinical failures received additional antibiotics for inadequate response.

Of the subjects designated as clinical failures, two of four subjects in the trovafloxacin 3-day group had repeat cultures that showed persistence of *Escherichia coli*, one of four subjects in the trovafloxacin 7-day group had a repeat culture that showed persistence of *Enterococcus faecalis* and *Staphylococcus haemolyticus* and three of ten subjects in the norfloxacin group had repeat cultures that showed persistence of *Escherichia coli*.

Clinical Relapse: Fifteen trovafloxacin 3-day subjects, eight trovafloxacin 7-day subjects, and 11 norfloxacin subjects were designated as clinical relapses at the end of study. Ten of the 15 trovafloxacin 3-day, five of the eight trovafloxacin 7-day, and Nine of the 11 norfloxacin subjects designated as clinical relapses received additional antibiotics for inadequate response.

Of the subjects designated as clinical relapses, seven of 15 subjects in the trovafloxacin 3-day group had repeat cultures that showed persistence of *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Enterococcus faecalis*, or *Citrobacter freundii*, five of eight subjects in the trovafloxacin 7-day group had a repeat culture that showed persistence of *Escherichia coli* or *Klebsiella pneumoniae* and five of 11 subjects in the norfloxacin group had repeat cultures that showed persistent of *Escherichia coli*, *Klebsiella pneumoniae* or *Enterococcus faecalis* at either the end of treatment and/ or end of study. With the exception of two subjects in the trovafloxacin 3-day group and two subjects in the norfloxacin group with pathogen outcomes of eradication, all other subjects with a sponsor- defined subject bacteriological response of relapse had pathogens with outcomes of presumed persistence.

Cross-Tabulation of Clinical Response and Bacteriological Response in Bacteriologically and Clinically Evaluable Patients:

Medical Officer's Comment: *There were inconsistent results, that is clinical success with bacteriologic persistence or clinical failure with bacteriologic eradication in 42 subjects. The sponsor presented this information in the form of 2 tables (5.6.1 and 5.7.1) which are summarized below:*

Specifically, 2 trovafloxacin 3-day patients were clinical failures with bacteriologic eradication, both with Escherichia coli, and 17 patients were clinically cured or improved with bacteriologic persistence. Of these 17, 7 had Escherichia coli, 7 had Enterococcus faecalis (one patient had polymicrobial UTI), and there was 1 Citrobacter freundii, 1 Klebsiella pneumoniae, and 1 Enterobacter cloacae. The 1 patient with 3 organisms also had a Staphylococcus haemolyticus.

On the trovafloxacin 7-day arm, 2 patients were clinical failures with bacteriologic eradication, 1 each with Escherichia coli and Enterococcus faecalis. The remainder were clinical cures with bacteriologic persistence, with 4 Escherichia coli, 1 Klebsiella pneumoniae, 1 Pseudomonas aeruginosa, and 1 Staphylococcus epidermidis

On the norfloxacin arm, 4 patients were clinical failures with bacteriologic eradication, all with Escherichia coli. 9 patients were clinical cures with bacteriologic persistence, 5 with Escherichia coli, 1 Staphylococcus aureus, 2 Enterococcus faecalis, and 1 Klebsiella pneumoniae

Sponsor's Conclusion:

Copied below are portions of the sponsor's conclusion from pages 51 and 52 of the study report (modified by MO in Times New Roman font):

Administration of trovafloxacin 100 mg once daily for 3 days and administration of trovafloxacin 100 mg once daily for 7 days were shown to be effective for the treatment of uncomplicated urinary tract infections. Among bacteriologically evaluable subjects, pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined subject bacteriological responses at the end of treatment (86% (120/139), trovafloxacin 3 day, 93% (132/142), trovafloxacin 7 day, 88% (109/124), norfloxacin) supported equivalence of trovafloxacin 3-day versus norfloxacin, and trovafloxacin 7-day versus norfloxacin.

Sponsor-defined subject eradication rates at the end of study were comparable among the three treatment groups (74% (95/128), trovafloxacin 3-day, 84% (99/118), trovafloxacin 7-day, 73% (80/109), norfloxacin). Similar results were observed among bacteriological intent-to-treat subjects and subjects with a baseline uropathogen ≥10'5 CFU/ML.

Among bacteriologically evaluable subjects, sponsor-defined pathogen eradication rates for the most frequently isolated baseline pathogen (*Escherichia coli*) were comparable among the three treatment groups at the end of treatment (92% (105/114), trovafloxacin 3-day, 95% (103/108), trovafloxacin 7-day, 90% (87/97), norfloxacin) and at the end of study (81% (85/105), trovafloxacin 3-day, 83% (74/89), trovafloxacin 7-day, 74% (62/84), norfloxacin). Similar results were observed among bacteriological intent-to-treat subjects and subjects with a baseline uropathogen ≥10 5 CFU/ML.

Among clinically evaluable subjects, sponsor-defined clinical success rates (cure + improvement) at the end of treatment were comparable among the three treatment groups (97% (136/140), trovafloxacin 3-day, 97% (140/144), trovafloxacin 7-day, 92% (115/125), norfloxacin).

Sponsor-defined clinical success rates at the end of study were comparable between the trovafloxacin 3-day group (114/133:86%) and the norfloxacin group (93/114:82%). A higher clinical success rate was noted in the trovafloxacin 7-day group compared to the norfloxacin group at the end of study (115/127 (91%) and 93/114 (82%), respectively). Additionally, these findings were

supported by marked decreases in the presence of clinical signs and symptoms of infection from baseline to the end of treatment and the end of study in all three treatment groups. Similar results were observed among clinical intent-to-treat subjects.

Medical Officer's Comment: *The MO agreed that trovafloxacin 100 mg PO daily for 3 days appeared equivalent to norfloxacin 400 mg PO bid for 3 days in terms of the primary and secondary efficacy variables.*

The sponsor is requesting approval for the 3-day regimen and needs to show equivalence only with the norfloxacin arm of the study.

Interestingly, it may be that neither 3-day arm is as good as the trovafloxacin 7-day arm, however, norfloxacin is an approved agent for this indication at the dose requested.

Medical Officer's Analysis of Efficacy:

The MO elected to accept as the FDA evaluable population, the sponsor's bacteriologically evaluable population with baseline counts of ≥ 10'5 CFU/mL. Although there was an initial discussion about the lower bound of the EOT "window of analysis", being set early, a review of the data indicated that NO patients on the 3-day arms of this study would have been excluded because of an early evaluation. This was not the case for the 7-day arm, where 65 patients would have been excluded from the analysis if the lower bound was set at day 13. Because the sponsor is requesting approval for the 3-day regimen and only needs to show equivalence with an approved comparator, the MO accepted the sponsor's numbers.

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

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

Of the original 560 patients, 18 were withdrawn prior to randomization. This was uniformly due to withdrawal of consent. Of the 542 remaining patients, 182 were randomized to trovafloxacin 3-day, 182 to trovafloxacin 7-day, and 178 to norfloxacin.

The MO in provided an analysis of the excluded patients on the section pertaining to the sponsor's demographics. The sponsor's bacteriologically evaluable population was 143, 142 and 125 patients per arm respectively, as compared to the MO's, which is 120, 113 and 106 per arm respectively. This difference of 23, 19 and 19 patients is because the Reviewer excluded those patients with colony counts of ≤ 10'5 CFU/mL.

Table 116.7:
Bacteriologically Evaluable Population (as per the MO)

MO's Bacteriologically Evaluable Population (≥ 10'5 CFU/mL)			
Reason for exclusion	**Trova 3-day**	**Trova 7-day**	**Norflox 3-day**
	N=542		
Total Randomized	N=182	N=182	N =178
No Baseline Pathogen	32	27	44
BSL count < 10'3	3	3	4
BSL count > 10'3 but < 10'5	23	29	19
Withdrawn because of insufficient R/x/ con. AB or no consent prior to EOT	4	10	5
Total Evaluable	**120**	**113**	**106**
No. not evaluated at EOT but at EOS	4	-	1
Total Evaluated at EOT	**116**	**113**	**105**
No. not evaluated at EOS but at EOT	12	15	12
Total Evaluated at EOS	**104**	**98**	**93**

Specifically, patients that were withdrawn were:

Trovafloxacin 3-day (N = 4):

- 50110366: Insufficient r/x, no postbaseline culture
- 50410187: No postbaseline culture, no consent
- 57970619: Clin. Eval but not bact. No culture, consent
- 58010617: Concomitant antimicrobial

Trovafloxacin 7-day (N = 10):

- 50130373: Insufficient R/x, concomitant antimicrobial
- 50050184: Insufficient R/x, concomitant antimicrobial
- 50050300: No postbaseline culture/consent
- 51380013: No postbaseline culture in window
- 54920228: Insufficient R/x, no culture
- 56810154: No postbaseline assessment in window
- 56810160: No postbaseline assessment in window
- 58210741: Insufficient therapy, concomitant antimicrobial
- 57870222: No culture but clinically evaluable
- 57970622: No culture but clinically evaluable

Norfloxacin (N = 5):

- 50050173: Concomitant antimicrobial
- 50410191: Insufficient R/x
- 56360259: Insufficient R/x
- 56810151: Insufficient R/x
- 57878020: No postbaseline assessment in window

In addition to the above, there were 4 patients from the trovafloxacin 3-day arm who did not have a bacteriological assessment at the EOT although they did have one at the EOS. These patients are unevaluable as per the MO and are listed below:

- 56300064
- 56300211
- 56810159
- 57830159

On the norfloxacin arm there was 1 patient that was not evaluated at the EOT and therefore excluded: 57830089.

Presented in Table 116.8 are the bacteriologically evaluable patients by center. The MO's clinically evaluable population has been tied to the bacteriologically evaluable.

Table 116.8:

Bacteriologically Evaluable Population by Center/Sponsor/MO

			Trovafloxacin 100 mg x 3 days		Trovafloxacin 100 mg x 7 days.		Norfloxacin 400 mg b. i. d. x 3 days			
Center	Total Randomized N = 542 (100%)		Sponsor and MO Evaluable N = 116	%	Sponsor and MO Evaluable N = 113	%	Sponsor and MO Evaluable N = 105	%	Total evaluable N = 334 (100%)	
5003 *	35	6.4	6	5.1	6	5.3	6	5.7	18	5.3
5005*	54	9.9	11	9.4	13	11.5	11	10.4	35	10.4
5011 *	18	3.3	4	3.4	5	4.4	4	3.8	13	3.8
5013 *	27	4.9	7	6.0	3	2.6	2	1.9	12	3.5
5041 *	27	4.9	4	3.4	5	4.4	3	2.8	12	3.5
5138 *	14	2.5	2	1.7	2	1.7	1	.9	5	1.4
5492 *	48	8.8	10	8.6	10	8.8	8	7.6	28	8.3
5630 *	13	2.3	1	.8	2	1.7	1	.9	4	1.1
5632 *	28	5.1	3	2.5	5	4.4	4	3.8	12	3.5
5633 *	7	1.2	2	1.7	2	1.7	0	-	4	1.1
5635 *	8	1.4	1	,8	2	1.7	0	-	3	.89
5636 *	8	1.4	2	1.7	2	1.7	2	1.9	6	1.7
5637 *	10	1.8	2	1.7	2	1.7	4	3.8	8	2.3
5681 *	54	9.9	16	13.7	16	14.1	17	16.1	49	14.6
5733 *	29	5.3	6	5.1	4	3.5	5	4.7	15	4.4
5783	18	3.3	5	4.3	3	2.6	4	3.8	12	3.5
5784	17	3.1	4	3.4	4	3.5	4	3.8	12	3.5
5785	6	1.1	2	1.7	1	.8	2	1.9	5	1.4
5786	6	1.1	2	1.7	2	1.7	1	.9	5	1.4
5787	19	3.5	3	2.5	4	3.5	5	4.7	12	3.5
5792	2	0.3	-	-	-	-	-	-	-	-
5794	13	2.3	2	1.7	2	1.7	3	2.8	7	2.0
5797	2	0.3		-	-	-	-	-	-	-
5798	7	1.2	1	.8	2	1.7	1	.9	4	1.1
5799	5	1.4	2	1.7	2	1.7	1	.9	5	1.4
5801	12	2.2	3	2.5	1	.8	2	1.9	6	1.7
5802	10	1.8	3	2.5	3	2.6	3	2.8	9	2.6
5803	4	0.7	-	-	-	-	-	-	-	-
5804	24	4.4	8	6.8	5	4.4	7	6.6	20	5.9
5821	17	3.1	4	3.4	5	4.4	4	3.8	13	3.8

None of the randomized and treated patients from centers 5792, 5797, and 5803 met the Reviewer's criteria for evaluability.

Only center 5681 had greater than 10%of the evaluable patients on all 3 arms. The US centers represent approximately 66.5% of the evaluable population.

The demographics of the FDA evaluable population can be seen in the following Table:

Table 116.9:
Demographic Characteristics of the FDA Evaluable Population:

	Trova 3-day	Trova 7-day	Norflox 3-day
Characteristics	N = 116	N = 113	N = 105
Sex (Female)	**116**	**113**	**105**
Age (years) 16 -44	71	77	68
45 - 64	27	15	23
≥ 65	18	21	14
Mean	40.9	39.2	39.9
Race: Asian	1	3	0
Black	3	1	3
White	105	99	95
Hispanic	7	10	6
Nat Am.	0	0	1
Body weight (kg) mean	67.4	65.1	69.4

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

EFFICACY:

Table 116.10:
Table of Bacteriologic Efficacy by Patient (as per the MO):

	Trova 3-day			Trova 7-day			Norflox 3-day		
Timepoint	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
EOT	**116**	**101**	**87.1**	**113**	**105**	**92.9**	**105**	**94**	**89.5**
EOS	104	77	74	98	81	82.7	93	69	74.2

From Table 116.10, it is apparent that at the MO TOC, (EOT), there was equivalence between the trovafloxacin 3-day arm and the norfloxacin arm with a CI of -11.8% ,6.9% with CCF (Δ = 15%). The failure rate was 15 patients or 12.9% for the trovafloxacin 3-day arm as compared to 11 patients or 10.5% for the norfloxacin arm. Interestingly, there was also equivalence between the trovafloxacin 7-day and the norfloxacin arms with a CI of -5.1% 11.8% (Δ = - 10%) with CCF but NOT between the trovafloxacin 3-day and the trovafloxacin 7-day regimens: CI -14.4% 2.7% (Δ = - 10%) with CCF.

This difference persisted at the EOS where again there was equivalence between the trovafloxacin 3-day and norfloxacin regimens, CI -12.5% 13.5% (Δ= - 20%) with CCF and the norfloxacin and trovafloxacin 7-day regimens, CI 4.4% 20.8% (Δ = - 15%) with CCF but not between the trovafloxacin 3-day and 7-day regimens, CI -19.7% 4.4% (Δ = - 15%) with CCF.

Additional statistical analyses provided by Dr. Nancy Silliman, FDA STL, revealed that if the analyses were adjusted for 2 primary comparisons, then the 97.5% CI was –13.0%, 8.1% (Δ = 15%). Therefore, the trovafloxacin 3 day regimen remained equivalent to the norfloxacin regimen. If the analysis was adjusted for 3 primary comparisons, the 98.5% CI was –13.7%, 8.8% (Δ = 15%). Therefore, once again the trovafloxacin 3 day regimen was equivalent to the norfloxacin regimen.

Table 116.11:
Bacteriologic Efficacy by Pathogen at EOT:

Pathogen	Trova 3-day			Trova 7-day			Norflox 3-day		
	N	No. Erad	%	N	No. Erad	%	N	No. Erad.	%
Escherichia coli	96	88	92	90	85	93	81	75	93
Enterococcus faecalis	5	1	20	3	2	67	5	3	60
Proteus mirabilis	8	7	88	4	4	100	4	4	100
Enterobacteriaceae	7	4	66	8	7	87.5	9	7	71.4
Pseudomonas aeruginosa	1	1	100	1	0	0	0	0	0
Pseudomonas spp.	-	-	-	1	1	100	-	-	-
Staphylococcus haemolyticus	3	2	66.6	3	2	66.6	1	1	100
Staphylococcus saprophyticus	2	2	100	6	6	100	3	3	100
Staphylococcus aureus	2	2	100	-	-	-	3	2	66.6
Other *Staphylococci*	2	2	100	-	-	-	1	1	100
Beta-hemolytic Streptococci	-	-	-	-	-	-	1	1	100
Other Streptococci	-	-	-	-	-	-	1	1	100
Morganella morganii.	-	-	-	-	-	-	1	1	100
Acinetobacter spp	-	-	-	-	-	-	1	1	100
Total	**126**	**109**	**86.5**	**116**	**107**	**92.2**	**111**	**100**	**90**

From Table 116.8, it appeared as if the overall eradication rate for all bacterial isolates was 86.5% for trovafloxacin 3-day arm compared to 92.2% for the 7-day arm and 90% for the norfloxacin arm. The CIs for these results were:

- Trovafloxacin 3-day vs. Norfloxacin: -12.6%, 5.4% with CCF, (Δ = -10%): NOT equivalent;
- Trovafloxacin 7-day vs. Norfloxacin: -6.1%, 10.4% (Δ = -10%)
- Trovafloxacin 3-day vs. Trovafloxacin 7-day: -14.3%, 2.3% (Δ = - 10%) NOT equivalent;

Therefore, equivalence was mot shown between the 3-day treatment arms versus the bacterial isolates as a whole.

If the coagulase-negative Staphylococci including *Staphylococcus haemolyticus* are excluded (but including *Staphylococcus saprophyticus)* and the Streptococci other than *Enterococcus faecalis* are excluded these rates are:

- Trovafloxacin 3-day vs. Norfloxacin: 105/121 (86.7%) CI -12.2%, 6.3% (Δ = -15%),
- Trovafloxacin 7-day vs. Norfloxacin: 105/113 (92.9%) CI -5.2%, 11.6% (Δ = - 10%) and
- Trovafloxacin 3-day vs. Trovafloxacin 7-day: 96/107 (89.7%),CI - 14.7, 2.4% (Δ = - 10%)

Therefore there was equivalence for the 3-day regimens only and not between the trovafloxacin 3 and 7 day arms.

The CIs for *Escherichia coli* alone were:

- Trovafloxacin 3-day vs. Norfloxacin: - 10.0%, 8.2% (Δ = - 10%)
- Trovafloxacin 7-day vs. Norfloxacin: - 6.7%, 10.4% (Δ = - 10%)
- Trovafloxacin 3-day vs. Trovafloxacin 7-day: - 11.1%, 5.6 % (Δ = - 10%) NOT EQUIVALENT

Thus the 3-day regimens were again equivalent but the 7-day regimen was superior to both.

Overall trovafloxacin 100 mg for 3 days was equivalent to norfloxacin 400 mg bid for 3 days both for overall bacteriologic efficacy as well as for *Escherichia coli* eradication.

A by center analysis for both bacteriological efficacy and clinical efficacy is available, however there were no "outlier" centers and additionally, the number of patients per center was too small to detect any significant differences.

Table 116.12:
Clinical Efficacy (Bacteriologically Evaluable Population/as per the MO)

	Trova 3-day			Trova 7-day			Norflox 3-day		
Timepoint	N	No. Cured	%	N	No. Cured	%	N	No. Cured	%
EOT	**116**	**113**	**97.4**	**113**	**110**	**97.3**	**105**	**97**	**92.4**
EOS	107	91	85.0	101	90	89.1	98	81	82.7

From Table 116.12, it is apparent that the trovafloxacin 3-day arm was as effective as the comparator in the treatment of uncomplicated UTI from the standpoint of clinical efficacy, (95% CI : -1.7 %, 11.7 % (Δ = - 10%) at the EOT/TOC and at the EOS -8.1%, 13.6% (Δ = - 10%) for the trovafloxacin 3-day vs. norfloxacin arms).

Table 116.13:
Cross Tabulation of Clinical and Bacteriological Efficacy at the EOT for FDA Evaluable Population:

	Trova 3-day N =116				Trova 7-days N = 113				Norflox 3-day N = 105			
	Bact. Assessment Erad.		Pers		Bact. Assessment Erad.		Pers		Bact. Assessment Erad.		Pers	
	N	%	N	%	N	%	N	%	N	%	N	%
Clinical Assessment												
Success	100	86.2	13	11.2	104	92.0	6	5.3	90	85.7	7	6.7
Failure	1	0.9	2	1.7	1	0.9	2	1.8	4	3.8	4	3.8
Total	101	87.1	15	12.9	105	92.9	8	7.1	94	89.5	11	89.5

From Table 116.13, it is evident that there were disparate results between clinical success and bacteriologic eradication in 13 of the 113 clinical successes on the trovafloxacin 3-day arm, 6 of the 110 clinical successes on the trovafloxacin 7-day arm and 7 of the 97 clinical successes on the norfloxacin arm.

Additionally, there were 1 of 3 trovafloxacin 3-day clinical failures with bacteriologic eradication, 1 of 3 trovafloxacin 7-day patients and 4/8 norfloxacin patients had similar results.

From the line listings provided, the MO identified these subjects and provides below a list per arm with their EOS bacteriologic and clinical responses:

Trovafloxacin 3-day (N = 14):

PID	EOT Bact Resp	EOT CL. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf. Y /N	Reviewer Determination
50030098	Pers.	Cure	Pers.	Relapse	Y (*Klebsiella pneumoniae*)	*Persistence of original Escherichia coli/Bactrim Rx/Klebsiella pneumoniae ! NOT a true superinfection* N
50110027	Pers.	Cure	Pers.	Not Assessable		*Escherichia coli persistent at F/u, no further culture*
50130140	Pers.	Cure	Pers.	Cure	N	*Escherichia coli Erad/Group D persistent at F/u, , cleared without therapy* N
50130375	Pers	Impr.	Pers.	Impr.	N	*Escherichia coli cleared/Klebsiella pneumoniae Persistent Day12, no R/x, cleared and recurred at Day 42* N
50410188	Pers	Impr.	Pers	Impr	N	*Escherichia coli , decreased to at F/u but at Day 42:* N
56360260	Pers.	Cure	Pers.	Cure	N	*Escherichia coli persistent at both F/u visits* N
57330206	Pers.	Impr	Pers.	Relapse	N	*Proteus mirabilis Eradicated and at day 42* N
57830840	Pers.	Cure	Erad	Cure	N	*Escherichia coli, at F/u and Erad at day 42.* N
57980584	Pers.	Cure	Pers.	Not Assessable		*Group D at F/u, no EOS culture,* N
57990599	Pers	Impr.	Pers	Relapse	Y *(Escherichia coli)*	*Enterobacter spp., Klebsiella pneumoniae at initial culture, Enterobacter Pers., cleared with Cipro, Escherichia coli at at Day 42,* Y
58020573	Pers.	Cure	Erad.	Cure	Y (*Citrobacter fr./Pseudomonas fluorescens*)	*Original Escherichia coli Erad., all others*
58020578	Pers.	Cure	Pers.	Not Assessable	Y (*Klebsiella Pneumoniae*)	*Group D Pers., Klebsiella at F/u, no R/x, no F/u,* Y
58210735	Pers.	Impr.	Pers.	Relapse	Y (*Lecleria ad.*)	*Citrobacter 10'5 Erad after Day 12 w/o r/x, Bactrim day 43 for clinical complaints, Lecleria* N
54920346	Erad.	Failure	Pers.	Failure	N	*Escherichia coli Erad, Bactrim day 13 all cultures (-),* N

Trovafloxacin 7-day (N = 7):

50410192	Pers.	Impr.	Pers.	Cure	N	*Escherichia coli decreased to at F/u but at Day 42:* N
56330032	Pers.	Cure	Pers.	Relapse	N	*Klebsiella pneumoniae Pers. Day 12, Cipro R/x, no further cultures,* N
56360090	Pers.	Cure		Not Assessable		*Pseudomonas aeruginosa Pers., Erythro for tooth abscess*
57870798	Pers	Cure	Pers.	Relapse		*Escherichia coli Pers. At F/u, Noroxin R/x, cleared,* N
57980585	Pers.	Cure	Pers.	Not Assessable	Y (*Enterococcus faecalis/Staphylococcus haemolyticus)*	*Original pathogens cleared, both* Y
58210754	Pers.	Impr.	Erad.	Impr.	Y (*Enterococcus faecalis.)*	*Original Escherichia coli at day 42, Enterococcus* N

54920026	Erad.	Failure	Pers.	Failure	N	*Enterococcus faecalis, no culture at EOT, Cipro R/x, F/u (-),* **N**

Norfloxacin 3 day (N = 11):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf.Y /N	Reviewer Determination
50050138	Pers.	Cure	Pers.	Relapse	N	*Klebsiella pneumoniae Day 12, Cefuroxime cleared,* **N**
50130058	Pers.	Cure	Pers.	Cure	N	*Group D, Escherichia coli at day 1, decreased to at EOT, Escherichia coli at EOS,* **N**
50410007	Pers.	Impr.	Pers.	Relapse	N	*Escherichia coli Pers. , no R/x,* **N**
58020571	Pers.	Cure	Erad	Cure	Y(*Staphylococcus epidermidis*)	*Escherichia coli, Group D decreased at EOT, cleared w/o R/x, Staphylococcus epidermidis* **N**
58020580	Pers.	Cure	Pers.	Relapse	N	*Gp. D Pers., CiproR/x,* **N**
58040762	Pers.	Cure	Pers.	Cure	N	*Escherichia coli Pers., No R/x,* **N**
58210737	Pers.	Cure	Pers.	Cure	N	*Staphylococcus aureus decreased to but Citrobacter no r/x,* **N**
54920077	Erad.	Failure	Erad.	Failure	Y (*Klebsiella pneumoniae*)	*Escherichia coli Erad, Nitrofur. R/x for clinical, Klebsiella pneumoniae at EOS,* **Y**
56810289	Erad.	Failure	Erad.	Failure	N	*Escherichia coli Pers,* **N**
57330068	Erad.	Failure	Pers.	Failure	N	*Escherichia coli, Bactrim r/x,* **N**
57330302	Erad	Impr.	Erad.	Cure	N	*Escherichia coli Erad,* **N**

The MO did not discover any significant trends in the above list. Overall, most clinical failures remained failures at the EOS, with the exception of 1 norfloxacin patient. There was no definitive trend in the persistent/improvement group in terms of their evolution to cures or relapses.

Using the Reviewer's criteria, there were only 2 superinfections found on the trovafloxacin 3-day arm, and 1 on each of the other arms for a total of 4 amongst this population of patients where there were disparate bacteriologic and clinical outcomes.

Overall, the Reviewer agreed with the sponsor's determination of outcome in terms of failure/cure.

Clinical Relapses:

The following patients were classified as relapses, where applicable, patients from the previous list who are relapses have their PIDs bolded:

Trovafloxacin 3-day (N = 13):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf.Y /N	Reviewer Determination:
50030098	Pers.	Cure	Pers.	Relapse	Y(*Klebsiella pneumoniae*)	*Persistence of original Escherichia coli/Bactrim Rx/ Klebsiella pn. NOT a true superinfection* **N**
50030119	Erad.	Cure	Pers.	Relapse	N	*Staphylococcus saprophyticus Erad, then recurred, Bactrim R/x ,* **N but RECURRENCE**
50050424	Erad.	Impr.	Erad.	Relapse	Y (*Klebsiella pneumoniae*)	*Escherichia coli cleared/Klebsiella pneumoniae at EOS,* **Y**

50410465	Erad.	Cure.	Erad	Relapse	Y (*Escherichia coli*)	*Proteus mirabilis Erad, Escherichia coli at Day* **33, Y**
54920195	Erad.	Cure	Pers.	Relapse	N	*Group B Streptococcus and Staphylococcus aureus Staphylococcus aureus cleared, Group B decreased at EOT at EOS,* **N**
56360088	Erad.	Cure	Pers.	Relapse	Y (*Proteus Mirabilis*)	*Escherichia coli day 1, Proteus mirabilis Day 4, Cipro,* **Y**
56810052	Erad.	Cure	Pers.	Relapse	N	*Escherichia coli Erad,* **RECURRED,** *Nitrof. R/x,* **N**
56810203	Erad.	Cure	Pers.	Relapse	N	*Escherichia coli,* **RECURRED,** *Bactrim R/x,* **N**
56810292	Erad.	Cure	Pers.	Relapse	Y (*Escherichia coli*)	*Proteus mirabilis Erad. Escherichia coli r/x Bactrim,* **Y**
57330206	Pers.	Impr	Pers.	Relapse	N	*Proteus mirabilis Eradicated and at day 42* **N**
57990599	Pers	Impr.	Pers	Relapse	Y *(Escherichia coli)*	*Enterobacter, Klebsiella pneumoniae at initial culture, Enterobacter Pers., cleared with Cipro, Escherichia coli at at Day 42,* **Y**
58040760	Erad.	Cure	Pers.	Relapse	Y (*Enterobacter agglomerans/Proteus mirabilis*)	*Escherichia coli Erad. other orgs isolated Noroxin R/x Enterobacter agglomerans = S, Proteus = NO ,* **Y**
58210735	Pers.	Impr.	Pers.	Relapse	Y *(Lecleria ad.)*	*Citrobacter Erad after Day 12 w/o r/x, Bactrim day 43 for clinical complaints, Lecleria* **N**

Trovafloxacin 7-day (N = 8):

50410010	Erad.	Cure	Pers.	Relapse	N	*Escherichia coli Erad Day 12, EOS*
56330032	Pers..	Cure	Pers.	Relapse	N	*Klebsiella pneumoniae Pers. Day 12, Cipro R/x, no further cultures,* **N**
54920029	Erad..	Cure	Pers.	Relapse	N	*Escherichia coli Erad,* **RECURRENCE,** *Nitrof. R/x,* **N**
54920080	Erad..	Cure	Pers.	Relapse	N	*Escherichia coli Erad, no cultures, Nitrof R/x,* **N**
57870798	Pers	Cure	Pers.	Relapse	N	*Escherichia coli Pers. at F/u, Noroxin R/x, cleared,* **N**
58040728	Erad..	Impr	Pers.	Relapse	Y*(Acinetobacter calcotaenius/Enterobacter cloace/Escherichia coli)*	*Escherichia coli = S only, Noroxin R/x,* Y
58040761	Erad..	Cure	Pers.	Relapse	Y(*Staphylococcus saprophyticus*)	*S after original Escherichia coli cleared,* **Y**
58040728	Erad..	Impr	Pers.	Relapse	Y (*Escherichia coli.*)	*Escherichia coli superinf. after original Klebsiella pneumoniae Erad,* **Y**

Norfloxacin 3-day (N =8):

PID	EOT Bact Resp	EOT Cl. Resp	EOS Bact Resp	EOS Cl. Resp.	Sup/inf.Y /N	Reviewer Determination
50050138	Pers.	Cure	Pers.	Relapse	N	*Klebsiella pneumoniae Day 12, Cefuroxime cleared,* **N**
50410007	Pers.	Impr.	Pers.	Relapse	N	*Escherichia coli Pers. , no R/x,* **N**

50030107	Erad..	Cure	Pers.	Relapse	N	*Staphylococcus saprophyticus Erad but Nitrof. R/x,* **N**
50030109	Erad..	Cure	Pers.	Relapse	N	*Escherichia coli R/x with Macrobid, no repeat culture,* **N**
58020580	Pers.	Cure	Pers.	Relapse	N	*Enterococcus Pers., CiproR/x,* **N**
56360087	Erad..	Cure	Pers.	Relapse	N	*Enterococcus, no EOT culture, Lomeflox R/x,* **N**
56810153	Erad..	Cure	Pers.	Relapse	N	*Escherichia coli, Erad EOT,* **RECURRED** *EOS,* **N**
56810202	Erad..	Cure	Pers.	Relapse	Y	*(Klebsiella pneumoniae) Escherichia coli Erad., Klebsiella pneumoniae Day 42, nitrof. R/x,* **Y**

There were no significant trends identified in the patients who were clinical relapses. There were 13 relapses at the EOS on the trovafloxacin 3-day arm (8 in patients who were initially eradication/cures, 1 persistent/cure, 3 persistent/improved, and 1 eradication/improved). The respective numbers for the trovafloxacin 7-day arm were 8 relapses (4 eradication/cures, 2 persistent/cures and 2 eradication/improved) and 8 norfloxacin relapses (5 eradicated/cured, 2 persistent/cured and 1 persistent/improved).

Overall more patients with an EOT status of Eradicated/Improved were found to have superinfections.

These determinations reflect the sponsor's determinations of superinfecting organisms as opposed to the Reviewer's. The sponsor applied stricter criteria than the Reviewer did, and specifically, a superinfecting pathogen was any organism other than the original pathogen found any time after Day 10 in an amount of ≥ 10'3 CFU/mL. The Reviewer has adhered to DAIDP guidelines and determined as superinfecting pathogens, any organism associated with UTIs in an amount of ≥ 10'5 CFU/mL after original clearance.

Recurrence, a category not used by the sponsor refers to the culture of ≥ 10'5 CFU/mL of the original pathogen after documented clearance.

Persistence was also defined differently by the Reviewer. Persistence is defined as the culture of the original pathogen in an amount of ≥ 10'5 at the EOT whereas the sponsor determined persistence to be the culture of the original pathogen in an amount of ≥ 10'3 at EOT. The MO elected to accept the sponsor's definition (see introduction of MOR).

Based on the Reviewer's definition, although ALL of the patients constitute relapse or failures, the reviewer determined that there were 6 superinfections on the trovafloxacin 3-day arm as compared to the sponsor's 7 and that 3 of the 13 relapses were RECURRENCES of the original pathogen.

On the trovafloxacin 7-day arm and on the norfloxacin arm, the Reviewer agreed with the sponsor's determination of superinfection in all cases and recategorized 1 patient on each arm to RECURRENCE status. Amongst the organisms that were recurrent one was a *Staphylococcus saprophyticus* on the trovafloxacin 3-day arm, and all others were *Escherichia coli* (2, 1, 1) and all required further therapy.

Bacterial Superinfections:

Trovafloxacin 3-day (N = 17):

- 50030098: EOS clinical relapse with *Klebsiella pn*eumoniae/NOT a superinfecting pathogen per MO, < 10'5 CFU/mL, Bactrim® R/x.
- 50050424: EOS clinical relapse with *Klebsiella pneumoniae*/MO agreed.
- 50410465: EOS clinical relapse with *Escherichia coli*/MO agreed.

- 56330033: EOS cure with *Enterococcus faecalis* in urine/MO agreed.
- 56360088: EOS clinical relapse with *Proteus mirabilis*/MO agreed, Cipro® r/x.
- 56810292: EOS clinical relapse with *Escherichia coli*/MO agreed, Bactrim® r/x.
- 56810309: EOS cure with *Enterobacter aerogenes* in urine/MO agreed. No R/x.
- 57870793: EOS cure with *Enterobacter cloacae* in urine/MO agreed. No R/x.
- 57940982: EOS cure with *Staphylococcus haemolyticus* in urine. Not a superinfecting pathogen per Reviewer.
- 57990599: EOS clinical relapse with *Escherichia coli*/MO agreed.
- 58020573: EOS cure with *Citrobacter freundii* and *Pseudomonas fluorescens* in urine. NOT superinfecting pathogens per MO
- 58020578: EOS cure with *Klebsiella pneumoniae* in urine/MO agreed.
- 58040760 EOS clinical relapse with *Enterobacter agglomerans* and *Proteus mirabilis* in urine/*Enterobacter agglomerans* was a superinfecting pathogen per the Reviewer but NOT the *Proteus mirabilis*.
- 58040758: EOS cure with *Staphylococcus haemolyticus* in urine. Not a superinfecting pathogen per Reviewer.
- 58040765: EOS cure with *Staphylococcus haemolyticus* in urine. Not a superinfection per Reviewer but *Acinetobacter* in urine was a superinfecting pathogen.
- 58210735: EOS cure with *Lecleria adecarboxylata* in urine. NOT a superinfecting pathogen per MO.
- 58210753: EOS clinical relapse with *Acinetobacter* spp. MO agreed, but no R/x mentioned.

On the trovafloxacin 3-day arm, there were 17 patients with superinfecting organisms (20) as per the sponsor, however as per the Reviewer, there were 12 superinfecting organisms and 12 patients. Of these, only 3 received therapy at this timepoint. There were no identifiable trends in types of organisms isolated.

Trovafloxacin 7 day (N = 13):

- 50050132: EOS cure with *Providencia* spp. in urine. MO disagreed
- 51380231: EOS cure with *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* in urine. Not superinfecting pathogens per Reviewer
- 56300216: EOS cure with *Proteus mirabilis* in urine. Not superinfecting pathogen per MO
- 57330305: EOS cure with *Staphylococcus haemolyticus* and *Enterococcus faecalis* in urine. Not superinfecting pathogens per MO
- 57980585: EOS cure with *Staphylococcus haemolyticus* and *Enterococcus faecalis* in urine. MO agreed

- 58020574: EOS cure with *Staphylococcus epidermidis* in urine/Not a superinfecting pathogen per Reviewer.
- 58020576: EOS cure with *Staphylococcus epidermidis* in urine. Not a superinfecting pathogen per Reviewer.
- 58040728: EOS clinical relapse with *Escherichia coli, Enterobacter cloacae* and *Acinetobacter* spp. Only *Escherichia coli* was a superinfecting pathogen per the Reviewer . Noroxin® R/x.
- 58040726: EOS cure with *Acinetobacter* spp. in urine. Superinfecting pathogen per Reviewer, > 10'5
- 58040761: EOS clinical relapse with *Staphylococcus saprophyticus.* Superinfecting pathogen per Reviewer
- 58040763: EOS cure with *Pseudomonas putida.* in urine. Superinfecting pathogen per Reviewer
- 58040768: EOS clinical relapse with *Morganella morganii.* Not a superinfecting pathogen per Reviewer.
- 58210754: EOS cure with *Enterococcus faecalis* in urine. Not a superinfecting pathogen per MO

On the trovafloxacin 7-day arm, there were 13 patients with 18 superinfecting bacterial isolates as per the sponsor. As per the Reviewer, there were 5 patients with 6 superinfecting organisms. Only 1 patient received additional therapy at this timepoint.

Norfloxacin (N = 7):

- 54920077: EOS cure with *Klebsiella pneumoniae* in urine. MO agreed.
- 56810202: EOS clinical relapse with *Klebsiella pneumoniae*. MO agreed. Bactrim® R/x.
- 56810321: EOS cure with *Acinetobacter* spp. in urine. MO agreed.
- 57980588: EOS cure with *Enterococcus faecalis* in urine. Not a superinfecting pathogen per MO (< 10'4 CFU/mL).
- 58020571: EOS cure with *Staphylococcus epidermidis* in urine. Not a superinfecting pathogen per Reviewer.
- 58040725: EOS cure with *Enterobacter cloacae, Klebsiella oxytoca,* and *Staphylococcus haemolyticus.* None of the organisms were superinfecting pathogens per the Reviewer
- 58040731: EOS cure with *Escherichia coli* in urine. Superinfecting pathogen per Reviewer

On the norfloxacin arm the sponsor found 7 patients with 9 superinfecting organisms. The Reviewer agreed with 4 patients and 4 organisms. Only 1 received therapy at this timepoint.