CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20759/20760

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEC 9 1997

NDA, Drug Name, and Its Formulation:	20-759: Trovan® Tablets (Trovafloxacin Mesylate) 20-760: Trovan® Injection (Alatrofloxacin Mesylate Injection)
Drug Class:	1-S
Applicant:	Pfizer Inc.
Indications:	Of 17 indications totally, 9 by this reviewer 1.Complicated intra-abdominal infections 2.Gynecologic and pelvic infections 3.Surgical prophylaxis - elective colorectal surgery 4.Surgical prophylaxis - elective abdominal and vaginal hysterectomy 5.Non-gonococcal urethritis and cervicitis 6.Pelvic inflammatory disease 7.Uncomplicated urinary tract infection 9.Bacterial prostatitis For other 8 indications, see statistical review reports by Nancy Silliman, Ph.D. and Daphne Lin, Ph.D.
Documents Reviewed:	NDA volumes 1.1-1.8 dated December 19, 1996 and electronic submission
Type of Review	Clinical
Medical Officer:	Regina Alivisatos, M.D, Daniel Davis, M.D., Brad Leissa, M.D., HFD-590, Mamodikoe Makhene, M.D., HFD-520
Statistical Reviewer:	Joel Jiang, Ph.D., HFD-725
Project Manager:	Pauline Fogarty, HFD-590

I. COMPLICATED INTRA-ABDOMINAL INFECTIONS 3
I.A. INTRODUCTION 3
I.B. STUDY 154-124 3
I.B.1. METHODS 3
I.B.2. RESULTS 6
II. GYNECOLOGIC AND PELVIC INFECTIONS 9
II.A. INTRODUCTION 9
II.B. STUDY 154-144 9
II.B.1. METHODS 9
II.B.2. RESULTS 12
III. SURGICAL PROPHYLAXIS - ELECTIVE COLORECTAL SURGERY 16
III.A. INTRODUCTION 16
III.B. STUDY 154-128 16
III.B.1. METHODS 16
III.B.2. RESULTS 18
IV. SURGICAL PROPHYLAXIS - ELECTIVE ABDOMINAL AND VAGINAL HYSTERECTOMY 22
IV.A. INTRODUCTION 22
IV.B. STUDY 154-146 22

IV.B.1. METHODS....22
IV.B.2. RESULTS....24
V. NON-GONOCOCCAL URETHRITIS AND CERVICITIS....28
V.A. INTRODUCTION....28
V.B. STUDY 154-105....28
V.B.1. METHODS....28
V.B.2. RESULTS....30
V.C. STUDY 154-123....33
V.C.1. METHODS....33
V.B.2. RESULTS....36
VI. PELVIC INFLAMMATORY DISEASE....41
VI.A. INTRODUCTION....41
VI.B. STUDY 154-122....41
VI.B.1. METHODS....41
VI.B.2. RESULTS....44
VI.C. STUDY 154-125....46
VI.C.1 METHODS....46
VI.C.2. RESULTS....47
VII. UNCOMPLICATED URINARY TRACT INFECTIONS....51
VII.A. INTRODUCTION....51
VII.B. STUDY 154-103....51
VII.B.1. METHODS....51
VII.B.2. RESULTS....54
VII.C. STUDY 154-116....59
VII.C.1. METHODS....59
VII.C.2. RESULTS....60

IX. PROSTATITIS....86
IX.A. INTRODUCTION....86
IX.B. STUDY 154-119....86
IX.B.1. METHODS....86
IX.B.2. RESULTS....89
X. SUMMARY AND CONCLUSIONS....93

Review's Note: Throughout the review, the following terms are abbreviated and referred to as: CRF = Case Report Form, EOS = End of study Visit, EOT = End of Treatment Visit. Reviewer comments are given in italics throughout the review.

I. COMPLICATED INTRA-ABDOMINAL INFECTIONS

I.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-124, as evidence to support intravenous alatrofloxacin followed by 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 154-124 was a randomized, double-blind, multicenter trial which compared the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin for a maximum treatment duration of 14 days versus intravenous imipenem/cilastatin followed by oral amoxicillin/clavulanic acid for a maximum treatment duration of 14 days for the treatment of subjects with complicated intra-abdominal infections requiring hospitalization, surgery, or percutaneous drainage, and initial intravenous therapy.

I.B. STUDY 154-124

I.B.1. METHODS

In study 154-124, a total of approximately 300 subjects with a clinical diagnosis consistent with an intra-abdominal infection were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At baseline (Day 1), subjects who met the criteria for clinical diagnosis of intra-abdominal 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 inpatients, who were 18 years of age or older with clinically documented intra-abdominal infection.

At the baseline assessment (Day 1), baseline assessments were performed. At Day 4, efficacy observations were performed to assess response to study therapy. At Day 14 (EOT), efficacy observations were repeated to assess response to study therapy. Safety was also assessed. The investigator provided an evaluation of time of recovery and an evaluation of clinical response. At Day 30 (EOS), efficacy observations were repeated to assess response to study therapy. Safety was also 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 124.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug for intravenous administration was prepared by the study site pharmacist using a double-dummy technique to maintain blinding. Subjects received one of the following intravenous treatment regimens: 1. alatrofloxacin 300 mg (3x100 mg vials) in 200 ml of D5W administered once daily as a 60-minute infusion; 200 ml D5W (alatrofloxacin placebo) administered as a 60-minute infusion twice daily, once in the afternoon (1 vial) and once in the evening (1 vial); 2. imipenem/cilastatin 1 g (1x1 gram vial) in 200 ml of D5W administered every 8 hours as a 60-minute infusion. All subjects received intravenous study medication every 8 hours in combinations of active drug and placebos for active drug. Based upon clinical impressions, the subject was switched from intravenous to oral therapy to complete a total maximum treatment duration of 14 days. Study drug for oral administration was in the form of trovafloxacin tablets and amoxicillin/clavulanic acid suspension and was packaged using a double-dummy technique to maintain blinding. Eight hours after the last intravenous treatment with randomized study

medication, subjects received one of the following treatments orally: 1. trovafloxacin 200 mg (2x100 mg tablets) administered as a single daily dose in the morning and 10 ml of suspension administered every 8 hours (amoxicillin/clavulanic acid placebo); 2. amoxicillin/clavulanic acid 500 mg (1x10 ml suspension) administered every 8 hours and two tablets administered once daily in the morning (trovafloxacin placebo). All subjects received oral study medication three times daily (every 8 hours) in combinations of active drug and placebo for active drug. The decision to stop therapy was based on the investigator's assessment of clinical outcome.

TABLE 124.1: STUDY 154-124: VISIT TIMING AND PROCEDURES

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 4	Day 14	Day 30
Allowable Window	-48 hours	Day 3-5	Day 10-14	Day 28-42
Treatment Period	Day 1 to Day 14			
Follow-up Period	Day 15 to Day 42			
Informed Consent	X			
Demographic Information	X			
Physical Examination	X		X	X
Maximum Body Temperature	X		X	X
Vital Signs	X	X	X	X
Concomitant Medication	X	X	X	X
APACHE Scoring	X	X	X	
Dosing Record		X	X	
Clinical Signs & Symptoms	X		X	X
Assessment of Bowel Function	X		X	X
Microbiology				
• blood	X	X	X	X
• peritoneal	X			
Safety Laboratory Tests				
• hematology	X	X	X	abn
• biochemistry	X	X	X	abn
• urinalysis	X	X	X	abn
• pregnancy test	X			
Adverse Events	X		X	X
Investigator's Assessment of clinical response			X	X
Time of Recovery	X		X	X
Health Care Resource Utilization	X		X	X

abn Abnormal at previous visit or clinically significant adverse event.

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 clinical response at EOT, and pathogen outcomes at EOT and EOS.

Clinical response was determined by the sponsor and evaluated at EOT (Day 14) and at EOS (Day 30), or at the time of discontinuation from study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. The clinical

response was classified as cure, improvement, 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, vital signs, 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/trovafloxacin and imipenem/cilastatin/amoxicillin/clavulanac.

Efficacy analyses were based on the clinical and bacteriological responses at EOT and EOS. The treatment groups were compared with respect to 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 clinical success 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.

I.B.2. RESULTS

A total of 420 subjects were enrolled across centers in the USA (80), Canada (9), and Europe (31) between April 12, 1995 and June 20, 1996. Of these enrolled subjects, 7 were withdrawn prior to randomization because they did not meet study entrance criteria. Two hundred four subjects were randomized to receive alatrofloxacin/trovafloxacin and 210 subjects were randomized to receive imipenem/cilastatin/amoxicillin/clavulanac. Two hundred one alatrofloxacin/trovafloxacin and 207 comparator regimen subjects received treatment. Two hundred alatrofloxacin/trovafloxacin and 199 comparator regimen subjects were included in the clinical intent-to-treat analyses; 171 alatrofloxacin/ trovafloxacin and 164 comparator regimen subjects were included in the bacteriological intent-to-treat analyses. The most common reason for exclusion from clinically evaluable analyses was insufficient therapy. Reasons for exclusion from the bacteriologically evaluable analyses were no baseline pathogen or baseline culture performed outside of the evaluable window.

Reviewer's Note: *The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 124.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 124.2: STUDY 154-124: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP

Treatment Group for Response	Subjects Included	
	Alatrofloxacin Trovafloxacin (N=204)	Imipenem/cilastatin Amoxicillin/clavulanac (N=210)
Clinically ITT	200 (98.0%)	199 (94.8%)
Bacteriologically ITT	171 (83.8%)	164 (78.1%)
Applicant Clinically Evaluable		
Clinically Evaluable at EOT	155 (76.0%)	142 (67.6%)
Clinically Evaluable at EOS	156 (76.5%)	152 (72.4%)
Applicant Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	135 (66.2%)	123 (58.6%)
Bacteriologically Evaluable at EOS	135 (66.2%)	131 (62.4%)

The clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 124.3A and 124.3B, respectively. Confidence interval results from analyses showed that alatrofloxacin/trovafloxacin was therapeutically equivalent to imipenem/cilastatin/amoxicillin/clavulanac with respect to the success rates at both EOT and EOS.

TABLE 124.3A: STUDY 154-124: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Alatrofloxacin Trovafloxacin (N=155)	Imipenem/cilastatin Amoxicillin/clavulanac (N=142)
Success (cure+improvement)	136 (87.8%)	122 (85.9%)
Failure	19 (12.3%)	20 (14.1%)
A./T. vs I./C./A./C. by Success	1.8%, 95% C.I.: -6.6%, 10.2%	

TABLE 124.3B: STUDY 154-124: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin Trovafloxacin (N=156)	Imipenem/cilastatin Amoxicillin/clavulanac (N=152)
Success (cure+improvement)	129 (82.7%)	127 (83.6%)
Failure	27 (17.3%)	25 (16.4%)
A./T. vs I./C./A./C. by Success	-0.9%, 95% C.I.: -9.9%, 8.2%	

Analyses of the pathogen eradication rates of the Applicant bacteriologically evaluable subjects at EOT and EOS are displayed in Tables 124.4A and 124.4B, respectively. Comparisons (95% confidence intervals) of the difference in *E. coli* eradication rates between the two treatment groups supported equivalence of alatrofloxacin/trovafloxacin versus imipenem/cilastatin/amoxicillin/clavulanac at both timepoints.

TABLE 124.4A: STUDY 154-124: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Alatrofloxacin Trovafloxacin	Imipenem/cilastatin Amoxicillin/clavulanac	95% CI
E. coli	73/77 (94.8%)	53/58 (91.4%)	-6.8%, 13.7%
B. fragilis	30/30 (100%)	31/34 (91.2%)	
Streptococcus sp.	28/30 (93.3%)	40/41 (97.6%)	
S. viridans	19/20 (95.0%)	22/23 (95.7%)	
P. aeruginosa	15/16 (93.8%)	16/17 (94.1%)	

TABLE 124.4B: STUDY 154-124: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Alatrofloxacin Trovafloxacin	Imipenem/cilastatin Amoxicillin/clavulanac	95% CI
E. coli	67/77 (87.0%)	52/59 (88.1%)	-13.8%, 11.5%
B. fragilis	27/30 (90.0%)	28/36 (77.8%)	
Streptococcus sp.	26/30 (86.7%)	40/43 (93.0%)	
S. viridans	18/20 (90.0%)	19/23 (82.6%)	
P. aeruginosa	14/16 (87.5%)	15/18 (83.3%)	

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 124.5. The alatrofloxacin/ trovafloxacin group experienced a significantly higher rate of adverse events in the central and peripheral nervous system regardless of relationship to study drug than did the imipenem/cilastatin/amoxicillin/ clavulanac group.*

TABLE 124.5: STUDY 154-124: CLINICAL ADVERSE EVENT RATES

Safety Outcome	Alatrofloxacin/ Trovafloxacin (N=201)	Imipenem/Cilastatin /Amoxicillin/ Clavulanac Acid (N=207)	Fisher's P-value
At Least One AE	128/201 (63.7%)	120/207 (58.0%)	0.253
CENTRAL AND PERIPHERAL NERVOUS	32 (15.9%)	13 (6.3%)	0.002
Confusion	8 (4.0%)	5 (2.4%)	0.410
Dizziness	9 (4.5%)	2 (1.0%)	0.034
Headache	11 (5.5%)	5 (2.4%)	0.131
At Least One Treatment Related AE	29/201 (14.4%)	23/207 (11.1%)	0.373
CENTRAL AND PERIPHERAL NERVOUS	8 (4.0%)	2 (1.0%)	0.059
Dizziness	3 (1.5%)	2 (1.0%)	0.681
Headache	1 (0.5%)	0 (1.0%)	0.493
Discontinuations Due to an AE	19/201 (9.5%)	19/207 (9.2%)	1.000
Clinically Significant Lab Abnormalities	142/198 (71.7%)	153/205 (74.6%)	0.574

Eleven subjects in the alatrofloxacin/trovafloxacin group and 11 subjects in the comparator regimen died during this study. None of these deaths were considered by the investigator to be related to study drug. Thirty-four (17%) subjects in the alatrofloxacin/trovafloxacin group and 44 (21%) in the imipenem/ cilastatin/amoxicillin/clavulanac group had serious adverse events during this study, among which 32 subjects in the alatrofloxacin/trovafloxacin group and 44 subjects in the comparator regimen were considered by the investigator to be unrelated to study drug.

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

II. GYNECOLOGIC AND PELVIC INFECTIONS

II.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-144, as evidence to support intravenous alatrofloxacin followed by 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 154-144 was a randomized, double-blind, multicenter trial which compared the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin for a maximum total treatment duration of 14 days versus intravenous cefoxitin followed by oral amoxicillin/clavulanic acid for a maximum total treatment duration of 14 days for the treatment of female subjects with acute pelvic infections requiring initial intravenous therapy.

II.B. STUDY 154-144

II.B.1. METHODS

In study 154-144, a total of approximately 300 subjects with a clinical diagnosis consistent with acute pelvic infection were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. At the baseline assessment (Day 1), subjects who met the criteria for clinical diagnosis of acute pelvic 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 female inpatients or outpatients, who were 18 years of age or older with clinically documented acute pelvic infection.

At Day 1 (baseline), baseline assessments and clinical assessment of signs and symptoms of acute pelvic infection were performed. At Day 3, efficacy observations were performed to assess response to study therapy. Safety was assessed. The investigator provided an evaluation of clinical response. At Day 5, if the subject remained hospitalized, efficacy observations were repeated to assess response to study therapy. Safety was assessed. At Day 14 (EOT) efficacy observations were repeated. Safety was assessed. The investigator provided an evaluation of clinical response. At Day 30 (EOS), efficacy observations were performed to assess response to study therapy. 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 144.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug for intravenous administration was prepared by a study site pharmacist using a double-dummy technique to maintain blinding. Subjects received one of the following intravenous treatment regimens: 1. alatrofloxacin 300 mg in 200 ml of D5W administered once daily as a 60-minute infusion (3x100 mg vials) and 200 ml D5W with the addition of a multivitamin solution every 6 hours (cefoxitin placebo); 2. cefoxitin 2 g in 200 ml of D5W administered every 6 hours as a 60-minute infusion (2x1 gram vials) and 200 ml D5W once daily (alatrofloxacin placebo). All subjects received intravenous study medication every 6 hours in combinations of active drug and placebos for active drug. Six hours after the last intravenous treatment with randomized study medication subjects received one of the following treatments orally: 1. trovafloxacin 200 mg/day as a single active dose (2x100 mg tablets) and 10 ml of suspension three times

daily (amoxicillin/clavulanic acid placebo); 2. amoxicillin/clavulanic acid 1500 mg/ 30 ml/day in three equally divided doses and two tablets once daily (trovafloxacin placebo). All subjects received oral study medication three times daily (every 8 hours) in combinations of active drug and placebos for active drug. The decision to stop therapy was based on the investigator's assessment of clinical outcome. Typically, study drug therapy continued until the subject was afebrile for a period of 24 to 48 hours.

TABLE 144.1: STUDY 154-144: VISIT TIMING AND PROCEDURES

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Study Day	Day 1	Day 3	Day 5	Day 3-
Allowable Window	-48 hours	Day 2-4	Day 5-7	Day 28-42
Treatment Period	Day 1 to Day 14			
Follow-up Period	Day 15 to Day 12			
Informed Consent	X			
Demographic Information	X			
Maximum Body Temperature	X		X	
Targeted Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Clinical Signs and Symptoms	X	X	X	X
Concomitant Medication	X		X	X
Dosing Record	X		X	
Microbiology				
• pelvic areas	X	X	X	X
• blood	X	X	X	X
• urine	X	X	X	X
Safety Laboratory Tests				
• hematology	X	X	X	abn
• biochemistry	X	X	X	abn
• urinalysis	X	X	X	abn
Adverse Event	X		X	X
Investigator's Assessment of Clinical Response		X	X	X
Health Care Resource Utilization	X		X	X

abn Abnormal at previous visit or clinically significant adverse event.

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 clinical response at EOT, and pathogen outcomes at EOT and EOS.

Clinical response to therapy was determined by the sponsor and evaluated 48 hours after initiation of therapy (Day 3), at EOT (Day 14) and at EOS (Day 30) (primary endpoint), or at the time of discontinuation from the study. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation timepoint. The clinical response was classified as cure, improvement, or failure. Pathogen bacteriologic outcome was classified as eradication, presumed eradication, persistence, presumed persistent, superinfection, or colonization.

Reviewer's Note: *The Medical Officer also defined his clinically and bacteriologically evaluable subjects, and assessed clinical and bacteriological efficacy outcomes according to his 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 clinical laboratory tests, vital signs, 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/trovafloxacin and cefoxitin/amoxicillin/clavulanic.

Efficacy analyses were based on the clinical and bacteriological responses at EOT and EOS. The treatment groups were compared with respect to 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 clinical success 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 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.

II.B.2. RESULTS

A total of 317 subjects were enrolled at 55 centers in the USA between June 21, 1995 and May 3, 1996. Of the 160 alatrofloxacin/trovafloxacin and 157 cefoxitin/amoxicillin/clavulanic subjects, 47 and 29 subjects, respectively, were prematurely discontinued from treatment. One hundred fifty nine alatrofloxacin/ trovafloxacin and 157 cefoxitin/amoxicillin/clavulanic subjects were included in the clinical intent-to-treat analyses; 132 alatrofloxacin/trovafloxacin and 122 cefoxitin/amoxicillin/clavulanic subjects were included in the bacteriological intent-to-treat analyses. The Applicant clinically evaluable group at EOS comprised 226 subjects, and there were 203 subjects in the Medical Officer clinically evaluable group at EOS. The most common reason for exclusion from clinical evaluable analyses was concomitant antibiotic therapy for intercurrent illness. The only 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 either the Applicant or the Medical Officer, are presented in Table 144.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 144.2: STUDY 154-144: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP

Treatment Group for Response	Subjects Included	
	Alatrofloxacin Trovafloxacin (N=161)	Cefoxitin Amoxicillin/clavulanic (N=159)
Clinically ITT	159 (98.8%)	157 (98.7%)
Bacteriologically ITT	132 (82.0%)	122 (76.7%)
Applicant Clinically Evaluable		
Clinically Evaluable at EOT	93 (57.8%)	104 (65.4%)
Clinically Evaluable at EOS	107 (66.5%)	119 (74.8%)
MO Clinically Evaluable		
Clinically Evaluable at EOT	84 (52.2%)	91 (57.2%)
Clinically Evaluable at EOS	96 (59.6%)	107 (67.3%)
Applicant Bacteriologically Evaluable		
Bacteriologically Evaluable at EOT	77 (47.8%)	83 (52.2%)
Bacteriologically Evaluable at EOS	88 (54.7%)	93 (58.5%)
MO Bacteriologically Evaluable		
Bacteriologically Evaluable at EOS	78 (48.4%)	87 (54.7%)

Clinical responses at EOT and EOS are shown for the Applicant clinically evaluable subjects in Tables 144.3A and 144.3B, respectively. Confidence interval results from analyses showed that alatrofloxacin/ trovafloxacin was therapeutically equivalent to cefoxitin/amoxicillin/clavulanic with respect to the success rates at both EOT and EOS.

Reviewer's Note: *The clinical cure rates of the Medical Officer clinically evaluable subjects at EOT and EOS are presented in Tables 144.4A and 144.4B, respectively. Therapeutic equivalence of alatrofloxacin/ trovafloxacin to cefoxitin/amoxicillin/clavulanic with respect to clinical cure rates was demonstrated at both time points.*

TABLE 144.3A: STUDY 154-144: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Alatrofloxacin Trovafloxacin (N=93)	Cefoxitin Amoxicillin/clavulanic (N=104)
Success (cure+improvement) Failure	83 (89.2%) 10 (10.8%)	87 (83.7%) 17 (16.3%)
A./T. vs C./A./C. by Success	5.6%, 95% C.I.: -4.9%, 16.1%	

TABLE 144.3B: STUDY 154-144: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin Trovafloxacin (N=107)	Cefoxitin Amoxicillin/clavulanic (N=119)
Success (cure+improvement) Failure	96 (89.7%) 11 (10.3%)	102 (85.7%) 17 (14.3%)
A./T. vs C./A./C. by Success	4.0%, 95% C.I.: -5.4%, 13.4%	

TABLE 144.4A: STUDY 154-144: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOT		
Clinical Response	Alatrofloxacin Trovafloxacin (N=84)	Cefoxitin Amoxicillin/clavulanic (N=91)
Success (cure+improvement) Failure	74 (88.1%) 10 (11.9%)	75 (82.4%) 16 (17.6%)
A./T. vs C./A./C. by Success	5.7%, 95% C.I.: -5.9%, 17.3%	

TABLE 144.4B: STUDY 154-144: CLINICAL RESPONSE OF THE MO CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin Trovafloxacin (N=96)	Cefoxitin Amoxicillin/clavulanic (N=107)
Success (cure+improvement) Failure	85 (88.5%) 11 (11.5%)	89 (83.2%) 18 (16.8%)
A./T. vs C./A./C. by Success	5.4%, 95% C.I.: -5.2%, 15.9%	

Analyses of the pathogen eradication rates of the Applicant bacteriologically evaluable subjects at EOT and EOS are displayed in Tables 144.5A and 144.5B, respectively. Comparisons (95% confidence intervals) of the difference in *E. faecalis* eradication rates between the two treatment groups supported equivalence of alatrofloxacin/trovafloxacin versus cefoxitin/amoxicillin/clavulanic at both timepoints.

Reviewer's Note: *Table 144.6 shows the pathogen outcomes of the Medical Officer bacteriologically evaluable subjects at EOS. Alatrofloxacin/trovafloxacin showed therapeutic equivalence to* cefoxitin/ amoxicillin/clavulanic *at EOS with respect to the eradication rate of E. faecalis.*

TABLE 144.5A: STUDY 154-144: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOT (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Alatrofloxacin Trovafloxacin	Cefoxitin Amoxicillin/clavulanic	95% C.I.
E. faecalis	24/24 (100%)	25/28 (89.3%)	-4.6%, 26.0%
Peptostreptococcus sp.	11/13 (84.6%)	15/16 (93.8%)	
Prevotella sp.	14/15 (93.3%)	11/12 (91.7%)	
Corynebacterium sp.	17/20 (85.0%)	12/15 (80.0%)	
Enterococcus sp.	20/20 (100%)	20/25 (80.0%)	

TABLE 144.5A: STUDY 154-144: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Alatrofloxacin Trovafloxacin	Cefoxitin Amoxicillin/clavulanic	95% C.I.
E. faecalis	28/29 (96.6%)	29/32 (90.6%)	-9.4%, 21.3%
Peptostreptococcus sp.	14/16 (87.5%)	18/19 (94.7%)	
Prevotella sp.	17/18 (94.4%)	14/15 (93.3%)	
Corynebacterium sp.	20/23 (87.0%)	12/16 (75.0%)	
Enterococcus sp.	26/26 (100%)	22/27 (81.5%)	

TABLE 144.6: STUDY 154-144: PATHOGEN ERADICATION RATE OF THE APPLICANT BACTERIOLOGICALLY EVALUABLE SUBJECTS AT EOS (FOR MOST FREQUENTLY ISOLATED BASELINE PATHOGENS)			
Pathogen Bacteriological Outcome	Alatrofloxacin Trovafloxacin	Cefoxitin Amoxicillin/clavulanic	95% C.I.
E. faecalis	25/26 (96.2%)	26/30 (86.7%)	-8.3%, 27.3%
Peptostreptococcus sp.	12/14 (85.7%)	16/17 (94.1%)	
Prevotella sp.	16/17 (94.1%)	15/16 (93.8%)	
S. agalactiae	13/14 (92.9%)	9/13 (69.2%)	
S. epidermidis	12/14 (85.7%)	6/8 (75.0%)	

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 Table 144.7. With respect to all these adverse event rates except the rates of clinically significant laboratory abnormalities, alatrofloxacin/ trovafloxacin had significantly higher rates than cefoxitin/amoxicillin/clavulanic. The alatrofloxacin/ trovafloxacin group also had a significantly higher incidence rate of dizziness than its comparator group.*

TABLE 144.7: STUDY 154-144: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Alatrofloxacin/ Trovafloxacin (N=160)	Cefoxitin Amoxicillin/clavula. (N=157)	Fisher's P-value
At Least One AE	83/160 (51.9%)	56/157 (35.7%)	0.005
CENTRAL AND PERIPHERAL NERVOUS	25 (15.6%)	11 (7.0%)	0.021
Dizziness	11 (6.9%)	1 (0.6%)	0.005
Headache	15 (9.4%)	10 (6.4%)	0.406
At Least One Treatment Related AE	38/160 (23.8%)	10/157 (6.4%)	<0.001
CENTRAL AND PERIPHERAL NERVOUS	14 (8.8%)	1 (0.6%)	0.001
Dizziness	9 (5.6%)	1 (0.6%)	0.020
Headache	4 (2.5%)	0 (0%)	0.123
Discontinuations Due to an AE	30/160 (18.8%)	9/157 (5.7%)	0.001
Clinically Significant Lab Abnormalities	103/146 (70.6%)	99/152 (65.1%)	0.325

No subject in either treatment group died during this study. Fifteen (9%) subjects in the alatrofloxacin/ trovafloxacin group and 10 (6%) in the cefoxitin/amoxicillin/clavulanic group had serious adverse events during this study. Two subjects in the alatrofloxacin/trovafloxacin group had serious adverse events that were considered to be related to study drug.

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

III. SURGICAL PROPHYLAXIS - ELECTIVE COLORECTAL SURGERY

III.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-128, as evidence to support a single intravenous dose of alatrofloxacin 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 154-128 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of intravenous therapy with alatrofloxacin (200 mg single infusion) versus cefotetan (2 g single infusion) for the prophylaxis of primary site infection following elective colo-rectal surgery.

III.B. STUDY 154-128

III.B.1. METHODS

In study 154-128, a total of approximately 400 subjects (at least 15 subjects per center) who underwent elective colo-rectal surgery were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. During the Pre-dose (Pre-surgery) period, subjects who met the criteria for elective colo-rectal surgery, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of inpatient men or women, who were 18 years of age or older undergoing elective operations of the colon or rectum.

During the Pre-dose (Pre-surgery) period, baseline assessments and hematology, serum chemistry, and urinalysis determinations were performed. On Day 1 (Surgery Day), skin preparation and the operative technique were performed. Forty-eight hours after surgery, safety was assessed by repeating laboratory evaluations. Adverse events were recorded throughout the study. On the day of discharge from the hospital, the investigator recorded all symptoms and physical findings of any infections found during the hospitalization period. The severity of any primary wound infection was noted by the investigator. At Day 30 (Day 28-35, EOS, the final assessment), subjects had a targeted physical examination. The investigator assessed and recorded whether any infection occurred during the post-hospitalization period. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 128.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was in the form of intravenous solution and was supplied in vials using a double-dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. alatrofloxacin 200 ml single infusion; 2. cefotetan 20 ml single infusion. Alatrofloxacin was administered within 2 hours of surgical incision and cefotetan was administered within 30 to 60 minutes of surgical incision.

TABLE 128.1: STUDY 154-128: VISIT TIMING AND PROCEDURES			
Visit Number	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-48 hours		28-35
Informed Consent	X		
Demographic Information	X		
Physical Exam of the Abdomen	X	X	X
Maximum Body Temperature	X	X	X
Vital Signs	X	X	X
Concomitant Medication	X	X	X
Bowel Preparation	X		
Dosing Record		X	
Safety Laboratory Tests			
• hematology	X	X	abn
• biochemistry	X	X	abn
• urinalysis	X	X	abn
• pregnancy test	X		
Adverse Events	X	X	X
Investigator's Report of Infection History/Presence		X	X
Health Care Resource Utilization			X
abn Abnormal at previous visit or clinically significant adverse event.			

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoint was clinical response at hospital discharge.

Clinical response was determined by the sponsor and evaluated at hospital discharge and at EOS (Day 30). Clinical response was based primarily on the investigator's assessment of symptoms and physical findings of any wound infections found during the 30 day study period. Clinical response was classified as success or failure.

Reviewer's Note: *The Medical Officer agreed with clinical evaluability criteria chosen by the Applicant, and assessed clinical efficacy outcomes according to the Applicant 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 clinical laboratory tests, vital signs, 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 alatrofloxacin and cefotetan.

Efficacy analyses were based on clinical responses at hospital discharge and EOS. The treatment groups were compared with respect to the clinical success rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success 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 evaluable subjects and the Applicant clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection. All of the subjects in these groups were assessed for their 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.

III.B.2. RESULTS

A total of 518 subjects were enrolled across centers in the USA (76) and Canada (6) between April 10, 1995 and March 12, 1996. Of the 256 alatrofloxacin and 236 cefotetan subjects, seven alatrofloxacin subjects were prematurely discontinued from treatment during the 1-hour infusion period and one cefotetan subject was prematurely discontinued from treatment during the 5-minute infusion period. Of the 269 alatrofloxacin and 249 cefotetan randomized subjects, 23 alatrofloxacin and 13 cefotetan subjects were excluded from clinical intent-to-treat and evaluable analyses because of not having elective, uncomplicated surgery on the colon or rectum, and not having surgery or having frank stool found during surgery. Of the 246 alatrofloxacin and 236 cefotetan clinically intent-to-treat subjects, 85 in the alatrofloxacin group and 80 in the cefotetan group were not clinically evaluable; therefore, 161 subjects in the alatrofloxacin group and 156 subjects in the cefotetan group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was concomitant antibiotic therapy for intercurrent illness.

Reviewer's Note: *The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 128.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 128.2: STUDY 154-128: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Treatment Group for Response	Subjects Included	
	Alatrofloxacin (N=269)	Cefotetan (N=249)
Clinically ITT	246 (91.4%)	236 (94.8%)
Applicant Clinically Evaluable		
Clinically Evaluable at HOS	161 (59.9%)	156 (62.7%)
Clinically Evaluable at EOS	161 (59.9%)	156 (62.7%)
Applicant Clinically Evaluable +		
Clinically Evaluable + at HOS	210 (78.1%)	204 (81.9%)
Clinically Evaluable + at EOS	210 (78.1%)	204 (81.9%)
HOS Hospital Discharge + Plus subjects Receiving Concomitant Antibiotics for Distant Site Infection		

Clinical responses at hospital discharge and EOS are shown for the Applicant clinically evaluable subjects in Tables 128.3A and 128.3B, respectively. Confidence interval results from analyses show that alatrofloxacin was therapeutically equivalent to ciprofloxacin with respect to the success rates at both timepoints.

TABLE 128.3A: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT HOSPITAL DISCHARGE		
Clinical Response	Alatrofloxacin (N=161)	Cefotetan (N=156)
Success	127 (78.9%)	128 (82.1%)
Failure	34 (21.1%)	28 (17.9%)
Alatro. vs Cefot. by Success	-3.2%, 95% C.I.: -12.5%, 6.2%	

TABLE 128.3B: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS		
Clinical Response	Alatrofloxacin (N=161)	Cefotetan (N=156)
Success	116 (72.0%)	113 (72.4%)
Failure	45 (28.0%)	43 (27.6%)
Alatro. vs Cefot. by Success	-0.4%, 95% C.I.: -10.9%, 10.1%	

Tables 128.4A and 128.4B show clinical responses of the clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection at hospital discharge and EOS, respectively. Confidence interval results show that the two treatment groups were therapeutically equivalent with respect to the cure rates at both timepoints.

TABLE 128.4A: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION AT HOSPITAL DISCHARGE		
Clinical Response	Alatrofloxacin (N=210)	Cefotetan (N=204)
Success	165 (78.6%)	158 (77.5%)
Failure	45 (21.4%)	46 (22.5%)
Alatro. vs Cefot. by Success	1.1%, 95% C.I.: -7.3%, 9.6%	

TABLE 128.4B: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION AT EOS		
Clinical Response	Alatrofloxacin (N=210)	Cefotetan (N=204)
Success	152 (72.4%)	139 (68.1%)
Failure	58 (27.6%)	65 (31.9%)
Alatro. vs Cefot. by Success	4.2%, 95% C.I.: -5.0%, 13.5%	

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 128.5. With respect to the rate of treatment related adverse events, alatrofloxacin subjects had significantly higher rates than cefotetan subjects.*

TABLE 128.5: STUDY 154-128: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Alatrofloxacin (N=256)	Cefotetan (N=236)	Fisher's P-value
At Least One AE	156/256 (60.9%)	135/236 (57.2%)	0.410
CENTRAL AND PERIPHERAL NERVOUS	19 (7.4%)	15 (6.4%)	0.723
Confusion	7 (2.7%)	5 (2.1%)	0.774
Dizziness	3 (1.2%)	2 (0.9%)	1.000
Headache	8 (3.1%)	5 (2.1%)	0.580
At Least One Treatment Related AE	26/256 (10.2%)	6/236 (2.5%)	0.001
CENTRAL AND PERIPHERAL NERVOUS	2 (0.8%)	1 (0.4%)	1.000
Dizziness	2 (0.8%)	0 (0%)	0.500
Headache	0 (0%)	1 (0.4%)	0.480
Discontinuations Due to an AE	5/256 (2.0%)	0/236 (0%)	0.062
Clinically Significant Lab Abnormalities	191/246 (77.6%)	184/231 (79.7%)	0.655

Four subjects in the alatrofloxacin group and seven subjects in the cefotetan group died during or following completion of this study. Sixty-nine (27%) subjects in the alatrofloxacin group and 70 (30%) subjects in

the cefotetan group had serious adverse events during this study. One subject in each treatment group had serious adverse events that were considered to be related to study drug.

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

IV. SURGICAL PROPHYLAXIS - ELECTIVE ABDOMINAL AND VAGINAL HYSTERECTOMY

IV.A. INTRODUCTION

The Applicant submitted one pivotal controlled study, Study 154-146, as evidence to support a single oral dose of 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 154-146 was a randomized, double-blind, double-dummy, multicenter trial which compared the safety and efficacy of a single oral dose of trovafloxacin versus a single intravenous infusion of cefoxitin for the prophylaxis of infection following elective abdominal or vaginal hysterectomy.

IV.B. STUDY 154-146

IV.B.1. METHODS

In study 154-146, a total of approximately 350 subjects (at least 16 subjects per center) who underwent elective abdominal or vaginal hysterectomy were to be enrolled and to be randomized to one of the two treatment groups in a 1:1 ratio. During the Pre-dose (Pre-surgery) period, subjects who met the criteria for elective hysterectomy, gave informed consent, and met all additional inclusion criteria and none of the exclusion criteria, were eligible for randomization. Eligible study population consisted of inpatient women, who were 18 years of age or older undergoing elective abdominal or vaginal hysterectomy.

During the Pre-dose (Pre-surgery) period, baseline assessments were performed. On Day 1 (Surgery Day), skin preparation and the operative technique were performed. Forty-eight hours after surgery, safety was assessed by repeating laboratory evaluations. Adverse events were recorded throughout the study. On the day of discharge from the hospital, the investigator reviewed all relevant information and recorded all symptoms and physical findings of any infections found during the hospitalization period. At Day 30 (EOS, the final assessment), subjects had a targeted physical examination. The investigator assessed and recorded whether any infection occurred during the post-hospitalization period. The reasons for discontinuation of any subject were recorded on the CRF, as well as all concomitant medications. Table 146.1 demonstrates during treatment and post treatment procedures which were specified by the protocol.

Study drug was prepared using a double dummy technique to maintain blinding. Subjects received one of the following treatment regimens: 1. trovafloxacin 200 mg (2x100 mg tablets) administered once, 45 (±15) minutes prior to the estimated time of surgical incision and 50 ml D5W with 0.1 ml MVI administered no earlier than 30 minutes prior to, and no later than the time of, surgical incision as a 10 (±5) minute infusion (cefoxitin placebo); 2. cefoxitin 2 g in 50 ml of D5W administered no earlier than 30 minutes prior to, and no later than the time of, surgical incision as a 10 (±5) minute infusion and two tablets administered once, 45 (±15) minutes prior to the estimated time of surgical incision (trovafloxacin placebo).

TABLE 146.1: STUDY 154-146: VISIT TIMING AND PROCEDURES			
Visit Number	Pre-surgery	Start of Surgery to Hospital Discharge	Follow-up Day 30
Allowable Window	-72 hours		24-36
Informed Consent	X		
Demographic Information	X		
History & Physical	X		
Examination for Signs and Symptoms of Infection with Abdominal/Perineal Exam	X	X	X
Oral Body Temperature	X	X	X
Vital Signs	X	X	X
Concomitant Medication	X	X	X
Dosing Record	X		
Safety Laboratory Tests			
• hematology	X	X	abn
• biochemistry	X	X	abn
• urinalysis	X	X	abn
Adverse Events	X	X	X
Investigator's Assessment of Infection		X	X
Health Care Resource Utilization			X
abn Abnormal at previous visit or clinically significant adverse event.			

EFFICACY EVALUATION

Efficacy analyses were performed on the clinically evaluable subjects. The primary efficacy endpoint was clinical response at EOS. The secondary endpoint was clinical response at hospital discharge.

Clinical response was determined by the sponsor and evaluated at hospital discharge and at EOS (Day 30). Clinical response was based primarily on the investigator's assessment of symptoms and physical findings of any wound infections found during the 30 day study period. Clinical response was classified as success or failure.

Reviewer's Note: *The Medical Officer agreed with clinical evaluability criteria chosen by the Applicant, and assessed clinical efficacy outcomes according to the Applicant 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 clinical laboratory tests, vital signs, 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 cefoxitin.

Efficacy analyses were based on clinical responses at hospital discharge and EOS. The treatment groups were compared with respect to the clinical success rate. The primary efficacy analysis was the comparison of the treatment groups with respect to the clinical success 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 evaluable subjects, the Applicant clinically evaluable subjects except those receiving bicitra, and the Applicant clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection except those receiving bicitra. All of the subjects in these groups were assessed for their 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.

IV.B.2. RESULTS

One hundred and ninety six trovafloxacin and 191 cefoxitin randomized subjects were enrolled at 18 centers in the USA between January 18, 1996 and June 11, 1996. Of the 188 trovafloxacin and 175 cefoxitin treated subjects, five trovafloxacin and no cefoxitin subject were prematurely discontinued from treatment. The reasons for discontinuation were due to an unrelated adverse event, or surgery postponed, or penicillin allergy. Of the 183 trovafloxacin and 185 cefoxitin clinically intent-to-treat subjects, 50 in the trovafloxacin group and 58 in the cefoxitin group were not clinically evaluable; therefore, 133 subjects in the trovafloxacin group and 127 subjects in the cefoxitin group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was concomitant antibiotic therapy for intercurrent illness.

***Reviewer's Note**: The number and percentage of evaluable subjects included in each analysis group, evaluated by the Applicant, are presented in Table 146.2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 146.2: STUDY 154-146: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP

Treatment Group for Response	Subjects Included	
	Trovafloxacin (N=196)	Cefoxitin (N=191)
Clinically ITT	183 (93.4%)	185 (96.9%)
Applicant Clinically Evaluable		
Clinically Evaluable at HOS	133 (67.9%)	127 (66.5%)
Clinically Evaluable at EOS	133 (67.9%)	127 (66.5%)
Applicant Clinically Evaluable -		
Clinically Evaluable - at HOS	103 (52.6%)	97 (50.8%)
Clinically Evaluable - at EOS	103 (52.6%)	97 (50.8%)
Applicant Clinically Evaluable + -		
Clinically Evaluable + - at HOS	131 (66.8%)	130 (68.1%)
Clinically Evaluable + - at EOS	131 (66.8%)	130 (68.1%)

HOS Hospital Discharge
\- Excluding Subjects who Received Bicitra
\+ Plus subjects Receiving Concomitant Antibiotics for Distant Site Infection

Clinical responses at hospital discharge and EOS are shown for the Applicant clinically evaluable subjects in Tables 146.3A and 146.3B, respectively. Confidence interval results from analyses show that trovafloxacin was therapeutically equivalent to cefoxitin with respect to the clinical success rates at hospital discharge, but not at EOS. In fact, the clinical success rate for trovafloxacin at EOS was significantly lower than that for cefoxitin.

TABLE 146.3A: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT HOSPITAL DISCHARGE

Clinical Response	Trovafloxacin (N=133)	Cefoxitin (N=127)
Success	128 (96.2%)	122 (96.1%)
Failure	5 (3.8%)	5 (3.9%)
Trova. vs Cefot. by Success	0.2%, 95% C.I.: -5.3%, 5.6%	

TABLE 146.3B: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS AT EOS

Clinical Response	Trovafloxacin (N=133)	Cefoxitin (N=127)
Success	111 (83.5%)	117 (92.1%)
Failure	22 (16.5%)	10 (7.9%)
Trova. vs Cefot. by Success	-8.7%, 95% C.I.: -17.3%, 0%	

Tables 146.4A and 146.4B show clinical responses of the clinically evaluable subjects except those

receiving bicitra at hospital discharge and EOS, respectively. Confidence interval results show that the two treatment groups were therapeutically equivalent with respect to the success rates at hospital discharge, but not at EOS. Similar results were obtained for the clinically evaluable subjects plus subjects receiving concomitant antibiotics for distant site infection except those receiving bicitra, which are presented in Tables 146.5A and 146.5B.

TABLE 146.4A: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT HOSPITAL DISCHARGE		
Clinical Response	Trovafloxacin (N=103)	Cefoxitin (N=97)
Success Failure	99 (96.1%) 4 (3.9%)	93 (95.9%) 4 (41.%)
Trova. vs Cefot. by Success	0.2%, 95% C.I.: -6.2%, 6.7%	

TABLE 146.4B: STUDY 154-128: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT EOS		
Clinical Response	Trovafloxacin (N=103)	Cefoxitin (N=97)
Success Failure	91 (88.3%) 12 (11.7%)	88 (90.7%) 9 (9.3%)
Trova. vs Cefot. by Success	-2.4%, 95% C.I.: -11.8%, 7.1%	

TABLE 146.5A: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT HOSPITAL DISCHARGE		
Clinical Response	Trovafloxacin (N=131)	Cefoxitin (N=130)
Success Failure	123 (93.9%) 8 (6.1%)	126 (96.9%) 4 (3.1%)
Trova. vs Cefot. by Success	-3.0%, 95% C.I.: -8.9%, 2.8%	

TABLE 146.5B: STUDY 154-146: CLINICAL RESPONSE OF THE APPLICANT CLINICALLY EVALUABLE SUBJECTS PLUS SUBJECTS RECEIVING CONCOMMITANT ANTIBIOTICS FOR DISTANT SITE INFECTION EXCLUDING SUBJECTS WHO RECEIVED BICITRA AT EOS		
Clinical Response	Trovafloxacin (N=131)	Cefoxitin (N=130)
Success Failure	112 (85.5%) 19 (14.5%)	118 (90.8%) 12 (9.2%)
Trova. vs Cefot. by Success	-5.3%, 95% C.I.: -13.9%, 3.3%	

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 146.6. Trovafloxacin was not significantly different from cefoxitin with respect these safety variables.*

TABLE 146.6: STUDY 154-146: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Trovafloxacin (N=188)	Cefoxitin (N=175)	Fisher's P-value
At Least One AE	114/188 (60.6%)	97/175 (55.4%)	0.339
CENTRAL AND PERIPHERAL NERVOUS	15 (8.0%)	13 (7.4%)	1.000
Dizziness	6 (3.2%)	4 (2.3%)	0.752
Headache	8 (4.3%)	8 (4.6%)	1.000
At Least One Treatment Related AE	0/188 (0%)	2/175 (1.1%)	0.232
Discontinuations Due to an AE	1/188 (0.5%)	0/175 (0%)	1.000
Clinically Significant Lab Abnormalities	110/179 (61.5%)	95/172 (55.2%)	0.279

No subject in either treatment group died during this study. Twenty-six (14%) subjects in the trovafloxacin group and 10 (6%) in the cefoxitin group had serious adverse events during this study. All were considered by the investigator to be unrelated to study drug.

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