VII.B.2. RESULTS

A total of 221 subjects were enrolled at 16 centers in the USA between March 15, 1995 and November 13, 1995. Of these enrolled subjects, 18 subjects were prematurely discontinued from treatment. Seventy two trovafloxacin q.d., 74 trovafloxacin b.i.d., and 75 ciprofloxacin subjects were included in the clinical intent-to-treat analyses; 56 trovafloxacin q.d.; 57 trovafloxacin b.i.d., and 51 ciprofloxacin subjects were included in the bacteriological intent-to-treat analyses. The Applicant bacteriologically evaluable group at EOT comprised 124 subjects, and there were 73 subjects in the Medical Officer bacteriologically evaluable group at EOT. The most common reason for exclusion from the bacteriologically evaluable subset analysis was no post-baseline cultures. The most common reason for exclusion of subjects from the clinically evaluable subset was insufficient.

Reviewer's Note: *The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 103.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 103.2: STUDY 154-103: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Treatment Group for Response	Subjects Included		
	Trovafloxacin q.d. (N=72)	Trovafloxacin b.i.d. (N=74)	Ciprofloxacin (N=75)
Clinically ITT	71 (98.6%)	74 (100%)	75 (100%)
Bacteriologically ITT	56 (77.8%)	57 (77.0%)	51 (68.0%)
Applicant Clinically Evaluable			
Clinically Evaluable at EOT	44 (61.1%)	42 (56.8%)	45 (60.0%)
Clinically Evaluable at EOS	46 (63.9%)	44 (59.5%)	44 (58.7%)
MO Clinically Evaluable			
Clinically Evaluable at EOT	22 (30.6%)	22 (29.7%)	28 (37.3%)
Clinically Evaluable at EOS	18 (25.0%)	19 (25.7%)	22 (29.3%)
Applicant Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	43 (59.7%)	40 (54.1%)	41 (54.7%)
Bacteriologically Evaluable at EOS	39 (54.2%)	39 (52.7%)	39 (52.0%)
MO Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	22 (30.6%)	22 (29.7%)	29 (38.7%)
Bacteriologically Evaluable at EOS	21 (29.2%)	21 (28.4%)	27 (36.0%)

Subject bacteriological responses at EOT and EOS are shown for the Applicant bacteriologically evaluable subjects in Tables 103.3A and 103.3B, respectively. The subject eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT and EOS are presented in Tables 103.4A and 103.4B, respectively.

Pathogen bacteriological outcomes at EOT and EOS are shown for the Applicant bacteriologically evaluable subjects in Tables 103.5A and 103.5B, respectively. The pathogen eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT is presented in Tables 103.6.

Clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 103.7A and 103.7B, respectively. The success rates of the Medical Officer clinically evaluable subjects at EOT and EOS are presented in Tables 103.8A and 103.8B, respectively.

REVIEWER COMMENT: *With respect to all the efficacy variables, comparisons of the difference between treatment groups were performed. Numerically, the results showed that the three treatment groups were similar at EOT and at EOS. Because this study did not have sufficient power to show equivalence due to small sample size, no definitive conclusions regarding equivalency of the three treatments could be drawn.*

TABLE 103.3A: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT

Subject Bacteriological Response	Trova q.d. (N=43)	Trova b.i.d. (N=40)	Ciprofloxacin (N=41)
Eradication	41 (95.3%)	37 (92.5%)	38 (92.7%)
Persistent	2 (4.7%)	3 (7.5%)	3 (7.3%)
Trova q.d. vs Cipro	2.7%, 98.3% C.I.: -12.1%, 17.5%		
Trova b.i.d. vs Cipro	-0.2%, 98.3% C.I.: -16.6%, 16.2%		
Trova q.d. vs Trova b.i.d.	2.8%, 98.3% C.I.: -12.2%, 17.9%		

TABLE 103.3B: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trova q.d. (N=39)	Trova b.i.d. (N=39)	Ciprofloxacin (N=39)
Eradication	31 (79.5%)	34 (87.2%)	31 (79.5%)
Persistent	8 (20.5%)	5 (12.8%)	8 (20.5%)
Trova q.d. vs Cipro	0%, 98.3% C.I.: -24.5%, 24.5%		
Trova b.i.d. vs Cipro	7.7%, 98.3% C.I.: -15.0%, 30.4%		
Trova q.d. vs Trova b.i.d.	-7.7%, 98.3% C.I.: -30.4%, 15.0%		

TABLE 103.4A: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT

Subject Bacteriological Response	Trova q.d. (N=22)	Trova b.i.d. (N=22)	Ciprofloxacin (N=29)
Eradication	21 (95.5%)	19 (86.4%)	27 (93.1%)
Persistent	1 (4.5%)	3 (13.6%)	2 (6.9%)
Trova q.d. vs Cipro	2.4%, 98.3% C.I.: -17.1%, 21.8%		
Trova b.i.d. vs Cipro	-6.7%, 98.3% C.I.: -31.6%, 18.1%		
Trova q.d. vs Trova b.i.d.	9.1%, 98.3% C.I.: -15.9%, 34.1%		

TABLE 103.4B: STUDY 154-103: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trova q.d. (N=21)	Trova b.i.d. (N=21)	Ciprofloxacin (N=27)
Eradication	15 (71.4%)	18 (85.7%)	22 (81.5%)
Persistent	6 (28.6%)	3 (14.3%)	5 (18.5%)
Trova q.d. vs Cipro	-10.1%, 98.3% C.I.: -43.9%, 23.8%		
Trova b.i.d. vs Cipro	4.2%, 98.3% C.I.: -25.6%, 34.0%		
Trova q.d. vs Trova b.i.d.	-14.3%, 98.3% C.I.: -48.9%, 20.3%		

TABLE 103.5A: STUDY 154-103: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Trova q.d.	Trova b.i.d.	Ciprofloxacin
E. coli	37/38 (97.4%)	32/33 (97.0%)	30/31 (96.8%)
Trova q.d. vs Cipro Trova b.i.d. vs Cipro Trova q.d. vs Trova b.i.d.	0.6%, 98.3% C.I.: -12.2%, 13.3% 0.2%, 98.3% C.I.: -13.4%, 13.8% 0.4%, 98.3% C.I.: -11.9%, 12.7%		

TABLE 103.5B: STUDY 154-103: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Trova q.d.	Trova b.i.d.	Ciprofloxacin
E. coli	27/34 (79.4%)	29/32 (90.6%)	25/30 (83.3%)
Trova q.d. vs Cipro Trova b.i.d. vs Cipro Trova q.d. vs Trova b.i.d.	-3.9%, 98.3% C.I.: -30.3%, 22.5% 7.3%, 98.3% C.I.: -16.4%, 31.0% -11.2%, 98.3% C.I.: -34.9%, 12.5%		

TABLE 103.6: STUDY 154-103: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Trova q.d.	Trova b.i.d.	Ciprofloxacin
E. coli	19/19 (100%)	17/18 (94.4%)	21/21 (100%)
Trova q.d. vs Cipro Trova b.i.d. vs Cipro Trova q.d. vs Trova b.i.d.	0%, 98.3% C.I.: -5.0%, 5.0% -5.6%, 98.3% C.I.: -23.6%, 12.5% 5.6%, 98.3% C.I.: -12.8%, 23.9%		

TABLE 103.7A: STUDY 154-103: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT			
Clinical Response	Trova q.d. (N=44)	Trova b.i.d. (N=42)	Ciprofloxacin (N=45)
Success (cure+improvement) Failure (failure+relapse)	42 (95.5%) 2 (4.5%)	41 (97.6%) 1 (2.4%)	41 (91.1%) 4 (8.9%)
Trova q.d. vs Cipro Trova b.i.d. vs Cipro Trova q.d. vs Trova b.i.d.	4.3%, 98.3% C.I.: -10.5%, 19.2% 6.5%, 98.3% C.I.: -7.4%, 20.4% -2.2%, 98.3% C.I.: -13.9%, 9.6%		

TABLE 103.7B: STUDY 154-103: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS			
Clinical Response	Trova q.d. (N=46)	Trova b.i.d. (N=44)	Ciprofloxacin (N=44)
Success (cure+improvement) Failure (failure+relapse)	42 (91.3%) 4 (8.7%)	41 (93.2%) 3 (6.8%)	37 (84.1%) 7 (15.9%)
Trova q.d. vs Cipro Trova b.i.d. vs Cipro Trova q.d. vs Trova b.i.d.	7.2%, 98.3% C.I.: -11.5%, 26.0% 9.1%, 98.3% C.I.: -9.2%, 27.4% -1.9%, 98.3% C.I.: -17.6%, 13.8%		

TABLE 103.8A: STUDY 154-103: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT			
Clinical Response	Trova q.d. (N=22)	Trova b.i.d. (N=22)	Ciprofloxacin (N=29)
Success (cure+improvement) Failure (failure+relapse)	21 (95.5%) 1 (4.5%)	21 (95.5%) 1 (4.5%)	28 (96.6%) 1 (3.4%)
Trova q.d. vs Cipro Trova b.i.d. vs Cipro Trova q.d. vs Trova b.i.d.	-1.1%, 98.3% C.I.: -18.5%, 16.3% -1.1%, 98.3% C.I.: -18.5%, 16.3% 0%, 98.3% C.I.: -19.6%, 19.6%		

TABLE 103.8B: STUDY 154-103: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS			
Clinical Response	Trova q.d. (N=18)	Trova b.i.d. (N=19)	Ciprofloxacin (N=26)
Success (cure+improvement) Failure (failure+relapse)	16 (89.9%) 2 (11.1%)	17 (89.5%) 2 (10.5%)	22 (84.6%) 4 (15.4%)
Trova q.d. vs Cipro Trova b.i.d. vs Cipro Trova q.d. vs Trova b.i.d.	4.3%, 98.3% C.I.: -25.0%, 33.5% 4.9%, 98.3% C.I.: -23.6%, 33.3% -0.6%, 98.3% C.I.: -30.5%, 29.3%		

Reviewer's Note: *For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Tables 103.9A, 103.9B, and 103.9C. With respect to all these adverse event rates, significant differences were only detected in the number of subjects who reported at least one treatment related adverse events between the treatment groups of trovafloxacin 100 mg b.i.d. and ciprofloxacin, and there was a significantly higher rate in the trovafloxacin 100 mg b.i.d. group than in the ciprofloxacin group. Significantly more subjected had dizziness in both trovafloxacin groups when compared with ciprofloxacin.*

TABLE 103.9A: STUDY 154-103: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova q.d. (N=72)	Ciprofloxacin (N=75)	Fisher's P-value
At Least One AE	40/72 (55.6%)	42/75 (56.0%)	1.000
CENTRAL AND PERIPHERAL NERVOUS	26 (36.1%)	18 (24.0%)	0.149
Dizziness	18 (25.0%)	5 (6.7%)	0.003
Headache	12 (16.7%)	5 (6.7%)	0.073
At Least One Treatment Related AE	26/72 (36.1%)	21/75 (28.0%)	0.377
CENTRAL AND PERIPHERAL NERVOUS	16 (22.2%)	9 (12.0%)	0.125
Dizziness	10 (13.9%)	6 (8.0%)	0.297
Headache	11 (15.3%)	5 (6.7%)	0.116
Discontinuations Due to an AE	3/72 (4.2%)	2/75 (2.7%)	0.677
Clinically Significant Lab Abnormalities	9/40 (22.5%)	11/44 (25.0%)	0.804

TABLE 103.9B: STUDY 154-103: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova b.i.d. (N=74)	Ciprofloxacin (N=75)	Fisher's P-value
At Least One AE	48/74 (64.9%)	42/75 (56.0%)	0.316
CENTRAL AND PERIPHERAL NERVOUS	21 (28.4%)	18 (24.0%)	0.580
Dizziness	15 (20.3%)	5 (6.7%)	0.017
Headache	9 (12.2%)	5 (6.7%)	0.276
At Least One Treatment Related AE	36/74 (48.7%)	21/75 (28.0%)	0.012
CENTRAL AND PERIPHERAL NERVOUS	17 (23.0%)	9 (12.0%)	0.088
Dizziness	8 (10.8%)	6 (8.0%)	0.588
Headache	7 (9.5%)	5 (6.7%)	0.563
Discontinuations Due to an AE	8/74 (10.8%)	2/75 (2.7%)	0.056
Clinically Significant Lab Abnormalities	5/35 (14.3%)	11/44 (25.0%)	0.273

TABLE 103.9C: STUDY 154-103: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova q.d. (N=72)	Trova b.i.d. (N=74)	Fisher's P-value
At Least One AE	40/72 (55.6%)	48/74 (64.9%)	0.310
CENTRAL AND PERIPHERAL NERVOUS	26 (36.1%)	21 (28.4%)	0.377
Dizziness	18 (25.0%)	15 (20.3%)	0.555
Headache	12 (16.7%)	9 (12.2%)	0.486
At Least One Treatment Related AE	26/72 (36.1%)	36/74 (48.7%)	0.135
CENTRAL AND PERIPHERAL NERVOUS	16 (22.2%)	17 (23.0%)	1.000
Dizziness	10 (13.9%)	8 (10.8%)	0.622
Headache	11 (15.3%)	7 (9.5%)	0.322
Discontinuations Due to an AE	3/72 (4.2%)	8/74 (10.8%)	0.209
Clinically Significant Lab Abnormalities	9/40 (22.5%)	5/35 (14.3%)	0.393

No deaths were reported during this study. One of the 74 subjects (1%) in the trovafloxacin 100 mg b.i.d. group had a serious adverse event, however, this event was considered by the investigator to be unrelated to study drug.

Reviewer's Summary and Conclusions: *See Section X.*

VII.C. STUDY 154-116

VII.C.1. METHODS

In study 154-116, a total of approximately 540 subjects with uncomplicated urinary tract infections were to be enrolled and to be randomized to one of the three treatment groups in a 1:1:1 ratio. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for clinical diagnosis of uncomplicated urinary tract infection, gave informed consent, and met all inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of female outpatients, who were 16 years of age or older with clinically documented uncomplicated urinary tract infection.

Study visits were scheduled for Visit 1 (Day 1, baseline), Visit 2 (Day 12, EOT), and Visit 3 (Day 42, EOS). At Visit 1, baseline assessments and clinical assessments of signs and symptoms of urinary tract infection were performed. At Visit 2, microbiological tests and clinical assessments of signs and symptoms of urinary tract infection were performed. Safety was also assessed. Hematology, chemistry, and urinalysis determinations were repeated. The investigator provided an evaluation of clinical response. At Visit 3, efficacy and safety observations were the same as those performed at Visit 2. The investigator provided a final evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF. At each visit, the investigator obtained information about concomitant illnesses and therapeutic intervention. The reason for a subject discontinuing from the clinical trial was recorded on the CRF. Table 116.1 demonstrates during treatment and post treatment procedures which were specified by the protocol

Study drug was in the form of trovafloxacin tablets or norfloxacin capsules and was packaged in blister cards using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafloxacin 100 mg/day as a single dose (1x100 mg tablet) in the morning for 3 days; 2. trovafloxacin 100 mg/day as a single dose (1x100 mg tablet) in the morning for 7 days; 3. norfloxacin 800 mg/day in two equally divided doses (2x400 mg capsule) in the morning and evening for 3 days. All subjects took combinations of active drug and placebos for active drug.

TABLE 116.1: STUDY 154-116: VISIT TIMING AND PROCEDURES			
Visit Number	Visit 1	Visit 2	Visit 3
Study Day	Day 1	12	Day 42
Allowable Window	-48 hours	11-13	35-49
Treatment Period	Day 1 to Day 7		
Follow-up Period	Day 8 to Day 42		
Informed Consent	X		
Demographic Information	X		
Physical Examination	X		
Concomitant Medication	X	X	X
Vital Signs	X	X	X
Dosing Record		X	
Clinical Signs & Symptoms	X	X	X
Microbiology			
• analysis of unspun urine	X	X	X
• culture & sensitivity	X	X	X
Safety Laboratory Tests			
• hematology	X	X	abn
• biochemistry	X	X	abn
• urinalysis	X	X	abn
Pregnancy test	X		
Adverse Events			
• routine events		X	X
• serious adverse events		X	X
Investigator's Clinical Evaluation		X	X

abn Abnormal at previous visit or clinically significant adverse event.

Efficacy evaluation, safety evaluation, and statistical methods were similar to those described for Study 154-103 in Section VII.B.1.

VII.C.2. RESULTS

A total of 560 subjects were enrolled across centers in the USA (15) and in Europe (19) between March 15, 1995 and November 13, 1995. Of these enrolled subjects, 18 were withdrawn prior to randomization. No subject in any of the three treatment groups was discontinued from treatment due to inadequate response. One hundred eighty two of trovafloxacin 3 days, 182 of trovafloxacin 7 days, and 178 of norfloxacin subjects were included in the clinical intent-to-treat analyses; 147 of trovafloxacin 3 days; 152 of trovafloxacin 7 days, and 130 of norfloxacin subjects were included in the bacteriological intent-to-treat analyses. The Applicant bacteriologically evaluable group at EOT comprised 405 subjects, and there were 334 subjects in the Medical Officer bacteriologically evaluable group. The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline cultures in evaluable windows. The most common reason for exclusion from clinical evaluability was no post-baseline clinical assessment, no post-baseline assessment in evaluable analysis window, insufficient therapy, and concomitant antibiotic therapy.

***Reviewer's Note**: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 116.2. There were no*

statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

TABLE 116.2: STUDY 154-116: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP			
Treatment Group for Response	Subjects Included		
	Trova 3 Days (N=182)	Trova 7 Days (N=182)	Norfloxacin (N=178)
Clinically ITT	182 (100%)	182 (100%)	178 (100%)
Bacteriologically ITT	147 (80.8%)	152 (83.5%)	130 (73.0%)
Applicant Clinically Evaluable			
Clinically Evaluable at EOT	140 (76.9%)	144 (79.1%)	125 (70.2%)
Clinically Evaluable at EOS	133 (73.1%)	127 (69.8%)	114 (64.0%)
MO Clinically Evaluable			
Clinically Evaluable at EOT	116 (63.7%)	113 (62.1%)	105 (59.0%)
Clinically Evaluable at EOS	107 (58.8%)	101 (55.5%)	98 (55.1%)
Applicant Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	139 (76.4%)	142 (78.0%)	124 (69.7%)
Bacteriologically Evaluable at EOS	122 (70.3%)	118 (64.8%)	109 (61.2%)
MO Bacteriologically Evaluable			
Bacteriologically Evaluable at EOT	116 (63.7%)	113 (62.1%)	105 (59.0%)
Bacteriologically Evaluable at EOS	104 (57.1%)	98 (53.8%)	93 (52.2%)

Subject bacteriological responses at EOT and EOS are shown for the Applicant bacteriologically evaluable subjects in Tables 116.3A and 116.3B, respectively. Confidence interval results from analyses show that trovafloxacin 3 days and trovafloxacin 7 days were both therapeutically equivalent to norfloxacin at the two endpoints. Trovafloxacin 3 days was not considered therapeutically equivalent to trovafloxacin 7 days.

Reviewer's Note: *The subject eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT and EOS are presented in Tables 116.4A and 116.4B, respectively. Pairwise comparisons (98.3% confidence intervals) of the difference in subject bacteriological eradication rates among the three treatment groups at both EOT and EOS supported equivalence of trovafloxacin 3 days versus norfloxacin, and trovafloxacin 7 days versus norfloxacin, but not trovafloxacin 3 days versus trovafloxacin 7 days.*

TABLE 116.3A: STUDY 154-116: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT			
Subject Bacteriological Response	Trova 3 Days (N=139)	Trova 7 Days (N=142)	Norfloxacin (N=124)
Eradication	120 (86.3%)	132 (93.0%)	109 (87.9%)
Persistent	19 (13.7%)	10 (7.0%)	15 (12.1%)
Trova 3 Days vs Norfloxacin	-1.6%, 98.3% C.I.: -12.2%, 9.1%		
Trova 7 Days vs Norfloxacin	5.1%, 98.3% C.I.: -4.4%, 14.5%		
Trova 3 Days vs Trova 7 Days	-6.6%, 98.3% C.I.: -16.0%, 2.7%		

TABLE 116.3B: STUDY 154-116: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trova 3 Days (N=122)	Trova 7 Days (N=118)	Norfloxacin (N=109)
Eradication Persistent	95 (74.2%) 33 (25.8%)	99 (83.9%) 19 (16.1%)	80 (73.4%) 29 (26.6%)
Trova 3 Days vs Norfloxacin Trova 7 Days vs Norfloxacin Trova 3 Days vs Trova 7 Days	0.8%, 98.3% C.I.: -13.7%, 15.4% 10.5%, 98.3% C.I.: -3.4%, 24.4% -9.7%, 98.3% C.I.: -22.8%, 3.4%		

TABLE 116.4A: STUDY 154-116: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT			
Subject Bacteriological Response	Trova 3 Days (N=116)	Trova 7 Days (N=113)	Norfloxacin (N=105)
Eradication Persistent	101 (87.1%) 15 (12.9%)	105 (92.9%) 8 (7.1%)	94 (89.5%) 11 (10.5%)
Trova 3 Days vs Norfloxacin Trova 7 Days vs Norfloxacin Trova 3 Days vs Trova 7 Days	-2.5%, 98.3% C.I.: -13.7%, 8.8% 3.4%, 98.3% C.I.: -6.7%, 13.5% -5.9%, 98.3% C.I.: -16.2%, 4.5%		

TABLE 116.4B: STUDY 154-116: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trova 3 Days (N=104)	Trova 7 Days (N=98)	Norfloxacin (N=93)
Eradication Persistent	77 (74.0%) 27 (26.0%)	81 (82.7%) 17 (17.3%)	69 (74.2%) 24 (25.8%)
Trova 3 Days vs Norfloxacin Trova 7 Days vs Norfloxacin Trova 3 Days vs Trova 7 Days	-0.2%, 98.3% C.I.: -16.1%, 15.8% 8.5%, 98.3% C.I.: -6.8%, 23.7% -8.6%, 98.3% C.I.: -23.4%, 6.2%		

Analyses of the pathogen eradication rates of the Applicant bacteriologically evaluable subjects at both EOT and EOS are displayed in Tables 116.5A and 116.5B, respectively. Pairwise comparisons (98.3% confidence intervals) of the difference in *E. coli* eradication rates between treatment groups supported the equivalence of both trovafloxacin regimens versus norfloxacin, but not between the two trovafloxacin regimens at both EOT and EOS.

Reviewer's Note: *Tables 116.6A and 116.6B show the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at EOT and EOS, respectively. The results were the same as those from the Applicant bacteriologically evaluable subjects, except that the equivalence of trovafloxacin 3 days versus norfloxacin was not shown at EOT.*

Tables 116.7A and 116.7B show clinical responses of the Applicant clinically evaluable subjects at EOT and EOS, respectively. Confidence interval results show that the three treatment groups were therapeutically equivalent to each other with respect to the success rates at EOT and EOS, except trovafloxacin 3 days versus trovafloxacin 7 days at EOS.

Reviewer's Note: *Analyses of the success rates of the Medical Officer clinically evaluable subjects at*

both EOT and EOS are displayed in Tables 116.8A and 116.8B, respectively, which show the same results as those from the Applicant clinically evaluable subjects.

TABLE 116.5A: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
E. coli	105/114 (92.1%)	103/108 (95.4%)	87/97 (89.7%)
Trova 3 Days vs Norfloxacin Trova 7 Days vs Norfloxacin Trova 3 Days vs Trova 7 Days	2.4%, 98.3% C.I.: -8.1%, 12.9% 5.7%, 98.3% C.I.: -4.1%, 15.5% -3.3%, 98.3% C.I.: -11.9%, 5.4%		
E. faecalis	3/10 (30%)	4/6 (67%)	4/6 (67%)

TABLE 116.5B: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
E. coli	85/105 (81.0%)	74/89 (83.1%)	62/84 (73.8%)
Trova 3 Days vs Norfloxacin Trova 7 Days vs Norfloxacin Trova 3 Days vs Trova 7 Days	7.1%, 98.3% C.I.: -8.6%, 22.9% 9.3%, 98.3% C.I.: -6.7%, 25.4% -2.2%, 98.3% C.I.: -16.4%, 12.1%		
E. faecalis	1/9 (11.1%)	3/5 (60.0%)	3/6 (50.0%)

TABLE 116.6A: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
E. coli	88/96 (91.7%)	85/90 (94.4%)	75/81 (92.6%)
Trova 3 Days vs Norfloxacin Trova 7 Days vs Norfloxacin Trova 3 Days vs Trova 7 Days	-0.9%, 98.3% C.I.: -11.8%, 9.9% 1.9%, 98.3% C.I.: -8.4%, 12.1% -2.8%, 98.3% C.I.: -12.7%, 7.2%		
E. faecalis	1/5 (20.0%)	2/3 (66.7%)	3/5 (60.0%)

TABLE 116.6B: STUDY 154-116: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR THE MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trova 3 Days	Trova 7 Days	Norfloxacin
E. coli	73/90 (81.1%)	64/77 (83.1%)	54/72 (75.0%)
Trova 3 Days vs Norfloxacin Trova 7 Days vs Norfloxacin Trova 3 Days vs Trova 7 Days	6.1%, 98.3% C.I.: -10.8%, 23.1% 8.1%, 98.3% C.I.: -9.2%, 25.4% -2.0%, 98.3% C.I.: -17.4%, 13.4%		
E. faecalis	1/5 (20.0%)	0/2 (0%)	3/5 (60.0%)

TABLE 116.7A: STUDY 154-116: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT			
Clinical Response	Trova 3 Days (N=140)	Trova 7 Days (N=144)	Norfloxacin (N=125)
Success (cure+improvement)	136 (97.1%)	140 (97.2%)	115 (92.0%)
Failure (failure+relapse)	4 (2.9%)	4 (2.8%)	10 (8.0%)
Trova 3 Days vs Norfloxacin	5.1%, 98.3% C.I: -2.3%, 12.6%		
Trova 7 Days vs Norfloxacin	5.2%, 98.3% C.I.: -2.2%, 12.6%		
Trova 3 Days vs Trova 7 Days	-0.1%, 98.3% C.I.: -5.5%, 5.3%		

TABLE 116.7B: STUDY 154-116: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS			
Clinical Response	Trova 3 Days (N=133)	Trova 7 Days (N=127)	Norfloxacin (N=114)
Success (cure+improvement)	114 (85.7%)	115 (90.6%)	93 (81.6%)
Failure (failure+relapse)	19 (14.3%)	12 (9.4%)	21 (18.4%)
Trova 3 Days vs Norfloxacin	4.1%, 98.3% C.I.: -8.0%, 16.3%		
Trova 7 Days vs Norfloxacin	9.0%, 98.3% C.I.: -2.5%, 20.5%		
Trova 3 Days vs Trova 7 Days	-4.8%, 98.3% C.I.: -15.2%, 5.5%		

TABLE 116.8A: STUDY 154-116: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT			
Clinical Response	Trova 3 Days (N=116)	Trova 7 Days (N=113)	Norfloxacin (N=105)
Success (cure+improvement)	113 (97.4%)	110 (97.3%)	97 (92.4%)
Failure (failure+relapse)	3 (2.6%)	3 (2.7%)	8 (7.6%)
Trova 3 Days vs Norfloxacin	5.0%, 98.3% C.I.: -3.0%, 13.1%		
Trova 7 Days vs Norfloxacin	5.0%, 98.3% C.I.: -3.1%, 13.1%		
Trova 3 Days vs Trova 7 Days	0.1%, 98.3% C.I.: -5.9%, 6.0%		

TABLE 116.8B: STUDY 154-116: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS			
Clinical Response	Trova 3 Days (N=107)	Trova 7 Days (N=101)	Norfloxacin (N=98)
Success (cure+improvement)	91 (85.0%)	90 (89.1%)	81 (82.7%)
Failure (failure+relapse)	16 (15.0%)	11 (10.9%)	17 (17.3%)
Trova 3 Days vs Norfloxacin	2.4%, 98.3% C.I.: -10.9%, 15.7%		
Trova 7 Days vs Norfloxacin	6.5%, 98.3% C.I.: -6.3%, 19.2%		
Trova 3 Days vs Trova 7 Days	-4.1%, 98.3% C.I.: -16.1%, 8.0%		

Reviewer's Note: *For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Tables 116.9A, 116.9B, and 116.9C. The trovafloxacin 7 days group had significantly higher incidence rates of treatment related adverse events in*

the central and peripheral nervous system than the norfloxacin group.

TABLE 116.9A: STUDY 154-116: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova 3 Days (N=182)	Norfloxacin (N=178)	Fisher's P-value
At Least One AE	69/182 (37.9%)	60/178 (33.7%)	0.442
CENTRAL AND PERIPHERAL NERVOUS	35 (19.2%)	23 (12.9%)	0.116
Dizziness	18 (9.9%)	8 (4.5%)	0.066
Headache	22 (12.1%)	15 (8.4%)	0.299
At Least One Treatment Related AE	42/182 (23.1%)	36/178 (20.2%)	0.525
CENTRAL AND PERIPHERAL NERVOUS	25 (13.7%)	13 (7.3%)	0.059
Dizziness	16 (8.8%)	7 (3.9%)	0.083
Headache	11 (6.0%)	7 (3.9%)	0.470
Discontinuations Due to an AE	3/182 (1.7%)	4/178 (2.3%)	0.721
Clinically Significant Lab Abnormalities	25/180 (13.9%)	31/170 (18.2%)	0.308

TABLE 116.9B: STUDY 154-116: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova 7 Days (N=182)	Norfloxacin (N=178)	Fisher's P-value
At Least One AE	61/182 (33.5%)	60/178 (33.7%)	1.000
CENTRAL AND PERIPHERAL NERVOUS	37 (20.3%)	23 (12.9%)	0.067
Dizziness	18 (9.9%)	8 (4.5%)	0.066
Headache	20 (11.0%)	15 (8.4%)	0.478
At Least One Treatment Related AE	44/182 (24.2%)	36/178 (20.2%)	0.378
CENTRAL AND PERIPHERAL NERVOUS	27 (14.8%)	13 (7.3%)	0.029
Dizziness	15 (8.2%)	7 (3.9%)	0.122
Headache	12 (6.6%)	7 (3.9%)	0.347
Discontinuations Due to an AE	4/182 (2.2%)	4/178 (2.3%)	1.000
Clinically Significant Lab Abnormalities	25/175 (14.3%)	31/170 (18.2%)	0.381

TABLE 116.9C: STUDY 154-116: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trova 3 Days (N=182)	Trova 7 Days (N=182)	Fisher's P-value
At Least One AE	69/182 (37.9%)	61/182 (33.5%)	0.444
CENTRAL AND PERIPHERAL NERVOUS	35 (19.2%)	37 (20.3%)	0.895
Dizziness	18 (9.9%)	18 (9.9%)	1.000
Headache	22 (12.1%)	20 (11.0%)	0.870
At Least One Treatment Related AE	42/182 (23.1%)	44/182 (24.2%)	0.902
CENTRAL AND PERIPHERAL NERVOUS	25 (13.7%)	27 (14.8%)	0.881
Dizziness	16 (8.8%)	15 (8.2%)	1.000
Headache	11 (6.0%)	12 (6.6%)	1.000
Discontinuations Due to an AE	3/182 (1.7%)	4/182 (2.2%)	1.000
Clinically Significant Lab Abnormalities	25/180 (13.9%)	25/175 (14.3%)	1.000

There were no deaths reported during this study. One subject in the trovafloxacin 7 day group and two subjects in the trovafloxacin 3 day group had serious adverse events during this study that required hospitalization and were considered by the investigator to be unrelated to study drug.

Reviewer's Summary and Conclusions: *See Section X.*

19 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

IX. PROSTATITIS

IX.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-119, as evidence to support oral trovafloxacin regarding this indication, and statistical review focuses on this clinical trial which forms the basis of this application. The general design of the study is as follows:

Study 154-119 was a randomized, multicenter, double-blind, double-dummy trial which compared the efficacy and safety of trovafloxacin (200 mg q.d.) administered orally for 28 days versus ofloxacin (300 mg b.i.d.) administered orally for 42 days for treatment of bacterial prostatitis. The study was initiated on July 17, 1995 and completed on May 30, 1996.

IX.B. STUDY 154-119

IX.B.1. METHODS

In study 154-119, a total of approximately 300 subjects with a medical history and clinical and bacteriological findings consistent with bacterial prostatitis were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the screening visit (Day -5), subjects who met the criteria for a presumptive diagnosis of bacterial prostatitis, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for evaluation. At the baseline visit (Visit 1, Day 1), subjects with a confirmed diagnosis of bacterial prostatitis were randomized to receive treatment. Eligible study population consisted of male outpatients, who were 18 years of age or older with presumptive clinical diagnosis of bacterial prostatitis.

At the screening visit (Day -5), baseline assessments were performed. Hematology, serum chemistry, and urinalysis determinations were performed for safety testing. The investigator confirmed the diagnosis of bacterial prostatitis by quantitative bacteriological cultures. At the baseline visit (Visit 1, Day 1), the investigator began treatment as soon as bacterial pathogens were identified from the screening visit cultures. At Visits 2 (Day 4) and 3 (Day 20), efficacy observations and safety assessments were performed. At Visit 4 (Days 25-42, EOT for trovafloxacin), efficacy observations were obtained. A global clinical assessment was made, compared to the screening assessment. A quantitative bacteriological culture was repeated. At Visit 5 (Days 43-59, EOT for ofloxacin), efficacy observations were obtained. A global clinical assessment was made, compared to the screening assessment. Like Visit 4, quantitative bacteriological cultures were repeated. Visit 6 (Days 60-84, EOS) was included to assess rates of recurrent infections in those subjects cured or improved at Visit 5. At this visit, efficacy observations were obtained. A global clinical assessment was made. Like Visit 5, quantitative bacteriological cultures were repeated. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 119.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of tablets, packaged in blister cards, and capsules, packaged in bottles, using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafloxacin 200 mg (2x100 mg tablet) q.d. as a single dose on Days 1-28 and one capsule

twice daily (ofloxacin placebo) on Days 1-42; 2. ofloxacin 300 mg (1x300 mg capsule) b.i.d. on Days 1-42 and two tablets (trovafloxacin placebo) on Days 1-28. All subjects received two tablets and one capsule in the morning and one capsule at night through Day 28 of the treatment period. From Day 29 through Day 42, subjects took one capsule in the morning and one capsule at night in combinations of active drug and placebo for active drug.

TABLE 119.1: STUDY 154-119: VISIT TIMING AND PROCEDURES

Visit Number	Screen	Baseline	Visit 2	Visit 3	Visit 4	EOT	Visit 5	Visit 6
Study Day	Day -5	Day 1	Day 4	Day 20	Day 35	Day 42	Day 49	Day 63-84
Allowable Window	Day -5	Day 1	Day 3-5	Day 18-22	Day 33-37	Day 42	Day 47-51	Day 63-84
Treatment Period	Day 1 to Day 42							
Follow-up Period	Day 43 to Day 84 after EOT							
Compliance Checks			X	X	X		X	
Informed Consent	X							
Demographic Information	X							
Targeted Physical Exam	X							
Concomitant Medication	X		X	X	X		X	X
Vital Signs		X	X	X		X	X	
Assessment								
Clinical	X		X	X	X	X	X	X
Laboratory								
• hematology	X		X	X	X		X	X*
• serum chemistry	X		X	X	X		X	X*
• urinalysis	X		X	X	X		X	X*
• fractionated urine culture	X				X		X	X
• urine culture			X	X				
Adverse Event	X		X	X	X	X	X	

* To be done only if there are significant abnormalities at Visit 5

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically and bacteriologically evaluable subjects. The primary efficacy endpoint was clinical response at EOT, which referred to Visit 4 for trovafloxacin or Visit 5 for ofloxacin. The secondary endpoints were clinical response at EOS, subject bacteriological responses at EOT and EOS, and pathogen outcomes at EOT and EOS.

Clinical response, subject bacteriological response, and pathogen outcome were determined by the sponsor and evaluated at Visit 4 (EOT for trovafloxacin), Visit 5 (EOT for ofloxacin), and Visit 6 (EOS). Clinical response was classified as cure, improvement, or failure. Subject bacteriologic response was classified as eradication (complete or partial), complete persistence, or superinfection. Pathogen outcome was classified as eradication (complete or partial), complete persistence, or superinfection.

Reviewer's Note: *The Medical Officer also defined her clinically and bacteriologically evaluable subjects, and assessed clinical and bacteriological efficacy outcomes according to her clinical and bacteriological criteria.*

Please refer to the Medical Officer's review for detailed descriptions of the Applicant's and Medical Officer's efficacy outcome definitions.

SAFETY EVALUATION

All subjects who received at least one dose of study medication were evaluable for safety. The data obtained for evaluation of safety included results of physical examinations, clinical laboratory tests, vital sign measurements, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality, and was monitored up to Visit 5 (Days, 47-51). All observed or volunteered adverse events and intercurrent illnesses that occurred during the clinical trial regardless of treatment group or suspected causal relationship to study drug were recorded on the CRF.

STATISTICAL METHODS

The comparisons of interest in the study were conducted between trovafloxacin and ofloxacin.

Efficacy analyses were based on the clinical and bacteriological responses at Visits 4, 5, and 6. The treatment groups were compared with respect to the clinical success rate (cure+improvement), the subject bacteriological eradication rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success rate at EOT in the clinically evaluable population for the purpose of establishing the equivalence of the two treatments.

Evaluation of safety data was based on review of displays of adverse events within treatment groups for all subjects who received at least one dose of study drug.

Reviewer's Note: *All efficacy analyses were conducted for the Medical Officer clinically and bacteriologically evaluable subjects, and the Applicant clinically and bacteriologically evaluable subjects. All of the subjects in these groups were assessed for their clinical or bacteriological responses. Equivalence between the treatments with respect to efficacy variables was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective is judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.*

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, evaluability status, and medication compliance. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

IX.B.2. RESULTS

A total of 660 subjects were enrolled at 34 centers in the USA between July 17, 1995 and May 30, 1996. Of these enrolled subjects, 385 subjects were withdrawn prior to randomization because they did not meet entrance criteria, the majority of whom had no pathogen at baseline. One hundred forty two subjects were randomized to receive trovafloxacin, and 135 subjects were randomized to receive ofloxacin. One hundred thirty four trovafloxacin and 129 ofloxacin subjects were included in the clinical intent-to-treat analyses; 122 trovafloxacin and 118 ofloxacin subjects were included in the bacteriological intent-to-treat analyses. The Applicant clinically evaluable group at EOT comprised 224 subjects, and there were 126 subjects in the Medical Officer clinically evaluable group at EOT. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy for trovafloxacin subjects, and no post-baseline clinical response in evaluable window for ofloxacin subjects.

***Reviewer's Note**: The number and percentage of evaluable subjects included in each analysis group, evaluated by either the Applicant or the Medical Officer, are presented in Table 119.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 119.2: STUDY 154-119: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Treatment Group for Response	Subjects Included	
	Trovafloxacin (N=142)	Ofloxacin (N=135)
Clinically ITT	134 (94.4%)	129 (95.6%)
Bacteriologically ITT	122 (90.1%)	118 (87.4%)
Applicant Clinically Evaluable		
Clinically Evaluable at EOT	113 (79.6%)	111 (82.2%)
Clinically Evaluable at EOS	107 (75.4%)	103 (76.3%)
MO Clinically Evaluable		
Clinically Evaluable at EOT	68 (47.9%)	58 (43.0%)
Clinically Evaluable at EOS	56 (39.4%)	39 (28.9%)
Applicant Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	98 (69.0%)	98 (72.6%)
Bacteriologically Evaluable at EOS	86 (60.6%)	92 (68.1%)
MO Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	68 (47.9%)	58 (43.0%)
Bacteriologically Evaluable at EOS	54 (38.0%)	35 (25.9%)

Clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 119.3A and 119.3B, respectively. Confidence interval results from analyses show that trovafloxacin was therapeutically equivalent to ofloxacin with respect to the success rates at both EOT and EOS.

***Reviewer's Note:** The success rates of the Medical Officer clinically evaluable subjects at EOT and EOS are presented in Tables 119.4A and 119.4B, respectively. Comparisons (95% confidence intervals) of the difference in success rates at EOT between the two treatment groups showed marginal equivalence of trovafloxacin versus ofloxacin. Therapeutic equivalence was shown at EOS.*

TABLE 119.3A: STUDY 154-119: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Trovafloxacin (N=113)	Ofloxacin (N=111)
Success (cure+improvement)	101 (89.4%)	96 (86.5%)
Failure (failure+relapse)	12 (10.6%)	15 (13.5%)
Trova vs Oflox by Cure	2.9%, 95% C.I.: -6.5%, 12.3%	

TABLE 119.3B: STUDY 154-119: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Trovafloxacin (N=107)	Ofloxacin (N=103)
Success (cure+improvement)	74 (69.2%)	71 (68.9%)
Failure (failure+relapse)	33 (30.8%)	32 (31.1%)
Trova vs Oflox by Cure	0.2%, 95% C.I.: -13.2%, 13.7%	

TABLE 119.4A: STUDY 154-119: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Trovafloxacin (N=68)	Ofloxacin (N=58)
Success (cure+improvement)	62 (91.2%)	52 (89.7%)
Failure (failure+relapse)	6 (8.8%)	6 (10.3%)
Trova vs Oflox by Cure	1.5%, 95% C.I.: -10.4%, 13.5%	

TABLE 119.4B: STUDY 154-119: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Trovafloxacin (N=56)	Ofloxacin (N=39)
Success (cure+improvement)	37 (66.1%)	23 (59.0%)
Failure (failure+relapse)	19 (33.9%)	16 (41.0%)
Trova vs Oflox by Cure	7.1%, 95% C.I.: -14.9%, 29.1%	

Table 119.5 shows bacteriological response of the Applicant bacteriologically evaluable subjects at EOT. Confidence interval results show that the two treatment groups were not therapeutically equivalent with respect to the eradication rates at EOT.

A summary of the pathogen eradication rates at EOT for the most frequent isolated baseline pathogens is presented for the Applicant bacteriologically evaluable subjects in Table 119.7.

Reviewer's Note: *Analyses of the eradication rates of the Medical Officer bacteriologically evaluable subjects at both EOT and EOS are displayed in Tables 119.6A and 119.6B, respectively, which failed to show equivalence of trovafloxacin versus ofloxacin at either EOT or EOS.*

Table 119.8 shows the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at

EOT.

TABLE 119.5: STUDY 154-119: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT		
Subject Bacteriological Response	Trovafloxacin (N=98)	Ofloxacin (N=98)
Eradication Persistent	89 (90.8%) 9 (9.2%)	94 (95.9%) 4 (4.1%)
Trova vs Oflox by Eradication	-5.1%, 95% C.I.: -13.1%, -2.8%	

TABLE 119.6A: STUDY 154-119: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT		
Subject Bacteriological Response	Trovafloxacin (N=68)	Ofloxacin (N=58)
Eradication Persistent	57 (83.8%) 11 (16.2%)	52 (89.7%) 6 (10.3%)
Trova vs Oflox by Eradication	-5.8%, 95% C.I.: -19.2%, 7.5%	

TABLE 119.6B: STUDY 154-119: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS		
Subject Bacteriological Response	Trovafloxacin (N=54)	Ofloxacin (N=35)
Eradication Persistent	38 (70.4%) 16 (29.6%)	28 (80.0%) 7 (20.0%)
Trova vs Oflox by Eradication	-9.6%, 95% C.I.: -30.0%, 10.7%	

TABLE 119.7: STUDY 154-119: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)		
Pathogen Bacteriological Outcome	Trovafloxacin	Ofloxacin
S. epidermidis	24/33 (72.7%)	22/34 (64.7%)
C. (-). Staphylococci	28/28 (100%)	33/33 (100%)
S. haemolyticus	14/19 (73.7%)	18/21 (85.7%)
E. faecalis	14/17 (82.4%)	15/18 (83.3%)
E. coli	13/14 (92.9%)	18/18 (100%)

TABLE 119.8: STUDY 154-119: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)		
Pathogen Bacteriological Outcome	Trovafloxacin	Ofloxacin
E. faecalis	11/14 (78.6%)	11/14 (78.6%)
E. coli	12/13 (92.3%)	16/16 (100%)
S. epidermidis	8/10 (80.0%)	5/6 (83.3%)
S. haemolyticus	4/6 (66.7%)	8/8 (100%)
K. pneumoniae	4/6 (66.7%)	1/1 (100%)

Reviewer's Note: *For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuations due to adverse events, and the rates of clinically significant laboratory abnormalities, are presented in Tables 119.9. With respect to the subjects reporting adverse events related to study medication and the subjects discontinuing due to adverse events, the rates were significantly higher in the trovafloxacin group than in the ofloxacin group. There were significantly more trovafloxacin subjects who experienced dizziness and headache.*

TABLE 119.9 STUDY 154-119: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trovafloxacin (N=142)	Ofloxacin (N=133)	Fisher's P-value
At Least One AE	114/142 (80.3%)	95/133 (71.4%)	0.092
CENTRAL AND PERIPHERAL NERVOUS	66 (46.5%)	21 (15.8%)	<0.001
Dizziness	46 (32.4%)	7 (5.3%)	<0.001
Headache	32 (22.5%)	14 (10.5%)	0.009
At Least One Treatment Related AE	61/142 (43.0%)	39/133 (29.3%)	0.024
CENTRAL AND PERIPHERAL NERVOUS	40 (28.2%)	9 (6.8%)	<0.001
Dizziness	32 (22.5%)	4 (3.0%)	<0.001
Headache	18 (12.7%)	4 (3.0%)	0.003
Discontinuations Due to an AE	25/142 (17.6%)	9/133 (6.8%)	0.009
Clinically Significant Lab Abnormalities	28/140 (20.0%)	23/132 (17.4%)	0.642

No deaths were reported during this study. Four subjects in the trovafloxacin group each had a serious adverse event in the study, all of which were considered unrelated to study drug and attributed to other illnesses. Three subjects in the ofloxacin group each had a serious adverse event in the study, all of which were considered unrelated to study drug and attributed to other illnesses.

Reviewer's Summary and Conclusions: *See Section X.*

X. SUMMARY AND CONCLUSIONS
(Which May be Conveyed to the Sponsor)

COMPLICATED INTRA-ABDOMINAL INFECTIONS

This indication was supported by one pivotal study, Study 154-124, to demonstrate the efficacy and safety of alatrofloxacin/trovafloxacin.

The following statements pertain to Study 154-124:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of alatrofloxacin/trovafloxacin minus imipenem/cilastatin/amoxicillin/clavulanac for the Applicant clinically evaluable subjects at EOS was $_{156,\ 152}$ (-9.9%, 8.2%) $_{82.7\%,\ 83.6\%}$. The result demonstrated that alatrofloxacin/ trovafloxacin was therapeutically equivalent in efficacy to its comparator in the treatment of complicated intra-abdominal infections.

2. The two treatment groups were not significantly different in safety with respect to the rates of at least one adverse event, the rates of treatment related adverse events, the rates of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. However, significantly more alatrofloxacin/trovafloxacin subjects experienced adverse events in the central and peripheral nervous system.

REVIEWER CONCLUSIONS: *For the pivotal study 154-124, the efficacy analyses of the clinically evaluable subjects demonstrated that alatrofloxacin/trovafloxacin was therapeutically equivalent in efficacy to imipenem/cilastatin/amoxicillin/clavulanac in the treatment of complicated intra-abdominal infections. Results from the safety analysis also suggested that alatrofloxacin/trovafloxacin and its comparator yield nearly comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, alatrofloxacin 300 mg q.d. administered intravenously followed by oral trovafloxacin 200 mg q.d. administered for a total treatment duration of 14 days is recommended for approval in the treatment of complicated intra-abdominal infections.*

GYNECOLOGIC AND PELVIC INFECTIONS

This indication was supported by one pivotal study, Study 154-144, to demonstrate the efficacy and safety of alatrofloxacin/trovafloxacin.

The following statements pertain to Study 154-144:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at EOS between the treatment groups in the Medical Officer clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of alatrofloxacin/ trovafloxacin minus cefoxitin/amoxicillin/clavulanic acid for the Medical Officer clinically evaluable subjects at EOS was $_{96,\ 107}$ (-5.2%, 15.9%) $_{88.5\%,\ 83.2\%}$. The result demonstrated that alatrofloxacin/trovafloxacin was therapeutically equivalent in efficacy to its comparator in the treatment of gynecologic and pelvic infections.

2. The rate of at least one adverse event was significantly higher in the alatrofloxacin/trovafloxacin group (51.9%, 83/160) than the cefoxitin/amoxicillin/clavulanic acid group (35.7%, 56/157) (Fisher's exact p-value=0.005); the rate of at least one treatment related adverse event was significantly higher in the alatrofloxacin/trovafloxacin group (23.8%, 38/160) than the cefoxitin/amoxicillin/clavulanic acid group (6.4%, 10/157) (Fisher's exact p-value<0.001); the rate of discontinuations due to adverse events was significantly higher in the alatrofloxacin/trovafloxacin group (18.8%, 30/160) than the cefoxitin/ amoxicillin/clavulanic acid group (5.7%, 9/157) (Fisher's exact p-value=0.001). They were not significantly different in the rate of clinical significant laboratory abnormalities. Significantly more subjects experienced dizziness in the alatrofloxacin/trovafloxacin group.

REVIEWER CONCLUSIONS: *For the pivotal study 154-144, the efficacy analyses of the clinically evaluable subjects demonstrated that alatrofloxacin/trovafloxacin was therapeutically equivalent in efficacy to cefoxitin/amoxicillin/clavulanic acid in the treatment of gynecologic and pelvic infections. Results from the safety analysis showed that trovafloxacin had significantly higher rates than its comparator with respect to at least one adverse event and discontinuations due to adverse events, as well as dizziness.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from an efficacy standpoint, alatrofloxacin 300 mg q.d. administered intravenously followed by oral trovafloxacin 200 mg q.d. administered for a maximum of 14 days of total therapy is recommended for approval in the treatment of gynecologic and pelvic infections. However, the Medical Officer will have to determine whether this treatment regimen has an acceptable safety profile.*

SURGICAL PROPHYLAXIS - ELECTIVE COLORECTAL SURGERY

This indication was supported by one pivotal study, Study 154-128, to demonstrate the efficacy and safety of alatrofloxacin.

The following statements pertain to Study 154-128:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in success rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of alatrofloxacin minus cefotetan for the Applicant clinically evaluable subjects at EOS was $_{161, 156}$ (-10.9%, 10.1%) $_{72.0\%, 72.4\%}$. The result demonstrated that alatrofloxacin was therapeutically equivalent in efficacy to its comparator in the prophylaxis of primary site infection following elective colorectal surgery.

2. The two treatment groups were not significantly different in safety with respect to the rates of at least one adverse event, the rates of discontinuations due to an adverse events, and the rate of clinical significant laboratory abnormalities. However, significantly more subjects in the alatrofloxacin group (10.2%, 26/256) experienced treatment related adverse events than those in the cefotetan group (2.5%, 6/236) (Fisher's exact p-value=0.001).

REVIEWER CONCLUSIONS: *For the pivotal study 154-128, the efficacy analyses of the clinically evaluable subjects demonstrated that alatrofloxacin was therapeutically equivalent in efficacy to cefotetan in the prophylaxis of primary site infection following elective colorectal surgery. Results from the safety analysis also suggested that alatrofloxacin and its comparator yield nearly comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, alatrofloxacin 200 mg administered as a single intravenous dose and within 2 hours of surgical incision is recommended for approval in the prophylaxis of primary site infection following elective colorectal surgery.*

SURGICAL PROPHYLAXIS - ELECTIVE ABDOMINAL AND VAGINAL HYSTERECTOMY

This indication was supported by one pivotal study, Study 154-146, to demonstrate the efficacy and safety of trovafloxacin.

The following statements pertain to Study 154-146:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of trovafloxacin minus cefoxitin for the Applicant clinically evaluable subjects at EOS was $_{133, 127}$ (-17.3%, 0%) $_{83.5\%, 92.1\%}$. The result failed to demonstrate that trovafloxacin was therapeutically equivalent in efficacy to its comparator in the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy. In

fact, the result showed that trovafloxacin was significantly inferior to its comparator.

2. The two treatment groups were not significantly different in safety with respect to the rates of at least one adverse event, the rates of treatment related adverse events, the rates of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities.

REVIEWER CONCLUSIONS: *For the pivotal study 154-146, the efficacy analyses of the clinically evaluable subjects failed to demonstrate that trovafloxacin was therapeutically equivalent in efficacy to cefoxitin in the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy. In fact, the result showed that trovafloxacin was significantly worse than cefoxitin. Results from the safety analysis suggested that trovafloxacin and its comparator yield comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from an efficacy standpoint, an approvable regulatory decision toward trovafloxacin 200 mg administered as a single oral dose and within 45 minutes of surgical incision regarding the indication of the prophylaxis of post-operative infection following elective abdominal or vaginal hysterectomy can not be made at this time.*

NON-GONOCOCCAL URETHRITIS AND CERVICITIS

This indication was supported by two pivotal studies, Studies 154-105 and 154-123, to demonstrate the efficacy and safety of trovafloxacin. The controlled study 154-123 is of primary interest.

The following statements pertain to Study 154-105:

Statistical evaluations of efficacy and safety were described by summarizing data collected on the efficacy and safety variables. The primary efficacy variable was the eradication rate of bacteriologically evaluable subjects at EOS. The Applicant's bacteriologically evaluable populations were used in the analyses. Safety data came from all subjects receiving at least one dose of study medication.

1. Similar bacteriological responses were observed for Applicant bacteriologically evaluable male and female subjects at EOS. The subject bacteriological eradication rates at EOS were as follows: trovafloxacin 200 mg x 7 days, 9/9 (100%) males and 10/11 (90.9%) females; trovafloxacin 200 mg x 5 days, 9/9 (100%) males and 9/9 (100%) females; trovafloxacin 100 mg x 7 days, 5/6 (83.3%) males and 7/8 (87.5%) females; and trovafloxacin 50 mg x 7 days, 10/11 (90.9%) males and 10/10 (100%) females; however, the counts upon which these rates were based were small, especially when subset by gender.

2. The rate of at least one adverse event was 16.1% (5/31) of subjects in the trovafloxacin 200 mg x 7 days group, 17.6% (6/34) of subjects in the trovafloxacin 200 mg x 5 days group, 21.4% (6/28) of subjects in the trovafloxacin 100 mg x 7 days group, and 13.5% (5/37) of subjects in the trovafloxacin 50 mg x 7 days group. The percentage of subjects reporting at least one treatment-related adverse event was 3.2% (1/31) of subjects in the trovafloxacin 200 mg x 7 days group, 14.7% (5/34) of subjects in the trovafloxacin 200 mg x 5 days group, 10.7% (3/28) of subjects in the trovafloxacin 100 mg x 7 days group, and 8.1% (3/37) of subjects in the trovafloxacin 50 mg x 7 days group. No subject in any of the four treatment regimens was discontinued from treatment due to an adverse event. Clinically significant post-baseline laboratory abnormalities were observed for 20.0% (4/20), 11.8% (2/17), 22.2% (2/9), and 5.9% (1/17) of subjects in the trovafloxacin 200 mg x 7 days, 200 mg x 5 days, 100 mg x 7 days, and 50 mg x 7 days groups, respectively.

The following statements pertain to Study 154-123:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in subject bacteriological eradication rates at EOS between the treatment groups in the Medical Officer bacteriologically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence intervals of the subject bacteriological eradication rate of the Medical Officer bacteriologically evaluable subjects at EOS were $_{85,\ 94}$ (-12.9%, 1.1%) $_{92.9\%,\ 98.9\%}$, $_{150,\ 123}$ (-5.4%, 5.5%) $_{96.0\%,\ 95.9\%}$, and $_{235,\ 217}$ (-6.3%, 1.7%) $_{94.9\%,\ 97.2\%}$ for male subjects, female subjects, and all subjects combined, respectively. The results demonstrated that trovafloxacin was therapeutically equivalent in efficacy to doxycycline in the treatment of female subjects and all subjects combined with uncomplicated chlamydial urethritis/cervicitis, however, trovafloxacin was not shown to be equivalent to doxycycline at EOS in male subjects.

2. The rate of at least one adverse event was significantly higher in the trovafloxacin group (45.4%, 222/489) than the doxycycline group (38.5%, 185/481) (Fisher's exact p-value=0.032); the rate of at least one treatment related adverse event was significantly higher in the trovafloxacin group (39.9%, 195/489) than the doxycycline group (30.4%, 146/481) (Fisher's exact p-value=0.002). They were not significantly different in either the rate of discontinuations due to adverse events or the rate of clinical significant laboratory abnormalities. Significantly more subjects experienced dizziness and headache in the trovafloxacin group.

REVIEWER CONCLUSIONS: *For the pivotal study 154-123, the efficacy analyses of the bacteriologically evaluable subjects supported equivalence of trovafloxacin and doxycycline for the treatment of uncomplicated chlamydial urethritis/cervicitis in female subjects and all subjects combined, but failed to demonstrate equivalence of the two treatments in male subjects. Results from the safety analysis showed that trovafloxacin had significantly higher rates than its comparator with respect to at least one adverse event and at least one treatment related adverse event, as well as dizziness and headache.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from an efficacy standpoint, trovafloxacin 200 mg q.d. administered for 5 days is recommended for approval in the treatment of uncomplicated chlamydial urethritis/cervicitis only for female subjects. However, the Medical Officer will have to determine whether this treatment regimen has an acceptable safety profile.*

PELVIC INFLAMMATORY DISEASE

This indication was supported by two pivotal studies, Studies 154-122 and 154-125, to demonstrate the efficacy and safety of trovafloxacin or alatrofloxacin/trovafloxacin.

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of the difference in clinical cure rates at EOS between the treatment groups in the Applicant clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's

exact test.

The following statements pertain to Study 154-122:

1. The 95% confidence interval of the difference in clinical cure rates of alatrofloxacin/trovafloxacin minus cefoxitin/doxycycline for the Applicant clinical evaluable subjects at EOS was $_{53, 55}$ (-24.6%, 5.1%) $_{81.1\%, 90.9\%}$, failing to demonstrate therapeutic equivalence of alatrofloxacin/trovafloxacin to cefoxitin/ doxycycline in the treatment of pelvic inflammatory disease.

2. With respect to all safety parameters, there were no significant differences between alatrofloxacin/ trovafloxacin and cefoxitin/doxycycline.

The following statements pertain to Study 154-125:

1. The 95% confidence interval of the difference in clinical cure rates of trovafloxacin minus ofloxacin/ clindamycin for the Applicant clinical evaluable subjects at EOS was $_{101, 97}$ (-9.5%, 8.1%) $_{91.1\%, 91.8\%}$, demonstrating that trovafloxacin was therapeutically equivalent in efficacy to ofloxacin/clindamycin in the treatment of pelvic inflammatory disease.

2. Trovafloxacin and ofloxacin/clindamycin were not significantly different in safety with respect to the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to adverse events, and the rate of clinical significant laboratory abnormalities. However, the trovafloxacin subjects had significantly higher incidence rates of dizziness and headache than the ofloxacin/clindamycin subjects.

REVIEWER CONCLUSIONS: *For the pivotal study 154-125, the efficacy analyses of the clinically evaluable subjects demonstrated that trovafloxacin 200 mg q.d. was therapeutically equivalent in efficacy to ofloxacin/clindamycin in the treatment of pelvic inflammatory disease for ambulatory subjects. Study 154-125 also suggests that trovafloxacin and ofloxacin/clindamycin yield nearly comparable safety results. For the pivotal study 154-122, efficacy analysis of the clinically evaluable subjects failed to demonstrate that alatrofloxacin/trovafloxacin was therapeutically equivalent to cefoxitin/doxycycline.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, trovafloxacin 200 mg q.d. administered for 14 days is recommended for approval in the treatment of pelvic inflammatory disease for ambulatory subjects. Alatrofloxacin 200 mg q.d. followed by trovafloxacin 200 mg q.d., administered for a total of 14 days, is not recommended for approval.*

UNCOMPLICATED URINARY TRACT INFECTIONS

This indication was supported by two pivotal studies, Studies 154-103 and 154-116, to demonstrate the efficacy and safety of trovafloxacin. Study 154-103 was not powered to demonstrate therapeutic equivalence of the three treatment regimens studied, thus study 154-116 is of primary interest.

Statistical evaluation of efficacy is primarily based upon the two-sided 98.3% confidence interval of the difference in subject bacteriological eradication rates at EOT between the treatment groups in the Medical Officer bacteriologically evaluable subjects, where Bonferroni's adjustment for the multiple comparison is applied and a 95% family confidence interval is constructed.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the

treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

The following statements pertain to Study 154-103:

1. Subject bacteriological eradication rates of the Medical Officer bacteriologically evaluable subjects at EOT were 95.5% (21/22), 86.4% (19/22), and 93.1% (27/29) for trovafloxacin q.d., trovafloxacin b.i.d., and ciprofloxacin, respectively.

2. Fisher's exact test (p-value=0.012) indicates a significantly higher rate of subjects in trovafloxacin b.i.d. experienced at least one treatment related adverse even (48.6%, 36/74) than in ciprofloxacin (28.0%, 21/75). Significantly more subjects experienced dizziness in both trovafloxacin groups compared to ciprofloxacin.

The following statements pertain to Study 154-116:

1. The 98.3% confidence interval of the difference in subject bacteriological eradication rates of trovafloxacin 3 days minus norfloxacin for the Medical Officer bacteriologically evaluable subjects at EOT was $_{116,\ 105}$ (-13.7%, 8.8%) $_{87.1\%,\ 89.5\%}$, demonstrating that trovafloxacin 3 days was therapeutically equivalent in efficacy to norfloxacin in the treatment of female subjects with uncomplicated urinary tract infections.

2. The 98.3% confidence interval of the difference in subject bacteriological eradication rates of trovafloxacin 7 days minus norfloxacin for the Medical Officer bacteriologically evaluable subjects at EOT was $_{113,\ 105}$ (-6.7%, 13.5%) $_{92.9\%,\ 89.5\%}$, demonstrating that trovafloxacin 7 days was therapeutically equivalent in efficacy to norfloxacin in the treatment of female subjects with uncomplicated urinary tract infections.

3. The 98.3% confidence interval of the difference in subject bacteriological eradication rates of trovafloxacin 3 days minus trovafloxacin 7 days for the Medical Officer bacteriologically evaluable subjects at EOT was $_{116,\ 113}$ (-16.2%, 4.5%) $_{87.1\%,\ 92.9\%}$, demonstrating that trovafloxacin 3 days was not therapeutically equivalent in efficacy to trovafloxacin 7 days in the treatment of female subjects with uncomplicated urinary tract infections.

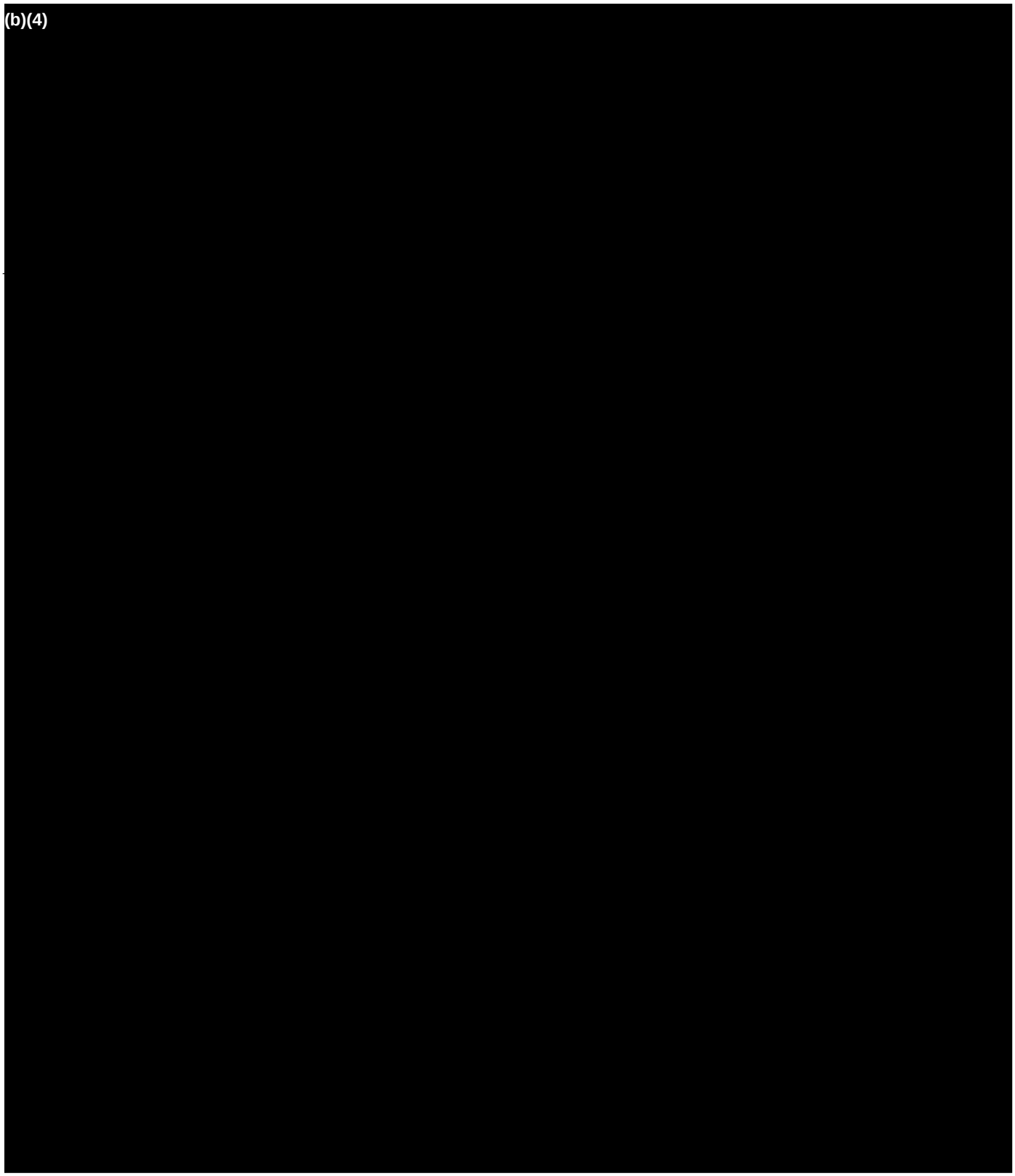
4. Trovafloxacin 3 days, trovafloxacin 7 days, and norfloxacin were not significantly different in safety with respect to the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of discontinuations due to an adverse events, and the rate of clinical significant laboratory abnormalities. However, the trovafloxacin 7 day group had significantly higher incidence rates of treatment related adverse events in the central and peripheral nervous system than the norfloxacin group.

REVIEWER CONCLUSIONS: *For the pivotal study 154-116, the efficacy analyses of the bacteriologically evaluable subjects demonstrated that both 3 days and 7 days of trovafloxacin 100 mg q.d. were therapeutically equivalent in efficacy to 3 days of norfloxacin 250 mg b.i.d. in the treatment of female subjects with uncomplicated urinary tract infections. Three days of trovafloxacin was not shown to be therapeutically equivalent to 7 days of trovafloxacin. Study 154-116 also suggested that both trovafloxacin regimens and its comparator yield nearly comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, both trovafloxacin regimens of 100 mg q.d. 3 days and 100 mg q.d. 7 days are recommended for approval in the treatment of female subjects with uncomplicated urinary tract infections. It is noteworthy that the 7 days trovafloxacin regimen appeared to be slightly more efficacious than the 3 days trovafloxacin regimen*

although this difference was not statistically significantly.

(b)(4)



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PROSTATITIS

This indication was supported by one pivotal study, Study 154-119, to demonstrate the efficacy and safety of trovafloxacin.

The following statements pertain to Study 154-119:

Statistical evaluation of efficacy is primarily based upon the two-sided 95% confidence interval of difference in clinical success rates at EOT between the treatment groups in the Medical Officer clinically evaluable subjects.

Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. The 95% confidence interval for the difference in clinical success rates of trovafloxacin minus ofloxacin for the Medical Officer clinically evaluable subjects at EOT was $_{68,\ 58}$ (-10.4%, 13.5%) $_{91.2\%,\ 89.7\%}$. The result demonstrated that trovafloxacin was marginally equivalent in efficacy to ofloxacin in the treatment of bacterial prostatitis.

2. The rate of at least one treatment related adverse event was significantly higher in the trovafloxacin group (43.0%, 61/142) than the ofloxacin group (29.3%, 39/133) (Fisher's exact p-value=0.024); the rate of discontinuations due to adverse events was significantly higher in the trovafloxacin group (17.6%, 25/142) than the ofloxacin group (6.8%, 9/133) (Fisher's exact p-value=0.009). The two treatment groups were not significantly different with respect to the rate of at least one adverse event and the rate of clinically significant laboratory abnormalities. Significantly more subjects experienced dizziness and headache in the trovafloxacin group.

REVIEWER CONCLUSIONS: *For the pivotal study 154-119, the efficacy analyses of the clinically evaluable subjects demonstrated that trovafloxacin was therapeutically equivalent in efficacy to ofloxacin in the treatment of bacterial prostatitis. Results from the safety analysis showed that trovafloxacin had significantly higher rates than its comparator with respect to at least one treatment related adverse event and discontinuations due to adverse events, as well as dizziness and headache.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from an efficacy standpoint,*

trovafloxacin 200 mg q.d. administered for 28 days is recommended for approval in the treatment of bacterial prostatitis. However, the Medical Officer will have to determine whether this treatment regimen has an acceptable safety profile.

/S/ 12/8/97

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cc:
Archival: NDA20759 and NDA20760
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This review contains 102 pages and 103 tables.
MicrosoftWord 7.0/NDA20760
12/8/97