

V. NON-GONOCOCCAL URETHRITIS AND CERVICITIS

V.A. INTRODUCTION

The Applicant submitted two pivotal studies as evidence to support oral trovafoxacin regarding this indication, in which Study 154-123 was a controlled study and Study 154-105 was an open label study. Statistical review focuses on 154-123 which forms the basis of this application. The general designs of these two studies are as follows:

Study 154-105 was an open, randomized, non-comparative, two-center, dose-ranging trial which evaluated the safety and efficacy of four different multiple dose regimens of trovafoxacin in the treatment of uncomplicated chlamydial urethritis/cervicitis.

Study 154-123 was a randomized, double-blind, double-dummy, comparative, multicenter trial which compared the safety and efficacy of trovafoxacin administered orally for 5 days versus doxycycline administered orally for 7 days for the treatment of uncomplicated chlamydial urethritis/cervicitis.

V.B. STUDY 154-105

V.B.1. METHODS

In study 154-105, up to 80 evaluable subjects with uncomplicated chlamydial urethritis/cervicitis were to be enrolled and assigned to one of four treatment groups in a 1:1:1:1 ratio. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for a presumptive diagnosis of genital chlamydial infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of male and female subjects, who were 18 years of age or older with presumptive chlamydial urethritis/cervicitis infection.

At Visit 1 (Day 1, baseline), baseline assessments were performed. At the follow-up visits (Visits 2 and 3, follow-up visits; Visit 4, EOS visit), all subjects with culture-confirmed chlamydial infection of any site returned for follow-up urethral/cervical cultures for *C. trachomatis*. Clinical signs and symptoms of urethritis/cervicitis were evaluated to assess subject responses to therapy. Safety was assessed. The investigator provided an evaluation of clinical response to therapy at Visits 2, 3, and 4. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 105.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of tablets or oral suspension that were supplied to each investigator in amounts sufficient to complete 10 evaluable subjects at each dose regimen. Subjects received one of the following regimens: 1. trovafoxacin 200 mg once daily for 7 days; 2. trovafoxacin 200 mg once daily for 5 days; 3. trovafoxacin 100 mg once daily for 7 days; 4. trovafoxacin 50 mg once daily for 7 days.

TABLE 105.1: STUDY 154-105: VISIT TIMING AND PROCEDURES				
Visit Number	Baseline	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 8	Day 15	Day 29
Allowable Window	Day 1	Day 5-9	Day 12-18	Day 25-35
Treatment Period	Day 1 to Day 7			
Follow-up Period	Day 7 to Day 29			
Historical and Physical Assessment	X			
Clinical Laboratory	X	X	X	X
• FTA or RPR	X			
• hematology	X	X	X	abn
• serum Chemistry	X	X	X	abn
• urinalysis	X	X	X	abn
• gram stain	X			
• cultures for <i>C. trachomatis</i>	X	X	X	X
• cultures for <i>N. gonorrhoeae</i>	X	X	X	X
• pregnancy tested	X			
Adverse Event		X	X	X

abn Abnormal at previous visit or clinically significant adverse event.

EFFICACY EVALUATION

Efficacy analyses were performed on the bacteriologically and clinically evaluable subjects. The primary efficacy endpoint was subject bacteriological response at EOS. The secondary endpoints were clinical response at EOS, and pathogen outcome at EOS.

Bacteriological response was evaluated separately for each site of infection with *C. trachomatis*, determined by the sponsor, and evaluated at the final evaluation which was classified as eradication or persistence. Clinical response was based primarily on the global evaluations at EOS and was classified as cure, improvement, or failure. Pathogen outcome was classified as eradication, persistence, or presumed persistent.

Reviewer's Note: *The Medical Officer agreed with both bacteriological and clinical evaluability criteria chosen by the Applicant, and assessed bacteriological and clinical efficacy outcomes according to the Applicant bacteriological and clinical criteria.*

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

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 significant objective test abnormality. 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

In this study, interest focused on summarizing data collected on the efficacy variables and obtaining descriptive information about trovafoxacin drawn from defined bacteriological and clinical subject populations.

Efficacy description by gender and overall subjects were based on the bacteriological and clinical responses at EOS. The treatment groups were summarized with respect to the subject bacteriological eradication rate, the clinical success (cure+improvement) rate, and the pathogen bacteriological eradication rate.

Description 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: *Since the sample sizes of the four trovafoxacin treatment groups were considerably small, no formal statistical analyses were conducted. All efficacy variables were summarized for the Applicant bacteriologically and clinically evaluable subjects. All of the subjects in these groups, were assessed for their bacteriological or clinical responses. Results were displayed both by gender and overall. This reviewer summarized safety information 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.*

V.B.2. RESULTS

A total of 130 subjects were enrolled at 2 centers in the USA between August 10, 1994 and February 6, 1996. Of these enrolled subjects, 44 subjects were withdrawn from the study (11 subjects were withdrawn during treatment and 33 subjects were withdrawn during follow-up). In all cases, the reason for discontinuation was lost to follow-up. No subject in any of the four treatment groups was discontinued from treatment due to inadequate response. Thus, 119 subjects (28, trovafoxacin 200 mg x 7 days; 32, trovafoxacin 200 mg x 5 days; 26, trovafoxacin 100 mg x 7 days; and 33, trovafoxacin 50 mg x 7 days) completed treatment and 86 subjects (21, trovafoxacin 200 mg x 7 days; 22, trovafoxacin 200 mg x 5 days; 19, trovafoxacin 100 mg x 7 days; and 24, trovafoxacin 50 mg x 7 days) completed the study. One hundred-three randomized subjects (50, males; 53, females) were included in the bacteriologically intent-to-treat analyses; 92 randomized subjects (42, males; 50, females) were included in the clinically intent-to-treat analyses. The Applicant bacteriologically evaluable group comprised 73 subjects (35, male; 38, female). The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline culture in the evaluable analysis window.

Reviewer's Note: *The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Tables 105.2A and 105.2B. There was no statistically significant treatment difference with respect to the percentage of subjects, as well as gender characteristics, included in each of four analysis groups.*

TABLE 105.2A: STUDY 154-105: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Treatment Group for Response	Subjects Included			
	Trovafoxacin 200mg x 7days (31)	Trovafoxacin 200mg x 5days (34)	Trovafoxacin 100mg x 7days (28)	Trovafoxacin 50mg x 7days (37)
Clinically ITT	25 (80.6%)	22 (64.7%)	20 (71.4%)	25 (67.6%)
Bacteriologically ITT	26 (83.9%)	23 (67.6%)	24 (85.7%)	30 (81.1%)
Applicant Clinically Evaluable	19 (61.3%)	17 (50.0%)	12 (42.9%)	19 (51.4%)
Applicant Bacteriologically Evaluable	20 (64.5%)	18 (52.9%)	14 (50.0%)	21 (56.8%)

TABLE 105.2B: STUDY 154-105: NUMBER OF MALE AND FEMALE SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Treatment Group for Response	Male Subjects Included			
	Trovafoxacin 200mg x 7days (16)	Trovafoxacin 200mg x 5days (19)	Trovafoxacin 100mg x 7days (13)	Trovafoxacin 50mg x 7days (16)
Clinically ITT	12 (75.0%)	11 (57.9%)	7 (53.8%)	12 (75.0%)
Bacteriologically ITT	13 (81.3%)	12 (63.2%)	11 (68.8%)	14 (73.7%)
Applicant Clinically Evaluable	8 (50.0%)	8 (42.1%)	4 (30.8%)	10 (62.5%)
Applicant Bacteriologically Evaluable	9 (56.3%)	9 (47.4%)	6 (37.5%)	11 (57.9%)
Treatment Group for Response	Female Subjects Included			
	Trovafoxacin 200mg x 7days (15)	Trovafoxacin 200mg x 5days (15)	Trovafoxacin 100mg x 7days (15)	Trovafoxacin 50mg x 7days (21)
Clinically ITT	13 (86.7%)	11 (73.3%)	13 (86.7%)	13 (61.9%)
Bacteriologically ITT	13 (86.7%)	11 (73.3%)	13 (86.7%)	16 (76.2%)
Applicant Clinically Evaluable	11 (73.3%)	9 (60.0%)	8 (53.3%)	9 (42.9%)
Applicant Bacteriologically Evaluable	11 (73.3%)	9 (60.0%)	8 (53.3%)	10 (47.6%)

Subject bacteriological response at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 105.3. Subject eradication rates were similar for male and female subjects in all four treatment groups at EOS; however, the counts upon which these rates were based were considerably small.

The pathogen eradication rates at EOS are presented by gender and overall for bacteriologically evaluable subjects in Table 105.4. Table 105.5 shows clinical response of the Applicant clinically evaluable subjects at EOS. Those results appeared similar among male and female subjects in all four treatment groups, however, these rates were based upon small counts.

TABLE 105.3: STUDY 154-105: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trovafoxacin 200mg x 7days	Trovafoxacin 200mg x 5days	Trovafoxacin 100mg x 7days	Trovafoxacin 50mg x 7days
Male				
Eradication	9 (100%)	9 (100%)	5 (83.3%)	10 (90.9%)
Persistent	0 (0%)	0 (0%)	1 (16.7%)	1 (9.1%)
Female				
Eradication	10 (90.9%)	9 (100%)	7 (87.5%)	10 (100%)
Persistent	1 (9.1%)	0 (0%)	1 (12.5%)	0 (0%)
Overall				
Eradication	19 (95.0%)	18 (100%)	12 (85.7%)	21 (100%)
Persistent	1 (5.0%)	0 (0%)	2 (14.3%)	0 (0%)

TABLE 105.4: STUDY 154-105: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Pathogen Bacteriological Outcome	Trovafoxacin 200mg x 7days	Trovafoxacin 200mg x 5days	Trovafoxacin 100mg x 7days	Trovafoxacin 50mg x 7days
Male				
<i>C. trachomatis</i>	8/8 (100%)	9/9 (100.0%)	5/6 (83.3%)	10/11 (90.9%)
<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	1/1 (100%)	0	0	0
Female				
<i>C. trachomatis</i>	9/10 (90.0%)	7/7 (100%)	4/5 (80.0%)	10/10 (100%)
<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	1/1 (100%)	2/2 (100%)	3/3 (100%)	0
Overall				
<i>C. trachomatis</i>	17/18 (94.4%)	16/16 (100%)	9/11 (81.8%)	20/21 (95.2%)
<i>N. gonorrhoeae/</i> <i>C. trachomatis</i>	2/2 (100%)	2/2 (100%)	3/3 (100%)	0

TABLE 105.5: STUDY 154-105: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trovafoxacin 200mg x 7days	Trovafoxacin 200mg x 5days	Trovafoxacin 100mg x 7days	Trovafoxacin 50mg x 7days
Male				
Success	8 (100.0%)	8 (100.0%)	4 (100.0%)	10 (100.0%)
Failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Female				
Success	11 (100%)	9 (100.0%)	7 (100.0%)	8 (88.9%)
Failure	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)
Overall				
Success	19 (100%)	17 (100.0%)	11 (100.0%)	18 (94.7%)
Failure	0 (0%)	0 (0%)	0 (0%)	1 (5.3%)

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 Table 105.6. No subject in any of the four treatment regimens was discontinued from treatment due to an adverse event. The percentage of subjects reporting at least one treatment related adverse event was 3.2% in the trovafoxacin 200 mg x 7 days group, and numerically it was considerably lower than the other treatment groups.

Safety Outcome	Trovafoxacin 200mg x 7days (N=31)	Trovafoxacin 200mg x 5days (N=34)	Trovafoxacin 100mg x 7days (N=28)	Trovafoxacin 50mg x 7days (N=37)
At Least One AE	5/31 (16.1%)	6/34 (17.6%)	6/28 (21.4%)	5/37 (13.5%)
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	1 (3.2%)	5 (14.7%)	2 (7.1%)	0 (0%)
Dizziness	1 (3.2%)	5 (14.7%)	1 (3.6%)	0 (0%)
At Least One Treatment Related AE	1/31 (3.2%)	5/34 (14.7%)	3/28 (10.7%)	3/37 (8.1%)
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	1 (3.2%)	5 (14.7%)	1 (3.6%)	0 (0%)
Dizziness	1 (3.2%)	5 (14.7%)	1 (3.6%)	0 (0%)
Discontinuations Due to an AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Clinically Significant Lab Abnormalities	4/20 (20.0%)	2/17 (11.8%)	2/9 (22.2%)	1/17 (5.9%)

No serious adverse events or deaths were reported in any of the four treatment groups. Overall, the most common treatment related adverse event was dizziness.

Reviewer's Summary and Conclusions: See Section X.

V.C. STUDY 154-123

V.C.1. METHODS

In study 154-123, a total of approximately 500 subjects with uncomplicated chlamydial urethritis/cervicitis were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio in order to obtain 400 evaluable subjects, with 100 males and 100 females per treatment group. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for a presumptive diagnosis of genital chlamydial infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of male and female outpatients, who were 16 years of age or older with clinically and laboratory documented uncomplicated chlamydial urethritis/cervicitis.

At Visit 1 (Day 1, baseline), baseline assessments were performed. Clinical assessments of signs and symptoms of uncomplicated chlamydial urethritis/cervicitis were recorded as present or absent. At Visit 2 (Day 10, EOT), efficacy observations were performed to assess response to study therapy. At Visit 3 (Day 21), efficacy observations were performed to assess response to study therapy. At Visit 4 (Day 35, EOS), efficacy observations were performed, and a final evaluation of clinical response was provided by the investigator. The reasons for discontinuation of any subject were recorded on the CRF, as well as all

concomitant medications. Table 123.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of trovafloxacin tablets and doxycycline capsules. Drugs were packaged in blister cards using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafloxacin 200 mg/day as a single dose (2x100 mg tablets) and doxycycline placebo twice daily (one capsule); 2. doxycycline 100 mg twice daily (1x100 mg capsule) and trovafloxacin placebo once daily (two tablets). All subjects received study medication in the morning and evening in combinations of active drug and placebos for active drug, and trovafloxacin was administered orally for 5 days while doxycycline was administered orally for 7 days.

TABLE 123.1: STUDY 154-123: VISIT TIMING AND PROCEDURES				
Visit Number	Baseline	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 10	Day 21	Day 35
Allowable Window	Day 1	Day 9-11	Day 19-23	Day 31-39
Treatment Period	Day 1 to Day 7			
Follow-up Period	Day 7 to Day 39			
Compliance Checks Historical and Physical	X	X		
Assessment				
Clinical	X	X	X	X
Laboratory				
• FTA or RPR	X			
• hematology	X	X	abn	abn
• serum Chemistry	X	X	abn	abn
• urinalysis	X	X	abn	abn
• gram stainc	X			
• cultures for <i>C. trachomatis</i>	X	X	X	X
• cultures for <i>N. gonorrhoeae</i>	X	X	X	X
• pregnancy tested	X			
Adverse Event	X	X	X	

abn Abnormal at previous visit or clinically significant adverse event.

EFFICACY EVALUATION

Efficacy analyses were performed on the bacteriologically and clinically evaluable subjects. The primary efficacy endpoint was subject bacteriological response at EOS. The secondary endpoints were clinical response at EOS, and pathogen outcome at EOS.

Subject bacteriological response, clinical response, and pathogen outcome were determined by the sponsor and evaluated for each subject at EOS (Visit 4; Day 35), or at the time of discontinuation from the study. Subject bacteriological response was classified as eradication or persistence; clinical response was classified as cure, improvement, or failure; pathogen outcome was classified as eradication, persistence, or presumed persistent.

Reviewer's Note: The Medical Officer also defined her bacteriologically and clinically evaluable subjects, and assessed bacteriological and clinical efficacy outcomes according to her bacteriological and clinical 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 significant objective test abnormality. 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 doxycycline.

Efficacy analyses, stratified by gender, were based on the bacteriological and clinical responses at EOS. The treatment groups were compared with respect to the subject bacteriological eradication rate, the clinical success (cure+improvement) rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the subject bacteriological eradication rate at EOS in the bacteriologically 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 bacteriologically and clinically evaluable subjects, and the Applicant bacteriologically and clinically evaluable subjects. All of the subjects in these groups were assessed for their bacteriological or clinical 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.

V.B.2. RESULTS

A total of 988 subjects were enrolled across centers in the USA (27) and UK (4) between March 27, 1995 and May 22, 1996. Of these enrolled subjects, 11 were withdrawn prior to randomization, 495 subjects were randomized to receive trovafloxacin, and 482 were randomized to receive doxycycline. Two hundred thirty seven trovafloxacin and 220 doxycycline subjects were included in the clinical intent-to-treat analyses; 332 trovafloxacin and 301 doxycycline subjects were included in the bacteriological intent-to-treat analyses. Most of those subjects were discontinued at Visit 2 because they had no baseline pathogens. The Applicant bacteriologically evaluable group comprised 511 subjects, and there were 452 subjects in the Medical Officer bacteriologically evaluable group. The most common reason for exclusion from bacteriological efficacy analyses was no post-baseline cultures in the EOS visit windows. The most common reason for exclusion from the clinically evaluable analyses was no baseline clinical signs and symptoms.

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 Tables 123.2A and 123.2B. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

TABLE 123.2A: STUDY 154-123: NUMBER OF SUBJECTS INCLUDED IN ANALYSIS GROUPS		
Treatment Group for Response	Subjects Included	
	Trovafoxacin (N=495)	Doxycycline (N=482)
Clinically ITT	237 (47.9%)	220 (45.6%)
Bacteriologically ITT	332 (67.1%)	301 (62.4%)
Applicant Clinically Evaluable	181 (36.6%)	179 (37.1%)
MO Clinically Evaluable	182 (36.8%)	179 (37.1%)
Applicant Bacteriologically Evaluable	265 (53.5%)	246 (51.0%)
MO Bacteriologically Evaluable	235 (47.5%)	217 (45.0%)

TABLE 123.2B: STUDY 154-123: NUMBER OF MALE AND FEMALE SUBJECTS INCLUDED IN ANALYSIS GROUPS

Treatment Group for Response	Male Subjects Included	
	Trovafoxacin (N=203)	Doxycycline (N=203)
Clinically ITT	95 (46.5%)	93 (45.8%)
Bacteriologically ITT	126 (62.1%)	123 (60.6%)
Applicant Clinically Evaluable	72 (35.5%)	79 (38.9%)
MO Clinically Evaluable	73 (36.0%)	79 (38.9%)
Applicant Bacteriologically Evaluable	100 (49.3%)	102 (50.2%)
MO Bacteriologically Evaluable	85 (41.9%)	94 (46.3%)
Treatment Group for Response	Female Subjects Included	
	Trovafoxacin (N=292)	Doxycycline (N=279)
Clinically ITT	142 (48.6%)	127 (45.5%)
Bacteriologically ITT	206 (70.5%)	178 (63.8%)
Applicant Clinically Evaluable	109 (37.3%)	100 (35.8%)
MO Clinically Evaluable	109 (37.3%)	100 (35.8%)
Applicant Bacteriologically Evaluable	165 (56.5%)	144 (51.6%)
MO Bacteriologically Evaluable	150 (51.4%)	123 (44.1%)

Subject bacteriological response at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 123.3. Confidence interval results from analyses show that trovafoxacin was therapeutically equivalent to doxycycline with respect to the eradication rates at EOS in female subjects and overall subjects. The two treatments were not considered equally effective at EOS for male subjects; lower eradication rates were observed in the trovafoxacin group compared to the doxycycline group. Indeed, the results indicated the inferiority of trovafoxacin to doxycycline in male subjects.

Reviewer's Note: The subject eradication rates of the Medical Officer bacteriologically evaluable subjects at EOS are presented in Table 123.4. Comparisons (95% confidence intervals) of the difference in subject bacteriological eradication rates at EOS between the two treatment groups supported the equivalence of trovafoxacin to doxycycline in female subjects and all subjects combined, but did not support the equivalence of the two treatments in male subjects.

TABLE 123.3: STUDY 154-123: SUBJECT BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Eradication	89 (89.0%)	101 (99.0%)	-17.4%, -2.6%
Persistent	11 (11.0%)	1 (0.0%)	
Female			
Eradication	157 (95.2%)	138 (96.5%)	-6.5%, 3.8%
Persistent	8 (4.8%)	5 (3.5%)	
Overall			
Eradication	246 (92.8%)	239 (97.6%)	-8.8%, -0.7%
Persistent	19 (7.2%)	6 (2.4%)	

TABLE 123.4: STUDY 154-123: SUBJECT BACTERIOLOGICAL RESPONSE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS			
Subject Bacteriological Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Eradication	79 (92.9%)	93 (98.9%)	-12.9%, 1.0%
Persistent	6 (7.1%)	1 (1.1%)	
Female			
Eradication	144 (96.0%)	118 (95.9%)	-5.4%, 5.5%
Persistent	6 (4.0%)	5 (4.1%)	
Overall			
Eradication	223 (94.9%)	211 (97.2%)	-6.3%, 1.7%
Persistent	12 (5.1%)	6 (2.8%)	

The pathogen eradication rates at EOS are presented by gender and overall for bacteriologically evaluable subjects in Table 123.5. Pathogen eradication rates for baseline isolates of *C. trachomatis* were comparable between the trovafoxacin and doxycycline groups at EOS in female subjects and overall subjects. Eradication rates for *C. trachomatis* at EOS were not considered comparable in male subjects.

Reviewer's Note: Table 123.6 shows the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at EOS, and similar trends were observed for males, females, and all subjects combined.

Table 123.7 shows clinical response of the Applicant clinically evaluable subjects at EOS. Comparisons (95% confidence intervals) of the difference in clinical success rates at EOS supported equivalence of the two treatments in female subjects and overall subjects, but failed to show equivalence in male subjects.

Reviewer's Note: Analyses of the cure rates of the Medical Officer clinically evaluable subjects at EOS are displayed in Table 123.8. The results showed that two treatments were therapeutically equivalent to doxycycline in female subjects and overall subjects, however, trovafoxacin was found to be inferior to doxycycline in males.

TABLE 123.5: STUDY 154-123: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS				
Pathogen Bacteriological Outcome	Source	Trovafoxacin	Doxycycline	95% C.I.
Male				
<i>C. trachomatis</i>	Urethra	86/96 (89.6%)	96/97 (99.0%)	-16.9%, 1.9%
<i>N. gonorrhoeae/ C. trachomatis</i>	Urethra	3/4 (75.0%)	5/5 (100%)	
Female				
<i>C. trachomatis</i>	Urethra/Cervix	153/160 (95.6%)	129/133 (97.0%)	-6.4%, 3.6%
<i>N. gonorrhoeae/ C. trachomatis</i>	Cervix	4/5 (80.0%)	9/10 (90.0%)	
Overall				
<i>C. trachomatis</i>	Urethra/Cervix	239/256 (93.4%)	225/230 (97.8%)	-8.5%, -0.5%
<i>N. gonorrhoeae/ C. trachomatis</i>	Urethra/Cervix	7/9 (77.8%)	14/15 (93.3%)	

TABLE 123.6: STUDY 154-123: PATHOGEN ERADICATION RATE OF THE MO BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS

Pathogen Bacteriological Outcome	Source	Trovafoxacin	Doxycycline	95% C.I.
Male				
<i>C. trachomatis</i>	Urethra	76/81 (93.8%)	88/89 (98.9%)	-11.9%, 1.8%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Urethra	3/4 (75.0%)	5/5 (100%)	
Female				
<i>C. trachomatis</i>	Urethra/Cervix	140/145 (96.6%)	111/115 (96.5%)	-5.2%, 5.3%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Cervix	4/5 (80.0%)	7/8 (87.5%)	
Overall				
<i>C. trachomatis</i>	Urethra/Cervix	216/226 (95.6%)	199/204 (97.5%)	-5.9%, 1.9%
<i>N. gonorrhoeae</i> / <i>C. trachomatis</i>	Urethra/Cervix	7/9 (77.8%)	12/13 (92.3%)	

TABLE 123.7: STUDY 154-123: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Success	68 (94.4%)	79 (100%)	-12.2%, 1.1%
Failure	4 (5.6%)	0 (0%)	
Female			
Success	105 (96.3%)	94 (94.0%)	-4.5%, 9.1%
Failure	4 (3.7%)	6 (6.0%)	
Overall			
Success	173 (95.6%)	173 (96.6%)	-5.6%, 3.5%
Failure	8 (4.4%)	6 (3.4%)	

TABLE 123.8: STUDY 154-123: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trovafoxacin	Doxycycline	95% C.I.
Male			
Success	67 (91.8%)	79 (100%)	-15.8%, -0.6%
Failure	6 (8.2%)	0 (0%)	
Female			
Success	104 (95.4%)	94 (94.0%)	-5.6%, 8.5%
Failure	5 (4.6%)	6 (6.0%)	
Overall			
Success	171 (94.0%)	173 (96.6%)	-7.6%, 2.2%
Failure	11 (6.0%)	6 (3.4%)	

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 Table 123.9. With respect to the subjects reporting adverse events and the subjects experiencing adverse events related to study medication, the rates were significantly higher in the trovafloxacin group than in the doxycycline group. Significantly more subjects had dizziness and headache in the trovafloxacin group.

TABLE 123.9: STUDY 154-123: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trovafoxacin (N=489)	Doxycycline (N=481)	Fisher's P-value
At Least One AE	222/489 (45.4%)	185/481 (38.5%)	0.032
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	141 (28.8%)	47 (9.8%)	<0.001
Dizziness	105 (21.5%)	17 (3.5%)	<0.001
Headache	55 (11.3%)	29 (6.0%)	0.004
At Least One Treatment Related AE	195/489 (39.9%)	146/481 (30.4%)	0.002
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	131 (26.8%)	38 (7.9%)	<0.001
Dizziness	102 (20.9%)	16 (3.3%)	<0.001
Headache	46 (9.4%)	22 (4.6%)	0.004
Discontinuations Due to an AE	11/489 (2.3%)	13/481 (2.7%)	0.684
Clinically Significant Lab Abnormalities	51/366 (13.9%)	58/381 (15.2%)	0.679

There were no deaths reported during or following completion of the study. Only one subject in the doxycycline group was hospitalized for acute appendicitis that was considered to be unrelated to study drug.

Reviewer's Summary and Conclusions: See Section X.

VI. PELVIC INFLAMMATORY DISEASE

VI.A. INTRODUCTION

The Applicant submitted two pivotal controlled studies, Study 154-122 and Study 154-125, as evidence to support oral trovafloracin regarding this indication, and statistical review focuses on the two clinical trials which form the basis of this application. The general designs of these two studies are as follows:

Study 154-122 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of alatrofloracin administered intravenously followed by oral trovafloracin versus cefoxitin plus doxycycline administered intravenously followed by oral doxycycline for the treatment of acute pelvic inflammatory disease (PID) in hospitalized subjects. Each subject was administered intravenous study medication for a period of at least 48 hours following an improvement in clinical signs and symptoms of PID, followed by oral study medication to complete 14 days of total therapy.

Study 154-125 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of trovafloracin versus ofloxacin and clindamycin for the treatment of acute pelvic inflammatory disease (PID) in ambulatory subjects. Subjects received study medication orally for a duration of 14 days.

VI.B. STUDY 154-122

VI.B.1. METHODS

In study 154-122, a total of approximately 300 subjects with acute pelvic inflammatory disease were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the baseline visit (Visit 1, Day 1), subjects who met the criteria for a presumptive diagnosis of genital chlamydial infection, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of hospitalized female subjects, who were 16 years of age or older with presumptive diagnosis of acute PID.

At Visit 1 (Day 1, baseline), baseline assessments was performed. The investigator assessed the degree of direct and rebound abdominal tenderness. At Visit 2 (72 hours after initiation of therapy), all clinical signs and symptoms of acute PID were assessed. At Visit 3 (2-4 days following completion of therapy), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. At Visit 4 (2-4 weeks following completion of therapy, EOS), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. The investigator provided an evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 122.1 demonstrates during treatment, and post treatment procedures which were specified by the protocol.

Study drug for intravenous administration was prepared by a designated pharmacist who kept assigned drug information strictly confidential. Subjects received one of the following intravenous treatment regimens: 1. alatrofloracin 200 mg in 200 ml of D5W administered once daily as a 60-minute infusion (2x100 mg vials) and 200 ml D5W with multivitamins (cefloxitin placebo) every 6 hours and 200 ml D5W

with multivitamins (doxycycline placebo) every 12 hours; 2. cefoxitin 2 g in 200 ml administered every 6 hours as a 60-minute infusion and doxycycline 100 mg in 200 ml of D5W solution administered every 12 hours as a 60-minute infusion and 200 ml D5W once daily (alatrofoxacin placebo). All subjects received intravenous study medication every 6 hours in combinations of active drug and placebos for active drug until the investigator had determined that there had been a substantial improvement in clinical signs and symptoms of acute PID for at least 48 hours. At this time the subject was switched from intravenous to oral therapy. Study drug for oral administration was in the form of trovafoxacin tablets and doxycycline capsules and was packaged in blister packs, using a double-dummy technique to maintain blinding. Following the completion of intravenous therapy, subjects received one of the following treatments orally: 1. trovafoxacin 200 mg/day as a single active dose (2x100 mg tablets) and one capsule twice daily (doxycycline placebo); 2. doxycycline 200 mg/day in two equally divided doses (1x100 mg capsule per dose) and two tablets once daily (trovafoxacin placebo). All subjects received oral study medication in the morning and evening in combinations of active drug and placebos to complete a total treatment duration of 14 days.

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	72 Hours	Day 16-18	Day 28-42
Treatment Period	Day 1 to Day 14			
Post Therapy Period	Day 16 to Day 42			
Compliance Checks		X	X	X
Informed Consent	X			
Demographic Information	X			
Targeted Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Clinical Assessment*	X	X	X	X
Culdocentesis Endometrial Biopsy, and/or Laparoscope	X		X	
Laboratory				
• hematology	X	X	X	X
• serum chemistry	X	X	X	X
• urinalysis	X	X	X	X
• microbiology				
a. <i>N. gonorrhoeae</i> cultures	X		X	X
b. <i>C. trachomatis</i> cultures	X		X	X
c. Anaerobic/aerobic cultures	X		X	
• FTA or RPR	X			
• pregnancy test	X		X	
Adverse Event	X	X	X	X

* Assessments to be done daily during hospitalization

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically and bacteriologically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoints were bacteriological response at EOS and pathogen outcome at EOS.

Clinical response was determined by the sponsor and evaluated at two interim timepoints: Visit 2 and Visit 3. A final evaluation was given at Visit 4 (EOS). Clinical response was classified as cure or failure. Bacteriological response was determined by the sponsor and evaluated at Visit 3 and at Visit 4 (EOS). Bacteriological response for each subject was classified as satisfactory or unsatisfactory. Pathogen clinical outcome was classified as cure or failure. Pathogen bacteriologic outcome was classified as eradication, presumed eradication, persistence, presumed persistent, superinfection, or colonization.

Reviewer's Note: *The Medical Officer agreed with both clinical and bacteriological evaluability criteria chosen by the Applicant, and assessed clinical and bacteriological efficacy outcomes according to the Applicant clinical and bacteriological criteria.*

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

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 clinical laboratory tests and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or clinically important test abnormality. 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 alatrofloxacin/trovafoxacin and cefoxitin/doxycycline.

Efficacy analyses were based on the clinical and bacteriological responses at EOS. The treatment groups were compared with respect to the clinical cure rate, the subject bacteriological satisfactory rate, the pathogen clinical cure rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical cure rate at EOS 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 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.

VI.B.2. RESULTS

A total of 161 subjects were enrolled across centers in the USA (36) and South Africa (5) between June 8, 1995 and May 9, 1996. Three subjects were withdrawn prior to randomization because they did not meet entrance criteria. Seventy nine subjects were randomized to receive alatrofloxacin/trovafoxacin and 79 subjects were randomized to receive cefoxitin/doxycycline. All randomized subjects in both treatment groups received treatment. Fifty-six alatrofloxacin/trovafoxacin and 69 cefoxitin/doxycycline subjects completed treatment, and 60 alatrofloxacin/trovafoxacin and 62 cefoxitin/doxycycline subjects completed the study. Of the 79 alatrofloxacin/trovafoxacin and 79 cefoxitin/doxycycline clinical intent-to-treat subjects, 53 subjects in the alatrofloxacin/trovafoxacin group and 55 subjects in the cefoxitin/doxycycline group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was no post-baseline clinical assessments. Of the clinically evaluable subjects, 31 subjects in the alatrofloxacin/trovafoxacin and 33 subjects in the cefoxitin/doxycycline group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 122.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

Treatment Group for Response	Subjects Included	
	Alatrofloxacin/ Trovafoxacin (N=79)	Cefoxitin/ Doxycycline (N=79)
Clinically ITT	79 (100%)	79 (100%)
Bacteriologically ITT	51 (64.6%)	49 (62.0%)
Applicant Clinically Evaluable	53 (67.1%)	55 (69.6%)
Applicant Bacteriologically Evaluable	31 (39.2%)	33 (41.8%)

Clinical response at EOS is shown for the Applicant clinically evaluable subjects in Table 122.3. Confidence interval results from analyses failed to show that alatrofloxacin/trovafoxacin was therapeutically equivalent to cefoxitin/doxycycline with respect to the cure rates at EOS.

Subject bacteriological response at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 122.4.

Pathogen clinical outcome at EOS is shown for the Applicant clinically evaluable subjects in Table 122.5. The pathogen bacteriological outcome at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 122.6.

TABLE 122.3: STUDY 154-122: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Alatrofloxacin/ Trovafoxacin (N=53)	Cefoxitin/ Doxycycline (N=55)
Cure	43 (81.1%)	50 (90.9%)
Failure	10 (18.9%)	5 (9.1%)
A./T. vs C./D. by Cure	-9.8%, 95% C.I.: -24.6%, 5.1%	

TABLE 122.4: STUDY 154-122: BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Alatrofloxacin/ Trovafoxacin (N=31)	Cefoxitin/ Doxycycline (N=33)
Satisfactory	21 (67.7%)	27 (81.8%)
Unsatisfactory	10 (32.3%)	5 (18.2%)
A./T. vs C./D. by Satisfactory	-14.1%, 95% C.I.: -38.3%, 10.1%	

TABLE 122.5: STUDY 154-122: PATHOGEN CURE RATE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Clinical Outcome	Alatrofloxacin/ Trovafoxacin	Cefoxitin/ Doxycycline
<i>N. gonorrhoeae</i>	11/18 (61.1%)	16/17 (94.1%)
<i>Peptostreptococcus sp.</i>	8/11 (72.7%)	11/13 (84.6%)
<i>C. trachomatis</i>	4/6 (66.7%)	10/10 (100%)
<i>E. coli</i>	5/5 (100%)	4/5 (80.0%)

TABLE 122.6: STUDY 154-122: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Alatrofloxacin/ Trovafoxacin	Cefoxitin/ Doxycycline
<i>N. gonorrhoeae</i>	10/18 (55.6%)	14/16 (87.5%)
<i>C. trachomatis</i>	4/5 (80.0%)	10/10 (100%)
<i>Peptostreptococcus sp</i>	3/5 (60.0%)	5/7 (71.4%)

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 Table 122.7. Alatrofloxacin/trovafoxacin was not significantly different from cefoxitin/doxycycline with respect to these safety variables..

TABLE 122.7: STUDY 154-122: CLINICAL ADVERSE EVENT RATES			
Safety outcome	Alatrofoxacin/ Trovafoxacin (N=79)	Cefoxitin/ Doxycycline (N=79)	Fisher's P-value
At Least One AE	57/79 (72.2%)	53/79 (67.1%)	0.604
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	11 (13.9%)	8 (10.1%)	0.626
Dizziness	3 (3.8%)	2 (2.5%)	1.000
Headache	10 (12.7%)	6 (7.6%)	0.430
At Least One Treatment Related AE	37/79 (46.8%)	36/79 (45.6%)	1.000
<u>CENTRAL AND PERIPHERAL NERVOUS</u>	5 (6.3%)	3 (3.8%)	0.719
Dizziness	3 (3.8%)	1 (1.3%)	0.620
Headache	4 (5.1%)	2 (2.5%)	0.681
Discontinuations Due to an AE	10/79 (12.7%)	4/79 (5.1%)	0.160
Clinically Significant Lab Abnormalities	42/75 (58.3%)	44/77 (57.1%)	1.000

No subject from either treatment group died during the study. The alatrofoxacin/trovafoxacin group (11, 14%) had a significantly higher rate of serious adverse events than the cefoxitin/doxycycline group (2, 3%) (p=0.017 using Fisher's exact test). Only one subject in the cefoxitin/doxycycline group experienced an adverse event that was considered by the investigator to be related to study drug.

Reviewer's Summary and Conclusions: See Section X.

VI.C. STUDY 154-125

VI.C.1 METHODS

In study 154-125, a total of approximately 300 subjects with acute pelvic inflammatory disease were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the baseline assessment (Visit 1, Day 1), subjects who met the criteria for clinical diagnosis of acute PID, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of ambulatory female subjects, who were 16 years of age or older with presumptive diagnosis of acute PID.

At Visit 1 (Day 1, baseline), baseline assessments were performed. The investigator assessed the degree of direct and rebound abdominal tenderness. At Visit 2 (72 hours after initiation of therapy), all clinical signs and symptoms of acute PID were assessed. At Visit 3 (2 weeks following initiation of therapy), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. Visit 4 (EOS; 4-6 weeks following initiation of therapy), efficacy observations were performed to assess response to study therapy. Bacteriological response was assessed. The investigator provided an evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 125.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of trovafoxacin tablets and ofloxacin and clindamycin capsules, packaged in blister packs using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafoxacin 200 mg/day as a single dose (2x100 mg tablets) and two capsules (ofloxacin placebo) twice daily and three capsules (clindamycin placebo) four times daily; 2. ofloxacin 800 mg/day in two equally divided doses (2x200 mg capsules) plus clindamycin 1800 mg/day in four equally divided doses (3x150 mg capsules) and two tablets (trovafoxacin placebo) once daily. All subjects received oral study medication four times daily in combinations of active drug and placebo for active drug for 14 days.

TABLE 125.1: STUDY 154-125: VISIT TIMING AND PROCEDURES				
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	72 Hours	Day 14-20	Day 28-42
Treatment Period	Day 1 to Day 14			
Post Therapy Period	Day 14 to Day 42			
Compliance Checks		X	X	X
Informed Consent	X			
Demographic Information	X			
Targeted Physical Examination	X			
Concomitant Medication	X	X	X	X
Vital Signs	X	X	X	X
Clinical Assessment*	X	X	X	X
Culdocentesis Endometrial Biopsy	X		X	X
Laboratory				
• hematology	X	X	X	X
• serum chemistry	X	X	X	X
• urinalysis	X	X	X	X
• microbiology				
a. <i>N. gonorrhoeae</i> cultures	X		X	X
b. <i>C. trachomatis</i> cultures	X		X	X
c. Anaerobic/aerobic cultures	X		X	X
• FTA or RPR	X			
• pregnancy test	X		X	
Adverse Event	X	X	X	X

* Assessments to be done daily during hospitalization

Efficacy evaluation, safety evaluation, and statistical methods were similar to those described for Study 154-122 in Section VI.B.1.

VI.C.2. RESULTS

A total of 327 subjects were enrolled across centers in the USA (55) and South Africa (1) between June 5, 1995 and May 8, 1996. Twelve subjects were withdrawn prior to randomization because they did not meet entrance criteria. One hundred fifty-five subjects were randomized to receive trovafoxacin and 161 subjects were randomized to receive ofloxacin/clindamycin. One hundred forty-nine trovafoxacin and 156 ofloxacin/clindamycin subjects received treatment. One hundred twenty-one trovafoxacin and 109 ofloxacin/clindamycin subjects completed treatment; 124 trovafoxacin and 126 ofloxacin/clindamycin

subjects completed the study. Of the 152 trovafloxacin and 159 ofloxacin/clindamycin clinical intent-to-treat subjects, 101 subjects in the trovafloxacin group and 97 subjects in the ofloxacin/clindamycin group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was no post-baseline clinical assessments. Of the clinical intent-to-treat subjects, 40 subjects in the trovafloxacin group and 43 subjects in the ofloxacin/clindamycin group were included in the bacteriological intent-to-treat analysis; 21 subjects in the trovafloxacin and 27 subjects in the ofloxacin/clindamycin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen.

Reviewer's Note: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 125.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.

Treatment Group for Response	Subjects Included	
	Trovafoxacin (N=155)	Ofloxacin/ Clindamycin (N=161)
Clinically ITT	152 (98.1%)	159 (98.8%)
Bacteriologically ITT	40 (25.8%)	43 (26.7%)
Applicant Clinically Evaluable	101 (65.2%)	97 (60.2%)
Applicant Bacteriologically Evaluable	21 (13.5%)	27 (16.9%)

Clinical response at EOS is shown for the Applicant clinically evaluable subjects in Table 125.3. Confidence interval results from analyses showed that trovafloxacin was therapeutically equivalent to ofloxacin/clindamycin with respect to the cure rates at EOS.

Clinical Response	Trovafoxacin (N=101)	Ofloxacin/ Clindamycin (N=97)
Cure	92 (91.1%)	89 (91.8%)
Failure	9 (8.9%)	8 (8.2%)
Trova. vs. O./C. by Cure	-0.7%, 95% C.I.: -9.5%, 8.1%	

Table 125.4 shows subject bacteriological response of the Applicant bacteriologically evaluable subjects at EOS. Trovafoxacin showed therapeutic equivalence to ofloxacin/clindamycin.

Pathogen clinical outcome at EOS is shown for the Applicant clinically evaluable subjects in Table 125.5. Pathogen bacteriological outcome at EOS is shown for the Applicant bacteriologically evaluable subjects in Table 125.6.

TABLE 125.4: STUDY 154-125: BACTERIOLOGICAL RESPONSE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS

Subject Bacteriological Response	Trovafoxacin (N=21)	Ofloxacin/ Clindamycin (N=27)
Satisfactory	21 (100%)	25 (92.6%)
Unsatisfactory	0 (0%)	2 (7.4%)
Trova. vs. O./C by Satisfactory	7.4%, 95% C.I.: -6.7%, 21.5%	

TABLE 125.5: STUDY 154-125: PATHOGEN CURE RATE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Clinical Outcome	Trovafoxacin	Ofloxacin/ Clindamycin
<i>N. gonorrhoeae</i>	12/12 (100%)	8/8 (100%)
<i>C. trachomatis</i>	11/12 (91.7%)	14/14 (100%)

TABLE 125.6: STUDY 154-125: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICAL EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)

Pathogen Bacteriological Outcome	Trovafoxacin	Ofloxacin/ Clindamycin
<i>N. gonorrhoeae</i>	10/10 (100%)	8/8 (100%)
<i>C. trachomatis</i>	10/10 (100%)	13/13 (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 Table 125.7. There were significantly more trovafoxacin subjects who experienced dizziness and headache.

TABLE 125.7: STUDY 154-125: CLINICAL ADVERSE EVENT RATES

Safety outcome	Trovafoxacin (N=149)	Ofloxacin /Clindamycin (N=156)	Fisher's P-value
At Least One AE	114/149 (76.5%)	110/156 (70.5%)	0.246
CENTRAL AND PERIPHERAL NERVOUS	65 (43.6%)	24 (15.4%)	<0.001
Dizziness	55 (36.9%)	10 (6.4%)	<0.001
Headache	31 (20.8%)	12 (7.7%)	0.002
At Least One Treatment Related AE	91/149 (61.1%)	94/156 (60.3%)	0.907
CENTRAL AND PERIPHERAL NERVOUS	58 (38.9%)	17 (10.9%)	<0.001
Dizziness	47 (31.5%)	8 (5.1%)	<0.001
Headache	22 (14.8%)	7 (4.5%)	0.003
Discontinuations Due to an AE	19/149 (12.8%)	24/156 (15.4%)	0.622
Clinically Significant Lab Abnormalities	44/141 (31.2%)	41/140 (29.3%)	0.795

No subject from either treatment group died during the study. Four (3%) subjects in the trovafoxacin group and seven (4%) subjects in the ofloxacin/clindamycin group had serious adverse events during this study. Only one subject in the ofloxacin/clindamycin group experienced an adverse event that was considered by the investigator to be related to study drug.

Reviewer's Summary and Conclusions: See Section X.

VII. UNCOMPLICATED URINARY TRACT INFECTIONS

VII.A. INTRODUCTION

The Applicant submitted two pivotal controlled studies, Study 154-103 and Study 154-116, as evidence to support oral trovafoxacin regarding this indication, and statistical review focuses on the two clinical trials which form the basis of this application. The general designs of these two studies are as follows:

Study 154-103 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of two doses of trovafoxacin (100 mg q.d. or 100 mg b.i.d.) versus ciprofloxacin hydrochloride (250 mg b.i.d.) administered orally for 7 days for the treatment of subjects with uncomplicated urinary tract infections. The study was initiated on December 10, 1993 and completed on June 16, 1994.

Study 154-116 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of 3 and 7 days of oral therapy with trovafoxacin (100 mg q.d.) versus 3 days of oral therapy with norfloxacin (400 mg b.i.d.), for the treatment of uncomplicated acute urinary tract infections. The study was initiated on March 15, 1995 and completed on November 13, 1995.

VII.B. STUDY 154-103

VII.B.1. METHODS

In study 154-103, a total of approximately 200 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 male and female outpatients (about 95% of subjects were female), who were 18 years of age or older and 65 years of age or younger with clinically documented uncomplicated urinary tract infection.

At Visit 1 (Day 1, baseline), baseline assessments and clinical assessments of signs and symptoms of urinary tract infection were performed. At Visit 2 (Day 5), subjects with no clinical improvement were requested to return to the clinic to have a formal evaluation. At Visit 3 (Day 15, 1 week following study drug completion, EOT), microbiological tests and clinical assessments of signs and symptoms of urinary tract infection were performed. Vital signs were recorded and hematology, chemistry, and urinalysis determinations were repeated. The investigator provided an evaluation of clinical response. At Visit 4 (Day 36, 4 weeks following study drug completion, EOS), microbiological tests and clinical assessments were the same as those performed at Visit 3. Repeat laboratory tests were only performed if a clinically significant abnormality was present at Visit 3 (Day 15). Additionally, the investigator provided a final evaluation of clinical response. The reasons for discontinuation of any subject were recorded on the CRF. All concomitant medications were recorded. Table 103.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of tablets and 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); 2. trovafloxacin 200 mg/day in two equally divided doses (1x100 mg tablet); 3. ciprofloxacin 500 mg/day in two equally divided doses (1x250 mg tablet). All subjects received study medication in the morning and evening in combinations of active drug and placebos for active drug, administered orally for 7 days.

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 12	Day 15	Day 36
Allowable Window	Day 1	Day 4-6	Day 11-19	Day 29-43
Treatment Period	Day 1 to Day 8			
Follow-up Period	Day 9 to Day 36			
Informed Consent	X			
Demographic Information	X			
Medical History	X			
Physical Examination	X			
Concomitant Medication	X		X	X
Vital Signs	X		X	X
Dosing Record		X	X	
Adverse Experiences			X	X
Clinical Signs & Symptoms	X	X		X
Urine Assessments				
• pyuria	X		X	X
• quantitative urine				
• culture & sensitivity	X		X	X
Safety Laboratory Tests				abn
• ESR, PT, APTT	X		X	abn
• CBC+chemistry	X		X	abn
• urinalysis	X		X	
Pregnancy test	X			
Investigator's Clinical Evaluation		X	X	

abn Abnormal at previous visit or clinically significant adverse event.

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EFFICACY EVALUATION

Efficacy analyses were performed on the bacteriologically and clinically evaluable subjects. The primary efficacy endpoint was subject bacteriological response at EOT. The secondary endpoints were: subject bacteriological response at EOS, clinical responses at EOT and EOS, and pathogen outcomes at EOT and EOS.

Subject bacteriological response, clinical response, and pathogen outcome were determined by the sponsor and evaluated at Visit 3 (EOT) and Visit 4 (EOS). Subject bacteriologic response was classified as eradication or persistence; clinical response was classified as cure, improvement, failure, or relapse; pathogen outcome was classified as eradication, persistence, or presumed persistent.

Reviewer's Note: The Medical Officer also defined her bacteriologically and clinically evaluable subjects, and assessed bacteriological and clinical efficacy outcomes according to her bacteriological and clinical 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, concomitant medication use, vital sign measurements, and reports of adverse clinical events.

An adverse event was defined as a sign or symptom, illness, or significant objective test abnormality. 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

There are three pairwise comparisons of interest in the study: trovafoxacin q.d. versus ciprofloxacin, trovafoxacin b.i.d. versus ciprofloxacin, and trovafoxacin q.d. versus trovafoxacin b.i.d.

Efficacy analyses were based on the bacteriological and clinical responses at EOT (Day 15) and EOS (Day 36). The three treatment groups were compared with respect to the subject bacteriological eradication rate, the clinical success (cure+improvement) rate, and the pathogen bacteriological eradication rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the subject bacteriological eradication rate at EOT in the bacteriologically 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 bacteriologically and clinically evaluable subjects, and the Applicant bacteriologically and clinically evaluable subjects. All of the subjects in these groups were assessed for their bacteriological or clinical responses. Bonferroni's adjustment in the Type I error probability was applied for this multiple comparison. Equivalence between pairs of the three treatments with respect to efficacy variables was assessed by computing the two-tailed 98.3% confidence interval (95% family 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 pairwise comparisons among the three 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% family level of significance.