Fogarty

STATISTICAL REVIEW AND EVALUATION

NOV 29 1997

NDA#: 20-759 and 20-760

Name of Drug: TROVAN® tablets (trovafloxacin mesylate) and TROVAN® I.V. (alatrofloxacin mesylate injection)

Applicant: Pfizer Central Research, Medical Research Laboratory

Indication(s): 17 total, the following 6 by this reviewer:
(1) nosocomial pneumonia,
(2) community acquired pneumonia,
(3) acute exacerbation of chronic bronchitis,
(4) acute sinusitis,
(5) uncomplicated skin and skin structure infections, &
(6) complicated skin and skin structure infections.
(b)(4) [redacted]

The statistical review of the remaining nine indications was completed by Joel Jiang, Ph.D.

Documents Reviewed: Volumes 1.1 through 1.9 and electronic submission.

Review Type: Clinical.

Statistical Reviewer: Nancy Paul Silliman, Ph.D., HFD-725

Medical Officers: Regina Alivisatos, MD, Philip Coyne, MD, and Rigoberto Roca, MD, HFD-590

Project Manager: Pauline Fogarty, HFD-590

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Reviewer's Note: Much of the following is taken directly from the sponsor's electronic submission. Reviewer comments and analyses will either be given in italics or distinguished as such (e.g., by table headings which indicate "FDA" or "Medical Officer" populations and/or analyses).

The following abbreviations are used throughout this document:
EOT = End of Treatment visit
EOS = End of Study visit
MO = (Reviewing) Medical Officer
ITT = Intent-to-Treat (analysis or population)
CI = confidence interval.

I. INTRODUCTION

Clinical Program

The clinical program was designed to support a claim of effectiveness for (a) oral trovafloxacin 100 or 200 mg once daily, (b) intravenous (IV) alatrofloxacin equivalent to 200 mg trovafloxacin (single dose), or (c) IV alatrofloxacin equivalent to 200 or 300 mg trovafloxacin once daily followed by oral trovafloxacin 200 mg once daily (IV-to-oral regimen) in the treatment of the following conditions:

- respiratory tract infections, including acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, nosocomial pneumonia, and acute sinusitis;
- surgical infections including complicated intra-abdominal infections and acute gynecologic and pelvic infections;
- pelvic inflammatory disease;
- skin and skin structure infections, uncomplicated and complicated (including diabetic foot infections);
- urinary tract infections (UTI), uncomplicated [redacted]
- bacterial prostatitis;
- sexually transmitted diseases, including acute, uncomplicated gonorrhea and nongonococcal urethritis/cervicitis;
- [redacted]
- prophylaxis of infection associated with elective surgical procedures, including colorectal surgery, vaginal and abdominal hysterectomy.

The clinical program included 45 Phase I studies of oral trovafloxacin or IV alatrofloxacin. These studies examined the pharmacokinetics, bioavailability and bioequivalence, food and drug interactions, pharmacokinetic characteristics in special patient populations, and safety

issues associated with quinolone compounds, as well as tissue concentrations of trovafloxacin after administration of trovafloxacin or alatrofloxacin.

The Phase II/III clinical program included 33 studies which assessed the efficacy and safety of oral trovafloxacin, IV alatrofloxacin, or the IV-to-oral regimen for the indications described above as follows:

Table 1a. Clinical Studies

Indication	Protocol Numbers of Studies
Community-acquired pneumonia	154-102, 154-110, 154-111, 154-112, 154-134
Nosocomial pneumonia	154-113, 154-137
Acute bacterial exacerbation of chronic bronchitis	154-101, 154-109, 154-141
Acute sinusitis	154-114, 154-115, 154-138
Complicated intra-abdominal infection	154-124
Acute pelvic infection	154-144
Pelvic inflammatory disease	154-122, 154-125
Uncomplicated skin and skin structure infection	154-129, 154-130
Complicated skin and skin structure infection	154-131, 154-132, 154-139
Prostatitis	154-119
Surgical prophylaxis, elective colo-rectal surgery	154-128
Surgical prophylaxis, elective hysterectomy	154-146

Table 1b. Bacteriological Studies

Indication	Protocol Numbers of Studies
Uncomplicated UTI	154-103, 154-116
Sexually transmitted disease, chlamydia	154-105, 154-123
Sexually transmitted disease, gonorrhea	154-120

Clinical efficacy and safety data are presented for four additional studies: one supportive study of gonorrheal infection (154-107), one supportive study of acute bacterial exacerbation of chronic bronchitis (154-108) and one study of *Helicobacter pylori* infection (154-106). No claims of efficacy are made in this submission relative to these four studies.

Reviewer's Note: Nineteen studies are reviewed here: the eighteen studies listed in Table 1 above for the six specific indications assigned to this reviewer (nosocomial pneumonia, community acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinusitis, uncomplicated skin and skin structure infections, & complicated skin and skin structure infections), plus the one additional supportive study of acute bacterial exacerbation of chronic bronchitis (154-108).

The number of subjects evaluated for each indication is summarized for the oral trovafloxacin trials in Table 1c below.

Table 1c. Number of Subjects Treated in Phase II/III Clinical Development Program by Indication: Oral Trovafloxacin Trials

Indication	All Trovafloxacin[a]	Trovafloxacin 100 mg	Trovafloxacin 200 mg	Oral Comparators
Acute bacterial exacerbation of chronic bronchitis	768	559	134	530
Community-acquired pneumonia	430	0	378	379
Sinusitis	662	0	662	423
Urinary tract infection (UTI)	510	436	0	253
Prostatitis	142	0	142	133
Chlamydia	619	28	554	481
Gonorrhea	350	325	14	314
Pelvic inflammatory disease	149	0	149	156
Prophylaxis: hysterectomy	188	0	188	175
Skin and skin structure infection	361	361	0	363
Diabetic foot infection	225	0	225	0
Complicated skin and skin structure infection	160	0	160	156
Helicobacter pylori	39	17	10	0

a Includes 50 mg, 100 mg, 100 mg BID, 200 mg, and 300 mg oral dose regimens.

The number of subjects evaluated for each indication is summarized for the IV alatrofloxacin to oral trovafloxacin trials (adult indications only) in Table 1d below.

Table 1d. Number of Subjects Treated in Phase II/III Clinical Development Program by Indication: IV Alatrofloxacin or IV-to-oral Trials			
Indication	**Alatrofloxacin 200 mg →Trovafloxacin[a, b]**	**Alatrofloxacin 300 mg →Trovafloxacin[a]**	**IV → Oral Comparators**
Community-acquired pneumonia	411	0	422
Nosocomial pneumonia	0	262	277
Pelvic inflammatory disease	79	0	79
Abdominal infection	0	201	207
Acute pelvic infection	0	160	157
Prophylaxis: colo-rectal surgery	256	0	236
Complicated skin and skin structure infection	144	0	142
a Trovafloxacin dose was 200 mg for both IV-to-oral regimens. b Includes 200 mg alatrofloxacin single dose IV (no oral component) from study number 154-128.			

Efficacy

In general, subjects were required to have clinical signs and/or symptoms of bacterial infection prior to treatment along with bacteriological assessment of infection as appropriate. Bacteriologic evaluation was not required in two of the three acute sinusitis studies (154-115, 154-138). Subjects were evaluated at baseline, at the end of treatment, and at a follow-up visit or end of study visit. Assessments included clinical examinations, collection of samples for bacteriologic/serologic evaluation, and/or radiologic examinations as specified in the study protocol. The clinical response of each subject was assessed by the investigator. The sponsor then evaluated the clinical outcomes, primarily based on the investigator's assessments but also taking into account conditions that superseded the investigator's assessment such as administration of concomitant antibiotics. Both the investigator's original assessments and the sponsor-defined clinical outcomes are presented for each study.

Reviewer's Note: Results corresponding to sponsor-defined outcomes are presented in this review. Sponsor-defined outcomes tended to be more conservative than the investigators' original assessments. Results will be presented for the investigators' original assessments only if they differ substantially from those corresponding to sponsor-defined outcomes.

The analyses of efficacy were based on the sponsor's assessment of subject clinical response (success [cure or improvement] or failure) and/or subject bacteriological response (eradication, presumed eradication, persistence, or presumed persistence) or pathogen eradication rate. Generally, clinical response was classified as:

1 Cure - Resolution of all signs and symptoms to the level that existed before baseline.

2 Improvement - Incomplete resolution of signs and symptoms.

3 Failure - Lack of resolution or progression of any of the signs and symptoms and other indication specific rules such as taking a concomitant antibiotic for insufficient response or carrying forward a previous failure.

and clinical success rates were calculated as:

$$\text{Success Rate} = \frac{\text{Number of Cures and Improvements}}{\text{Number of patients in subset}}$$

For most indications, there were three categories for pathogen outcomes:

1 Eradication - Baseline organism is absent.
2 Persistence - Baseline organism is present.
3 Presumed Persistence - Included indication specific rules such as taking a concomitant antibiotic for insufficient response or in the absence of adequate culture material, a clinical response of failure.

In addition, for some of the indications, there was a fourth category:

4 Presumed Eradication - In the absence of adequate culture material, clinical response was a cure or improvement.

Eradication rates were calculated as:

$$\text{Pathogen Eradication Rate} = \frac{\text{Number of patients with baseline pathogens with outcomes of Eradication and Presumptive Eradication}}{\text{Number of patients in subset with the baseline pathogen identified}}$$

For all of the adult treatment studies, analyses were performed for both intent-to-treat (ITT) and evaluable subject groups. For all indications except sexually transmitted diseases, the clinical ITT subject group included all randomized subjects who had a baseline diagnosis of the condition under study regardless of whether study medication was received. The bacteriologic ITT subject group included all subjects in the clinical ITT subset who had at least one pathogen identified at baseline or, in the case of the UTI studies, all clinical ITT subjects who met disease-specific criteria for bacteriologic diagnoses. The clinically evaluable and bacteriologically evaluable subject groups included subjects in the respective ITT subsets who received study medication unless one or more of the criteria in Table 1e applied.

Table 1e. Evaluability Criteria

Clinical Evaluable Group

	Indications	
Criteria	Respiratory	Skin
Insufficient Therapy	✓	✓
Antibiotic Prior to Baseline for > 24 hours	✓	✓
Concomitant Antibiotic for Intercurrent Illness	✓	✓
Intercurrent Illness	✓	✓
Post-Baseline Clinical Assessment Not in Evaluable Window	✓	✓
Less than 80% compliant - Phase II Only (a)	✓	
Lost to Follow-Up - Phase II Only (a)	✓	

(a) protocols 101 and 102 ✓ = evaluability criteria applies

Bacteriological Evaluable Group

	Indications	
Criteria	Respiratory	Skin
Baseline Culture Not in Window	✓	✓
Post-Baseline Culture Not in Evaluable Window	✓	✓

✓ = evaluability criteria applies

For the analysis of the clinical intent-to-treat group, a 'last observation carried forward' strategy was used for subjects who were lost to follow-up before the End of Study visit. If, for any reason, no clinical assessment was made at the End of Treatment visit, but an assessment was made at the End of Study visit, the End of Treatment assessment was treated as missing data.

Reviewer's Note: We usually do not recommend carrying forward successes when patients are lost to follow-up. All patients lost to follow-up are usually treated as failures in the ITT analysis. However, since the ITT population is not of primary interest here, due to the fact that all of the controlled trials reviewed in this submission use an active control arm instead of placebo, this difference in "estimating" missing data is not of great concern.

Results are presented in this review for the evaluable patient groups. Results will be presented for the intent-to-treat groups only if they differ substantially from those for the evaluable groups.

Analyses were performed at the primary time point defined for each protocol and, in some cases, at secondary time points. Table 1f lists the time points and endpoints used in the clinical studies. The shaded areas of the table indicate that the time point or endpoint is primary. For example, the primary analysis for the skin studies consisted of analyzing sponsor-defined subject clinical response at the end-of-treatment.

Table 1f. Analysis Time Points and Endpoints

	Clinical Studies	
Time Points	Respiratory	Skin
Primary	EOT	EOT
Secondary	EOS	EOS
Endpoints		
Sponsor-Defined Subject Clinical Response	✓	✓
Investigator-Defined Subject Clinical Response	✓	✓
Pathogen Specific Eradication Rates	✓	✓

EOT = end of treatment visit, EOS = end of study visit
shaded area = primary time point / endpoint
Each endpoint was analyzed for every time point.
The primary analysis consisted of the combination of the primary endpoint and the primary time point.

The End of Treatment (EOT) and End of Study (EOS) windows for the evaluable and intent-to-treat analyses were defined as shown in Table 1g.

Table 1g. Analysis Windows

		Evaluable Analysis Windows		Intent-to-treat Analysis Windows	
Indication	**Protocol**	**End of Treatment**	**End of Study**	**End of Treatment**	**End of Study**
Sinusitis	114	3 to 18	19 to 40	1 to 18	19 to 45
	115	5 to 21	22 to 40	1 to 21	22 to 45
	138	5 to 18	19 to 40	1 to 18	19 to 45
Bronchitis	101	9 to 15	21 to 35	9 to 15	16 to 45
	All Others	3 to 18	19 to 40	1 to 18	19 to 45
CAP	All	5 to 20	21 to 40	1 to 20	21 to 45
NOS	All	7 to 20	21 to 40	1 to 20	21 to 45
Skin	All	5 to 20	21 to 40	2 to 20	21 to 41

Statistical Methods: Comparative Studies

The objective of each comparative study was to demonstrate that trovafloxacin, or alatrofloxacin followed by trovafloxacin, is "equivalent" to the comparative therapy. The definition of equivalence used in all trials was that suggested by the Division of Anti-Infective Drug Products in their "Points to Consider" guidance document. For example, assuming the primary clinical or microbiological effectiveness rate of the reference drug is 90%, the number of subjects for each treatment group required to ensure with 80% probability that the lower limit of the 95% confidence interval for the true difference in efficacy does not fall below -10% is 142 subjects per treatment group. If 10% of the subjects are expected to be non-evaluable then 158 subjects per group are required to protect the power of the study. The calculations are based on Makuch and Simon, Cancer Treatment Reports, Vol. 62, no. 7, July 1978, pp. 1037-1040 (modified to account for the 2-sided confidence interval).

The primary analysis for determination of equivalence of treatment groups was based on 95% confidence intervals (CI) for each pairwise difference in success rates (cure/improvement vs. failure) or eradication rates (eradication vs. persistence) between treatments. The calculation of CI was based on the normal approximation to the binomial distribution with no correction for continuity.

Reviewer's Note: Confidence intervals presented for FDA analyses will be produced by this reviewer using the normal approximation to the binomial distribution incorporating the correction for continuity.

Success rates or eradication rates between treatment groups were also compared by 1 degree of freedom (d.f.) chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment to account for investigator differences.

The distribution of clinical cures, successes, and failures among treatment groups was compared by a chi-squared test of general association using the Cochran-Mantel-Haenszel adjustment to account for investigator differences. For the End of Study analysis, the categories of failure and relapse were collapsed into one category: failure.

Investigators with fewer than five evaluable subjects per treatment arm were pooled together (within country) until one or more investigator 'group(s)' were formed with at least five evaluable subjects per treatment arm. For the intent-to-treat analyses, any investigator with no evaluable subjects was randomly assigned to an existing investigator group. Pooling of small centers was based on the primary patient subset only, which, for example, would be the clinically evaluable subset for studies where the clinical endpoint was primary.

Reviewer's Note: Since all of the comparative trials reviewed here are active-controlled trials (i.e., the comparator is another drug, not a placebo), the Cochran-Mantel-Haenszel (CMH) test is inappropriate and results are not presented in this review. The CMH test assumes that outcome rates in the two treatment groups are equal and then attempts to show otherwise. Failure to show a significant difference, however, does not then imply that outcome rates are, in fact, similar in the two treatment groups.

For pathogen eradication rate, no inferential statistics were presented if fewer than 15 subjects per treatment group had a particular baseline pathogen.

The baseline comparability of the treatment groups in the primary intent-to-treat subjects and primary evaluable subjects subsets was assessed by examining the age, gender, weight (within gender), race and disease characteristics of the subjects at baseline. If applicable, other risk factors such as duration of baseline condition and tobacco use was also compared among the treatment groups. Only descriptive statistics were used to compare baseline characteristics of the treatment groups. No inferential statistics were presented.

Safety

All treated subjects were included in the analysis of safety. Safety analyses included summaries of the incidence and severity of adverse events, the proportions of subjects who prematurely discontinued treatment or study, and the incidence of clinically significant laboratory abnormalities. Serious adverse events, including deaths, which occurred within 30 days after the last dose of study medication were summarized separately. Safety data were also analyzed by demographic subsets, including age, race, and gender.

Adverse events (excluding objective test findings) were summarized by body system and by severity. Three separate summaries included adverse events (all causality), adverse events determined by the investigator to be treatment related, and treatment emergent signs and symptoms (TESS). Assessment of relationship to treatment and TESS were independent of each other.

An adverse event was defined as a sign or symptom, intercurrent illness, or clinically important test abnormality that occurred during the trial. The analyses of adverse events are based on the investigators' assessments of severity and relationship to study drug. Adverse events classified by the sponsor as treatment-related include those considered by the investigator to be related or possibly related to study drug as well as those with unknown relationship and those for which no comment regarding causality was made. All adverse events occurring either during study drug treatment or within 7 days after the end of treatment were included in analysis.

The analysis of clinical laboratory abnormalities includes clinical laboratory tests performed during treatment and up to 7 days after the end of treatment. In order to be included in the analysis of clinical laboratory data, a subject must have had at least one post-baseline value, either during treatment or during the 7-day post-treatment period. For all clinical laboratory tests, post-treatment values were assessed according to one or two criteria for clinical significance depending on whether the test value was normal (Criteria 1) or abnormal (Criteria 1 and 2) at baseline. *Reviewer's Note: Please refer to the MO's review for a definition of these criteria.*

No statistical inference was made for any summary of adverse events.

Reviewer's Note: During the course of this review, it became obvious that dizziness is one of the more common adverse events associated with the use of alatrofloxacin/trovafloxacin. In fact, in seven of the seventeen controlled trials reviewed here, the rate of dizziness was significantly higher in the alatrofloxacin/trovafloxacin arm than in the comparator arm.

The number and percent of patients experiencing dizziness ("all causalities", i.e., regardless of whether the investigator considered the dizziness to be treatment related or not) is summarized in the following table by treatment arm and protocol for the indications covered by this review.

Number and Percent of Patients Experiencing Dizziness by Treatment Arm and Protocol

Indication	Protocol	Trovan Dose: n (%)	Comparator Drug: n (%)
Sinusitis	154-114	200 mg: 51 (20%)	N/A
	154-115*	200 mg: 69 (34%)	Clarithromycin: 5 (2%)
	154-138*	200 mg: 34 (17%)	Amoxicillin/Clavulanate: 2 (<1%)
Bronchitis	154-101*	100 mg: 4 (5%) 300 mg: 30 (40%)	Ofloxacin: 7 (10%)
	154-109	100 mg: 12 (6%)	Clarithromycin: 6 (3%)
	154-141	100 mg: 5 (4%)	Ciprofloxacin: 7 (6%)
Community-Acquired Pneumonia	154-102*	200 mg: 2 (4%) 300 mg: 16 (31%)	Cefaclor: 3 (6%)
	154-110	200 mg: 12 (6%)	Ciprofloxacin: 3 (2%)
	154-111*	200 mg: 21 (10%)	Ceftriaxone: 3 (1%)
	154-112	200 mg: 6 (4%)	Amoxicillin: 2 (1%)
	154-134*	200 mg: 24 (13%)	Clarithromycin: 8 (4%)
Nosocomial Pneumonia	154-113	300IV/200PO: 5 (4%)	Ciprofloxacin: 2 (1%)
	154-137	300IV/200PO: (<3%)	Ceftazidime/Ciprofloxacin: (<3%)
Uncomplicated Skin	154-129	100 mg: 4 (3%)	Flucloxacillin: 1 (<1%)
	154-130	100 mg: 9 (4%)	Vantin: 6 (3%)
Complicated Skin	154-131	200 mg: (<5%)	Zosyn/Vantin: (<5%)
	154-132	200 mg: 20 (9%)	N/A
	154-139*	200 mg: 12 (8%)	Augmentin: 1 (<1%)

n = number of patients experiencing dizziness
N/A = not applicable (i.e., no comparator arm)
*Difference in rates was statistically significant ($p<0.05$ using Fisher's exact test) and observed rates were higher in the trovafloxacin arm; for protocols 154-101 and 154-102, only the comparison between the 300 mg trovafloxacin arm and the comparator was significant.

II. NOSOCOMIAL PNEUMONIA

The efficacy and safety of the IV-to-oral regimen in the treatment of nosocomial pneumonia was assessed in two comparative trials, one double-blind (154-113) and one open-label (154-137). The comparator regimens were ciprofloxacin (IV-to-oral; 154-113) and IV ceftazidime followed by oral ciprofloxacin (154-137).

Reviewer's Note: The sponsor assessed whether efficacy differed in various subgroups in the nosocomial pneumonia trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, and race. A trend towards a lower clinical response rate was observed in elderly subjects (≥75 years of age versus subjects <75 years of age) in both the trovafloxacin and comparator treatment groups at EOT and EOS.

II.A. Protocol 154-113

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CIPROFLOXACIN FOLLOWED BY ORAL CIPROFLOXACIN FOR THE TREATMENT OF NOSOCOMIAL PNEUMONIA.

Study Dates: 3 February 1995 - 13 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin (with optional aztreonam and/or vancomycin) compared to intravenous ciprofloxacin followed by oral ciprofloxacin (with optional aztreonam, vancomycin, clindamycin, and/or metronidazole) for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

Reviewer's Note: Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional aztreonam or vancomycin to treat documented Pseudomonas infection or methicillin-resistant S. aureus, respectively, if approved it will need to be labeled this way.

Study Design: Study 154-113 was a randomized, multicenter, double-blind trial of alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment versus intravenous ciprofloxacin (1500 mg daily administered as 750 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (800 mg daily administered as 400 mg twice daily) to complete 10 to 14 days of total treatment for the treatment of nosocomial pneumonia requiring initial intravenous therapy. In addition, in subjects with documented *Pseudomonas* infection or methicillin-resistant *S. aureus*, aztreonam or vancomycin, respectively, may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added in blinded fashion to the ciprofloxacin treatment regimen.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥18 years of age at the baseline assessment, with clinically and radiologically documented nosocomial pneumonia requiring initial intravenous therapy were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) 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. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of pneumonia to the baseline level that existed prior to the occurrence of pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of pneumonia and a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

<u>Reviewer's Note:</u> The reviewing medical officer, Dr. Regina Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Sponsor Efficacy Results:

Analysis Groups

Table 2a.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Reviewer's Note: Somewhat fewer trovafloxacin patients completed treatment and were considered clinically evaluable, however these differences were not statistically significant (p=0.08 and 0.28, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 2a.1. Evaluation Groups

Evaluation Groups[a]:	Alatrofloxacin ↓ Trovafloxacin		Ciprofloxacin ↓ Ciprofloxacin	
Randomized	129		138	
All Treated	127	(100%)	137	(100%)
Completed Treatment	74	(58%)	94	(69%)
Completed Study	86	(68%)	90	(66%)
Evaluated for Efficacy[b]				
Clinical Intent-to-Treat	127	(98%)	135	(98%)
Clinically Evaluable[c]	88	(68%)	103	(75%)
Bacteriologically Intent-to-Treat	71	(55%)	68	(49%)
Bacteriologically Evaluable	47	(36%)	52	(38%)
Assessed for Safety[d]				
Adverse Events	127	(100%)	137	(100%)
Laboratory Tests	115	(91%)	126	(92%)

a The daily dose of alatrofloxacin was 300 mg and that of trovafloxacin was 200 mg. The daily dose of oral ciprofloxacin was 800 mg (400 mg administered twice daily) and the daily dose of intravenous ciprofloxacin was 1500 mg (750 mg administered twice daily).
b Percentages based on number of randomized subjects.
c Based on End of Treatment assessment.
d Percentages based on number of all treated subjects.

Of the 129 alatrofloxacin/trovafloxacin and 138 ciprofloxacin randomized subjects, two alatrofloxacin/trovafloxacin subjects and three ciprofloxacin subjects had an inappropriate baseline diagnosis (i.e., no clinical signs and symptoms of nosocomial pneumonia at baseline as defined by protocol) and were excluded from all intent-to-treat and evaluable analyses.

Of the 127 alatrofloxacin/trovafloxacin and 135 ciprofloxacin clinically ITT subjects, 39 in the alatrofloxacin/trovafloxacin group and 32 in the ciprofloxacin/ ciprofloxacin group were not clinically evaluable; therefore, 88 subjects in the alatrofloxacin/trovafloxacin group and 103 subjects in the ciprofloxacin group were clinically evaluable. The most common reasons for exclusion from clinical efficacy analyses were no post-baseline clinical assessments (20/129 [16%], alatrofloxacin/trovafloxacin and 16/138 [12%], ciprofloxacin), no post-baseline clinical assessments in evaluable window (20/129 [16%], alatrofloxacin/trovafloxacin and 16/138 [12%], ciprofloxacin) and insufficient therapy due to early discontinuation from treatment or study (27/129 [21%], alatrofloxacin/trovafloxacin and 23/138 [17%], ciprofloxacin). Other

reasons were randomized but not treated, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, and inappropriate use of optional study antibiotics against baseline pathogens.

Of the 127 alatrofloxacin/trovafloxacin and 135 ciprofloxacin clinically ITT subjects, 56 subjects in the alatrofloxacin/trovafloxacin group and 67 subjects in the ciprofloxacin group had negative baseline cultures; therefore, 71 subjects in the alatrofloxacin/trovafloxacin group and 68 subjects in the ciprofloxacin/ ciprofloxacin group were included in the bacteriological ITT analysis.

Of the 88 alatrofloxacin/trovafloxacin and 103 ciprofloxacin clinically evaluable subjects, 41 subjects in the alatrofloxacin/trovafloxacin group and 51 subjects in the ciprofloxacin group were not included in the bacteriologically evaluable analyses; therefore, 47 subjects in the alatrofloxacin/trovafloxacin group and 52 subjects in the ciprofloxacin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (41/129 [32%], alatrofloxacin/trovafloxacin and 51/138 [37%], ciprofloxacin). The other reason was no post-baseline cultures (the subjects [Subject 5175-0719, alatrofloxacin/trovafloxacin; Subject 5407-0349, ciprofloxacin] excluded for this reason had no baseline pathogen). (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 127 alatrofloxacin/trovafloxacin and 137 ciprofloxacin treated subjects, 53 alatrofloxacin/trovafloxacin and 43 ciprofloxacin subjects were prematurely discontinued from treatment as summarized in Table 2a.2.

Table 2a.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=137)	
	Number and Percentage (%) of Subjects			
Total Discontinued	53	(42%)	43	(31%)
Discontinuations Related to Study Drug:	17	(13%)	9	(7%)
Adverse Event	5	(4%)	0	
Insufficient Response	11	(9%)	8	(6%)
Laboratory Abnormality	1	(<1%)	1	(<1%)
Discontinuations Unrelated to Study Drug:	36	(28%)	34	(25%)
Adverse Event	6	(5%)	8	(6%)
Lost to Follow-up	0		1	(<1%)
Other	15	(12%)	12	(9%)
Subject Died	12	(9%)	10	(7%)
Protocol Violation	1	(<1%)	2	(1%)
Withdrawn Consent	2	(2%)	1	(<1%)

Demographics

Seventy-eight (78) of the 127 treated alatrofloxacin/trovafloxacin subjects (61%) were male and 49 (39%) were female and 76 of the 137 treated ciprofloxacin subjects (55%) were male and 61 (45%) were female. Treated subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups were generally comparable with respect to age, race, and weight. The distribution of treated subjects according to smoking classification was also similar between the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups (38% and 39% ex-smoker, 42% and 40% never smoked, and 20% and 21% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinically intent-to-treat subjects was nosocomial-acquired pneumonia. The median duration (range) since onset of pneumonia was 2 days (1-13 days) for subjects in the alatrofloxacin/trovafloxacin group and 2 days (1-12 days) for subjects in the ciprofloxacin group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups with respect to medical history at baseline.

Of clinically evaluable subjects, 29 in the alatrofloxacin/trovafloxacin group (33%) and 35 in the ciprofloxacin group (34%) required high fractional oxygen and/or mechanical ventilation at baseline. The mean APACHE II score at baseline for clinically evaluable subjects in both treatment groups was 13.09. Similar results were noted for clinically intent-to-treat subjects.

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 2a.3.
Alatrofloxacin/trovafloxacin was considered therapeutically equivalent to ciprofloxacin at both EOT and EOS.

Table 2a.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=88)		Ciprofloxacin ↓ Ciprofloxacin (N=103)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	88	(100%)	101	(100%)	
Success (Cure + Improvement)	68	(77%)	79	(78%)	(-12.8%, 10.9%)
Distribution of Clinical Response:					
Cure	42	(48%)	51	(50%)	
Improvement	26	(30%)	28	(28%)	
Failure	20	(23%)	22	(22%)	
End of Study:					
Number of Subjects Assessed	72	(100%)	79	(100%)	
Success (Cure + Improvement)	50	(69%)	54	(68%)	(-13.7%, 15.9%)
Distribution of Clinical Response:					
Cure	42	(58%)	53	(67%)	
Improvement	8	(11%)	1	(1%)	
Failure	20	(28%)	22	(28%)	
Relapse	2	(3%)	3	(4%)	

The number of clinically evaluable subjects with mild/moderate and severe nosocomial pneumonia at baseline was similar between the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups (mild/moderate pneumonia at baseline: 59 and 68 subjects, respectively; severe pneumonia at baseline : 29 and 35 subjects, respectively). Subjects were defined as having severe nosocomial pneumonia if they required mechanical ventilation or a fractional inspired oxygen concentration ≥0.35 to maintain an arterial oxygen tension of 60 mmHg.

Sponsor-defined clinical success rates (cure + improvement) were comparable for clinically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin treatment groups at EOT (49/59, 83% and 56/66, 85%, respectively) and at EOS (39/51, 76% and 40/53, 75%, respectively) for subjects with mild/moderate pneumonia at baseline and for subjects with severe pneumonia at baseline (EOT: 19/29, 66% and 23/35, 66%; EOS: 11/21, 52% and 14/26, 54%, respectively).

A summary of clinical success rates at the end of treatment and the end of study for the most frequently isolated baseline pathogens among clinically evaluable subjects is presented by treatment group in Table 2a.4.

Table 2a.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens[a] (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=47)	Ciprofloxacin ↓ Ciprofloxacin (N=52)	Alatrofloxacin ↓ Trovafloxacin (N=39)	Ciprofloxacin ↓ Ciprofloxacin (N=38)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
P. aeruginosa	10/15 (67%)	6/11	8/13	2/8
S. aureus	7/11	8/10	4/8	4/6
H. influenzae	7/8	8/9	5/6	6/7
E. coli	5/7	4/5	3/6	4/5
S. pneumoniae	2/4	5/6	2/4	3/4
K. pneumoniae	3/4	3/7	2/4	1/5
H. parainfluenzae	5/5	2/3	5/5	1/2

a Includes ≥5 isolates of a given pathogen in either treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at the end of treatment and at the end of study for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 2a.5.

Table 2a.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens[a] (Bacteriologically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=47)	Ciprofloxacin ↓ Ciprofloxacin (N=52)	Alatrofloxacin ↓ Trovafloxacin (N=39)	Ciprofloxacin ↓ Ciprofloxacin (N=38)
	Number and Percentage (%) of Pathogens			
Pathogen	End of Treatment		End of Study	
P. aeruginosa	9/15 (60%)	3/11	10/13	2/8
S. aureus	6/11	6/9	3/8	4/6
H. influenzae	7/8	9/9	5/6	7/7
E. coli	4/6	5/5	3/4	5/5
S. pneumoniae	2/4	6/6	2/4	4/4
K. pneumoniae	2/4	3/7	2/4	1/4
H. parainfluenzae	5/5	2/3	5/5	1/2

a Includes ≥5 isolates of a given pathogen in either treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

MO Efficacy Results: *The medical officer reassessed patients' evaluability and clinical outcome status. Table 2a.6 presents clinical response for the MO clinically evaluable patient group at EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, alatrofloxacin/trovafloxacin was considered therapeutically equivalent to ciprofloxacin at both EOT and EOS.*

Table 2a.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin	Ciprofloxacin ↓ Ciprofloxacin	95% CI
	Number and Percentage (%) of Subjects		
End of Treatment:			
Number of Subjects Assessed	70 (100%)	76 (100%)	
Success (Cure + Improvement)	50 (71%)	54 (70%)	(-15.7, 16.4)
End of Study:			
Number of Subjects Assessed	70 (100%)	77 (100%)	
Success (Cure + Improvement)	48 (69%)	52 (68%)	(-15.4, 17.5)

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation from treatment due to adverse events and clinically significant laboratory values is presented in Table 2a.7. Tables 2a.8 and 2a.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced adverse events (all causalities) and discontinued treatment due to adverse events ($p<0.001$ and $p=0.047$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 2a.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Alatrofloxacin ↓ Trovafloxacin	Ciprofloxacin ↓ Ciprofloxacin
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	121/127 (95%)	111/137 (81%)
Treatment-Related Adverse Events	28/127 (22%)	23/137 (17%)
Discontinuations From Treatment Due to an Adverse Event	19/127 (15%)	10/137 (7%)
Discontinuations From Treatment Due to a Treatment-Related Adverse Event	5/127 (4%)	0
Clinically Significant Laboratory Values	90/115 (78%)	98/126 (78%)

Table 2a.8. Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causality (All Treated Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=137)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	121	(95%)	111	(81%)
BODY SYSTEM WHO Term				
APPL./INJ./INCISION/INSERTION SITE	29	(23%)	24	(18%)
Appl./Inj./Incision/Insertion Site Infection/Inflammation	5	(4%)	8	(6%)
Appl./Inj./Incision/Insertion Site Pain	3	(2%)	5	(4%)
Appl./Inj./Incision/Insertion Site Reaction	11	(9%)	8	(6%)
Appl./Inj./Incision/Insertion/Device Complication	13	(10%)	11	(8%)
CARDIOVASCULAR	47	(37%)	42	(31%)
Cardiac Arrest	5	(4%)	6	(4%)
Cardiac Failure	6	(5%)	3	(2%)
Circulatory Failure	5	(4%)	6	(4%)
Edema Peripheral	8	(6%)	4	(3%)
Hypotension	7	(6%)	1	(<1%)
Phlebitis	6	(5%)	6	(4%)
CENTRAL AND PERIPHERAL NERVOUS	30	(24%)	25	(18%)
Confusion	10	(8%)	7	(5%)
Dizziness	5	(4%)	2	(1%)
Headache	10	(8%)	8	(6%)
GASTROINTESTINAL	61	(48%)	47	(34%)
Abdominal Pain	5	(4%)	2	(1%)
Constipation	15	(12%)	9	(7%)
Diarrhea	15	(12%)	12	(9%)
Nausea	16	(13%)	11	(8%)
Vomiting	19	(15%)	12	(9%)
GENERAL	30	(24%)	32	(23%)
Fever	3	(2%)	9	(7%)
Moniliasis	3	(2%)	6	(4%)
Pain	5	(4%)	2	(1%)
Sepsis	9	(7%)	5	(4%)
HEMATOPOIETIC	8	(6%)	2	(1%)
Purpura	5	(4%)	2	(1%)
OTHER ADVERSE EVENTS	9	(7%)	8	(6%)
Accidental Injury	7	(6%)	3	(2%)
PSYCHIATRIC	26	(20%)	20	(15%)
Agitation	8	(6%)	5	(4%)
Anxiety	6	(5%)	2	(1%)
Insomnia	3	(2%)	9	(7%)
RESPIRATORY	43	(34%)	47	(34%)
Aspiration	5	(4%)	3	(2%)
Dyspnea	7	(6%)	9	(7%)
Pleural Effusion	4	(3%)	6	(4%)
Pneumonia	7	(6%)	13	(9%)
Respiratory Insufficiency	11	(9%)	5	(4%)
SKIN/APPENDAGES	26	(20%)	30	(22%)
Rash	5	(4%)	11	(8%)
Rash Erythematous	7	(6%)	6	(4%)
Skin Disorder	6	(5%)	5	(4%)
URINARY SYSTEM	19	(15%)	13	(9%)
Urinary Tract Infection	9	(7%)	4	(3%)

a ≥4% of subjects in either treatment group.
b Includes data up to 7 days after last dose of active study medication

Table 2a.9. Summary of the Most Commonly Reported Treatment-Related Adverse Events[a,b] by Body System (All Treated Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=127)		Ciprofloxacin ↓ Ciprofloxacin (N=137)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	28	(22%)	23	(17%)
BODY SYSTEM WHO Term				
APPL./INJ./INCISION/INSERTION SITE	6	(5%)	7	(5%)
Appl./Inj./Incision/Insertion Site Reaction	4	(3%)	3	(2%)
Appl./Inj./Incision/Insertion/Device Complication	2	(2%)	1	(<1%)
CARDIOVASCULAR	5	(4%)	2	(1%)
Phlebitis	5	(4%)	2	(1%)
CENTRAL AND PERIPHERAL NERVOUS	4	(3%)	2	(1%)
Headache	2	(2%)	1	(<1%)
GASTROINTESTINAL	11	(9%)	6	(4%)
Diarrhea	2	(2%)	2	(1%)
Nausea	6	(5%)	1	(<1%)
Vomiting	2	(2%)	1	(<1%)
GENERAL	4	(3%)	3	(2%)
Moniliasis	3	(2%)	3	(2%)
REPRODUCTIVE	1	(<1%)	0	
Vaginitis	1	(2%)	0	
RESPIRATORY	0		6	(4%)
Respiratory Tract Infection	0		4	(3%)

a ≥2% of subjects in either treatment group.
b Includes data up to 7 days after last dose of active study medication.

- Thirty-five (35) subjects in the alatrofloxacin/trovafloxacin group and 38 subjects in the ciprofloxacin group died during this study, as follows:

- Six (6) subjects in the alatrofloxacin/trovafloxacin group and 6 subjects in the ciprofloxacin died while receiving therapy. All deaths were considered by the investigator to be unrelated to study drug.

- Twenty-five (25) subjects in the alatrofloxacin/trovafloxacin and 29 subjects in the ciprofloxacin group died within 30 days after the last dose of study drug. None of these deaths was considered by the investigator to be related to study drug.

- Four (4) subjects in the alatrofloxacin/trovafloxacin group and 3 subjects in the ciprofloxacin group died >30 days after the last dose of study drug. None of these deaths was considered by the investigator to be related to study drug.

Fifty-six (56) subjects in the alatrofloxacin/trovafloxacin group and 57 subjects in the ciprofloxacin group had serious adverse events. One subject in the alatrofloxacin/trovafloxacin group had a serious adverse event (multifocal myoclonus) that was considered by the investigator to be related to study drug. All other serious adverse events were attributed to other illnesses, the disease under study, or "other" reasons.

Sponsor's Summary and Conclusion: Alatrofloxacin (300 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for a total treatment duration of 10 to 14 days and intravenous ciprofloxacin (400 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (750 mg twice daily) for a total treatment duration of 10 to 14 days were comparable for the sponsor-defined clinical success rate at the end of treatment for both intent-to-treat and evaluable subjects. Sponsor-defined pathogen eradication rates for many of the most commonly isolated pathogens were comparable among bacteriologically evaluable subjects in the alatrofloxacin/trovafloxacin and ciprofloxacin groups at the end of treatment and end of study. The percentage of subjects discontinued from treatment due to adverse events was 15% in the alatrofloxacin/trovafloxacin group and 7% in the ciprofloxacin group. Five (5) subjects in the alatrofloxacin/trovafloxacin group and no subjects in the ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all and treatment-related adverse events was 95% and 22%, respectively, for subjects in the alatrofloxacin/trovafloxacin group and 81% and 17%, respectively, for subjects in the ciprofloxacin group. The most commonly reported treatment-related adverse event was nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and respiratory tract infection (3%) for subjects in the ciprofloxacin group.

Reviewer's Summary and Conclusion: *Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ciprofloxacin at both EOT and EOS in terms of clinical success rate for clinically evaluable patients for both the sponsor and the MO analysis. Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional aztreonam or vancomycin to treat documented Pseudomonas infection or methicillin-resistant S. aureus, respectively, if approved it will need to be labeled this way.*

A significantly higher percentage of alatrofloxacin/trovafloxacin patients experienced adverse events, 95% versus 81% for ciprofloxacin patients, and discontinued treatment due to adverse events, 15% versus 7% for ciprofloxacin patients ($p<0.001$ and $p=0.047$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

II.B. Protocol 154-137

A RANDOMISED, MULTICENTRE, OPEN TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CEFTAZIDIME FOLLOWED BY ORAL CIPROFLOXACIN WITH OPTIONAL GENTAMYCIN AND VANCOMYCIN FOR THE TREATMENT OF NOSOCOMIAL PNEUMONIA.

Reviewer's Note: "Open" is used here to indicate that the trial is unblinded.

Study Dates: 6 September 1995 - 21 August 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin (with optional vancomycin) compared to intravenous ceftazidime followed by oral ciprofloxacin (with optional

vancomycin, gentamycin, clindamycin, and/or metronidazole) for the treatment of subjects with nosocomial pneumonia requiring initial intravenous therapy.

Study Design: Study 154-137 was a randomized, unblinded, comparative, multicenter trial of alatrofloxacin (300 mg once daily) administered intravenously daily for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 10 to 14 days of total treatment versus intravenous ceftazidime (4000 mg daily administered as 2000 mg twice daily) for 2 to 7 days followed by oral ciprofloxacin (1500 mg daily administered as 750 mg twice daily) to complete 10 to 14 days of total treatment for the treatment of nosocomial pneumonia requiring initial intravenous therapy. In addition, in subjects with documented methicillin-resistant *S. aureus*, vancomycin may have been added to either treatment regimen. For suspected anaerobic infections, clindamycin or metronidazole may have been added to the ceftazidime/ciprofloxacin treatment regimen. For subjects with documented *Pseudomonas* infection, gentamycin may have been added to the ceftazidime/ciprofloxacin treatment regimen. Although not specified by protocol, subjects in the alatrofloxacin/trovafloxacin group with documented *P. aeruginosa* at baseline who were subsequently treated with gentamycin were considered to be evaluable for efficacy by the sponsor.

Reviewer's Note: Since the alatrofloxacin/trovafloxacin treatment regimen was studied in combination with other drugs, namely optional gentamycin or vancomycin to treat documented Pseudomonas infection or methicillin-resistant S. aureus, respectively, if approved it will need to be labeled this way.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥18 years of age at the baseline assessment, with clinically and radiologically documented nosocomial pneumonia requiring initial intravenous therapy were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological, clinical, and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum and blood specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) 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. Clinical assessment was to be based upon resolution or improvement of radiological and clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, and improvement or resolution of dyspnea, cough, and leukocytosis, as well as improvement in general physical condition. Clinical response was to be classified by the investigator as cure (resolution of signs and symptoms of nosocomial pneumonia to the baseline level that existed prior to the occurrence of nosocomial pneumonia), improvement (resolution of fever but incomplete resolution of the other signs and symptoms of nosocomial pneumonia and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of nosocomial pneumonia or a need for additional antibiotic).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 14) and at the end of study (Visit 4; Day 30) or at the time of discontinuation from study. Bacteriologic response was to be classified by the sponsor as eradication, presumptive eradication, persistence, presumed persistence, relapse, superinfection, or colonization.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOS;
- Investigator-defined clinical response at EOT, and sponsor-defined and investigator-defined clinical response at EOS.

Reviewer's Note: The reviewing medical officer, Dr. Regina Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.

Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Sponsor Efficacy Results:

Analysis Groups

Table 2b.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Reviewer's Note: A lower percentage of alatrofloxacin/trovafloxacin patients completed treatment, were included in the bacteriological ITT analysis group, and were considered bacteriologically evaluable. None of these differences were statistically significant, however (p=0.21, 0.14, and 0.15, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).