

Discontinuations

Of the 149 treated subjects, 20 subjects were prematurely discontinued from treatment as summarized in Table 3a.2.

Table 3a.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Trovafloxacin 200 mg (N=50)	Trovafloxacin 300 mg (N=52)	Cefaclor 500 mg TID (N=47)	Total (N=149)
Number and Percentage (%) of Subjects				
Total Discontinued	2 (4%)	11 (21%)	7 (15%)	20 (13%)
Discontinuations Related to Study Drug:	1 (2%)	7 (13%)	6 (13%)	14 (9%)
Adverse Event	1 (2%)	6 (12%)	2 (4%)	9 (6%)
Insufficient Clinical Response	0	1 (2%)	3 (6%)	4 (3%)
Laboratory Abnormality	0	0	1 (2%)	1 (<1%)
Discontinuations Unrelated to Study Drug:	1 (2%)	4 (8%)	1 (2%)	6 (4%)
Adverse Event	1 (2%)	1 (2%)	0	2 (1%)
Lost to Follow-up	0	1 (2%)	0	1 (<1%)
Other	0	1 (2%)	1 (2%)	2 (1%)
Withdrawn Consent	0	1 (2%)	0	1 (<1%)

Reviewer's Note: A higher percentage of trovafloxacin 300 mg and cefaclor patients discontinued treatment prematurely (p=0.04 using the Chi-square test). Discontinuations due to study drug appeared higher in the trovafloxacin 300 mg and cefaclor arms (this difference was marginally significant, p=0.07 using Fisher's exact test); within this category, there appeared to be a higher rate of discontinuations due to adverse events on the trovafloxacin 300 mg arm and a higher rate of discontinuations due to insufficient clinical response on the cefaclor arm, however these differences were not statistically significant (p=0.14 and 0.12, respectively, using Fisher's exact test). Discontinuations considered unrelated to study drug also appeared higher on the trovafloxacin 300 mg arm, although this difference was not statistically significant (p=0.37 using Fisher's exact test).

Demographics

The three treatment groups were comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar for the three treatment groups (ex smoker, never smoked, and smoker). The ratio of males to females was approximately 1:2 in the trovafloxacin 200 and cefaclor groups and 1:1 in the trovafloxacin 300 mg group. Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for all treated subjects was uncomplicated community-acquired bacterial pneumonia. The median duration since onset of pneumonia was 4.0 days for subjects in both of the trovafloxacin groups and 4.5 days for subjects in the cefaclor group. Similar results were observed for clinically evaluable subjects.

Subjects in the trovafloxacin 300 mg group had a higher percentage (29%) of subjects with chronic obstructive pulmonary diseases at baseline compared to subjects in the trovafloxacin

200 mg (10%) and cefaclor (15%) groups. There were no marked differences among subjects in the three treatment groups with respect to physical examination findings at baseline.

Clinical Response

A summary of clinical response rates for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 3a.3. Pairwise comparisons (95% confidence intervals) of the difference between treatment groups in sponsor-defined clinical success rates (cure + improvement) at the end of treatment and at the end of study showed that the three treatment groups were similar. Because this study was not powered to fall within the limits for equivalence, no definitive conclusions regarding equivalency of the three treatments could be drawn.

Table 3a.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)				
	Trovafloxacin 200 mg (N=47)	Trovafloxacin 300 mg (N=42)	Cefaclor 500 mg TID (N=42)	95% CI
Number and Percentage (%) of Subjects				
End of Treatment:				
Number of Subjects Assessed	44 (100%)	40 (100%)	41 (100%)	
Success (Cure + Improvement)	44 (100%)	39 (98%)	38 (93%)	
Trova 200 mg vs Trova 300 mg				(-2.3, 7.3)
Trova 200 mg vs Cefaclor				(-0.7, 15.3)
Trova 300 mg vs Cefaclor				(-4.5, 14.1)
Distribution of Clinical Response:				
Cure	32 (73%)	26 (65%)	22 (54%)	
Improvement	12 (27%)	13 (33%)	16 (39%)	
Failure	0	1 (3%)	3 (7%)	
End of Study:				
Number of Subjects Assessed	45 (100%)	39 (100%)	42 (100%)	
Success (Cure + Improvement)	43 (96%)	36 (92%)	38 (90%)	
Trova 200 mg vs Trova 300 mg				(-7.1, 13.6)
Trova 200 mg vs Cefaclor				(-5.6, 15.8)
Trova 300 mg vs Cefaclor				(-10.4, 14.0)
Distribution of Clinical Response:				
Cure	42 (93%)	34 (87%)	36 (86%)	
Improvement	1 (2%)	2 (5%)	2 (5%)	
Failure	0	1 (3%)	3 (7%)	
Relapse	2 (4%)	2 (5%)	1 (2%)	

Trova = trovafloxacin

Reviewer's Note: Since there are three pairwise treatment comparisons of interest, results should actually be adjusted for multiple comparisons. However, due to the fact that the study is underpowered to demonstrate equivalence for even one pairwise comparison, no adjustments were made by this reviewer.

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 3a.4.

Table 3a.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)						
	Trovafloxacin 200 mg (N=14)	Trovafloxacin 300 mg (N=20)	Cefaclor 500 mg TID (N=15)	Trovafloxacin 200 mg (N=16)	Trovafloxacin 300 mg (N=21)	Cefaclor 500 mg TID (N=16)
	Number of Subjects					
Pathogen	End of Treatment			End of Study		
<i>S. pneumoniae</i>	2/2	7/7	5/5	2/2	5/6	5/5
<i>H. influenzae</i>	5/5	4/4	3/3	4/5	2/3	3/3
<i>K. pneumoniae</i>	4/4	5/5	2/2	6/6	6/6	2/2
<i>C. pneumoniae^b</i>	2/2	4/4	0/1	2/2	4/4	0/1
<i>M. catarrhalis</i>	1/1	3/3	1/1	2/2	2/2	2/2

a ≥3 isolates of a given pathogen in any treatment group.
 b Bacteriological determination made by serology. All other pathogens were isolated from sputum.
 A subject could have had more than one pathogen isolated at baseline.
 Several subjects were not evaluated clinically at the end of treatment.

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 3a.5.

Table 3a.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)						
	Trovafloxacin 200 mg (N=14)	Trovafloxacin 300 mg (N=20)	Cefaclor 500 mg TID (N=15)	Trovafloxacin 200 mg (N=13)	Trovafloxacin 300 mg (N=18)	Cefaclor 500 mg TID (N=14)
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>S. pneumoniae</i>	2/2	6/7	5/5	2/2	5/6	5/5
<i>H. influenzae</i>	4/5	3/4	2/3	5/5	2/3	3/3
<i>K. pneumoniae</i>	4/4	5/5	2/2	4/4	5/5	2/2
<i>M. catarrhalis</i>	1/1	3/3	1/1	1/1	2/2	1/1
<i>C. pneumoniae^b</i>	2/2	4/4	0/1	2/2	4/4	0/1

a ≥3 isolates of a given pathogen in any treatment group.
 b Bacteriological determination made by serology. All other pathogens were isolated from sputum.
 A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 3a.6. Tables 3a.7 and 3a.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: A significantly higher proportion of trovafloxacin 300 mg patients experienced adverse events, both all causality and treatment-related ($p=0.01$ and $p<0.001$, respectively, using the Chi-square test). A higher proportion of trovafloxacin 300 mg patients also discontinued treatment due to an adverse event (this was marginally significant; $p=0.07$ using Fisher's exact test).

Table 3a.6. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values			
	Trovafloxacin 200 mg (N=50)	Trovafloxacin 300 mg (N=52)	Cefaclor 500 mg TID (N=47)
Number and Percentage (%) of Subjects			
Adverse Events: All Causalities	17 (34%)	32 (62%)	18 (38%)
Treatment-Related Adverse Events	8 (16%)	23 (44%)	6 (13%)
Discontinuations Due to an Adverse Event^a	2 (4%)	9 (17%) ^b	3 (6%) ^b
Clinically Significant Laboratory Values	26/50 (52%)	25/47 (53%)	23/45 (51%)
<p>a With the exception of one subject in the trovafloxacin 200 mg group, three subjects in the trovafloxacin 300 mg group, and one subject in the cefaclor group who were discontinued due to unrelated adverse events, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related.</p> <p>b Two subjects in the trovafloxacin 300 mg group and one subject in the cefaclor group experienced adverse events for which the investigator action taken was permanent discontinuation from the study; however, on the subject summary section of the case report form the investigator classified the reasons for withdrawal as either insufficient clinical response or other.</p>			

Table 3a.7. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)

	Trovafloxacin 200 mg (N=50)	Trovafloxacin 300 mg (N=52)	Cefaclor 500 mg TID (N=47)
	Number and Percentage (%) of Subjects		
Number of Subjects With at Least One Adverse Event ^c	17 (34%)	32 (62%)	18 (38%)
BODY SYSTEM			
WHO Term			
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	5 (10%)	18 (35%)	5 (11%)
Dizziness	2 (4%)	16 (31%)	3 (6%)
Headache	3 (6%)	3 (6%)	1 (2%)
GASTROINTESTINAL SYSTEM	9 (18%)	17 (33%)	6 (13%)
Nausea	6 (12%)	7 (13%)	5 (11%)
Vomiting	2 (4%)	4 (8%)	1 (2%)
Abdominal Pain	1 (2%)	4 (8%)	0
Gastritis	0	4 (8%)	0
GENERAL	3 (6%)	4 (8%)	6 (13%)
Asthenia	3 (6%)	0	1 (2%)
Back Pain	0	1 (2%)	3 (6%)
REPRODUCTIVE SYSTEM	2 (4%)	1 (2%)	1 (2%)
Prostatic disorder ^d	1 (7%)	0	0

a ≥5 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication

c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.

d Preferred term is gender specific; therefore the percentages are based on the number of males or females appropriately.

Table 3a.8. Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)					
	Trovafloxacin 200 mg (N=50)		Trovafloxacin 300 mg (N=52)		Cefaclor 500 mg TID (N=47)
Number and Percentage (%) of Subjects					
Number of Subjects With at Least One Adverse Event^c	8	(16%)	23	(44%)	6 (13%)
BODY SYSTEM					
WHO Term					
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	3	(6%)	14	(27%)	2 (4%)
Dizziness	1	(2%)	13	(25%)	2 (4%)
Headache	1	(2%)	3	(6%)	0
GASTROINTESTINAL SYSTEM	5	(10%)	15	(29%)	2 (4%)
Nausea	5	(10%)	7	(13%)	2 (4%)
Vomiting	1	(2%)	3	(6%)	0
Abdominal Pain	0		4	(8%)	0
Gastritis	0		4	(8%)	0
REPRODUCTIVE SYSTEM	0		1	(2%)	1 (2%)
Vaginitis ^d	0		1	(4%)	1 (3%)

a ≥3 % of subjects in any treatment group.
 b Includes data up to 7 days after last dose of active study medication.
 c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.
 d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.

Two subjects in each of the three treatment groups experienced serious adverse events that were considered by the investigator to be unrelated to study drug. No subjects in any of the three treatment groups died during this study.

Sponsor’s Summary and Conclusion: Trovafloxacin 200 mg or 300 mg once daily and cefaclor 500 mg TID were similar with respect to clinical response rates at the end of treatment and at the end of study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment and at the end of study. The incidence of adverse events for subjects in the trovafloxacin 200 mg group was comparable to that of subjects in the cefaclor group (34% and 38%, respectively), as was the incidence of adverse events leading to discontinuation (4% and 6%, respectively). Subjects in the trovafloxacin 300 mg group had a higher incidence of adverse events (62%) and a higher rate of discontinuation due to adverse events (17%) compared to the other two treatment groups. The most commonly reported adverse events for subjects in the trovafloxacin 200 mg and the cefaclor groups were those associated with the gastrointestinal system; nausea was the most commonly reported adverse event for both groups (12% and 11%, respectively). In the trovafloxacin 300 mg group, the most commonly reported adverse events were those associated with the central and peripheral nervous system; dizziness (31%) was the most commonly reported adverse event.

Reviewer's Summary and Conclusions: *This was a Phase II study to examine the efficacy and safety of two different trovafloxacin doses. Clinical response rates for trovafloxacin 200 mg, trovafloxacin 300 mg, and cefaclor appeared similar at both EOT and EOS. However, sample sizes were too small to allow for any definitive conclusions about equivalence.*

A significantly higher proportion of trovafloxacin 300 mg patients experienced adverse events, both all causality and treatment-related ($p=0.01$ and $p<0.001$, respectively, using the Chi-square test). A higher proportion of trovafloxacin 300 mg patients also discontinued treatment due to an adverse event (this was marginally significant; $p=0.07$ using Fisher's exact test).

III.B. Protocol 154-110

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CIPROFLOXACIN AND AMPICILLIN FOLLOWED BY ORAL CIPROFLOXACIN AND AMOXICILLIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Study Dates: 19 January 1995 - 30 January 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ciprofloxacin and ampicillin followed by oral ciprofloxacin and amoxicillin in the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-110 was a randomized, multicenter, double-blind trial of alatrofloxacin (200 mg once daily) administered intravenously for 2-7 days followed by oral trovafloxacin (200 mg once a day) to complete 7-10 days of total treatment versus intravenous ciprofloxacin (400 mg twice daily) and ampicillin (500 mg every 6 hours) for 2-7 days followed by oral treatment with ciprofloxacin (500 mg twice daily) and amoxicillin (500 mg three times daily) to complete 7-10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and 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 11) 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 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 11) 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.

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).

Efficacy:

Analysis Groups

Table 3b.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3b.1. Evaluation Groups

Evaluation Groups ^a :	Alatrofloxacin	Ciprofloxacin/Ampicillin
	Trovafloxacin	Ciprofloxacin/Amoxicillin
Entered Study ^b	198	202
All Treated	196 (100%)	200 (100%)
Completed Treatment	147 (75%)	168 (84%)
Completed Study	177 (90%)	180 (90%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	196 (99%)	201 (> 99%)
Clinically Evaluable	169 (85%)	181 (90%)
Bacteriological Intent-to-Treat	89 (45%)	94 (47%)
Bacteriologically Evaluable	76 (38%)	88 (44%)
Assessed for Safety		
Adverse Events	196 (100%)	200 (100%)
Laboratory Tests	192 (98%)	197 (99%)

- a The daily doses of alatrofloxacin and trovafloxacin were each 200 mg. The daily doses of intravenous and oral ciprofloxacin were 400 mg BID and 500 mg BID, respectively. The daily doses of ampicillin and amoxicillin were each 500 mg, administered every 6 hours (ampicillin) or TID (amoxicillin).
- b Subjects who were randomized.

Reviewer's Note: A significantly lower proportion of alatrofloxacin/trovafloxacin patients completed treatment ($p=0.026$ using the test of equal proportions based on the normal approximation to the binomial distribution).

Of the 198 alatrofloxacin/trovafloxacin and 202 ciprofloxacin/ampicillin/amoxicillin randomized subjects, two alatrofloxacin/trovafloxacin subjects (Subjects 5249-0263 and 5501-0329) and one ciprofloxacin/ampicillin/amoxicillin subject (Subject 5046-0327 [*Pneumocystis carinii* pneumonia]) had an inappropriate baseline diagnosis (i.e., no community-acquired pneumonia at baseline as defined by protocol) and were excluded from all clinical and bacteriological ITT and evaluable analyses.

Of the 196 alatrofloxacin/trovafloxacin and 201 ciprofloxacin/ampicillin/amoxicillin clinical ITT subjects, 27 in the alatrofloxacin/trovafloxacin group and 20 in the ciprofloxacin/ampicillin/amoxicillin were not clinically evaluable; therefore, 169 subjects in the alatrofloxacin/trovafloxacin group and 181 subjects in the ciprofloxacin/ampicillin/amoxicillin group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (17/198 [9%], alatrofloxacin/trovafloxacin and 10/202 [5%], ciprofloxacin/ampicillin/amoxicillin). Other reasons were randomized but not treated, no post-baseline clinical assessments, no post-baseline clinical response in evaluable window, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness. In addition, one subject in the alatrofloxacin/trovafloxacin group received only placebo dosing on the first day of treatment and was not considered to be clinically evaluable.

Of the 196 alatrofloxacin/trovafloxacin and 201 ciprofloxacin/ampicillin/amoxicillin clinical ITT subjects, 107 subjects in each treatment group had negative baseline cultures; therefore, 89

subjects in the alatrofloxacin/trovafloxacin group and 94 subjects in the ciprofloxacin/ampicillin/amoxicillin group were included in the bacteriological ITT analysis.

Of the 169 alatrofloxacin/trovafloxacin and 181 ciprofloxacin/ampicillin/amoxicillin clinically evaluable subjects, 93 subjects in each treatment group were not included in the bacteriologically evaluable analyses; therefore, 76 subjects in the alatrofloxacin/trovafloxacin and 88 subjects in the ciprofloxacin/ampicillin/amoxicillin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (92 subjects, each group). Other reasons were baseline culture outside window and no post-baseline cultures. (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 396 treated subjects, 81 subjects were prematurely discontinued from treatment as summarized in Table 3b.2.

Table 3b.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)				
	Alatrofloxacin ↓ Trovafloxacin (N=196)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=200)	
	Number and Percentage (%) of Subjects			
Total Discontinued	49	(25%)	32	(16%)
Discontinuations Related to Study Drug:	23	(12%)	15	(8%)
Adverse Event	13	(7%)	10	(5%)
Insufficient Response	10	(5%)	5	(3%)
Discontinuations Unrelated to Study Drug:	26	(13%)	17	(9%)
Adverse Event	8	(4%)	5	(3%)
Did Not Meet Randomization Criteria ^a	0		1	(<1%)
Laboratory Abnormality	1	(<1%)	0	
Lost To Follow-Up	2	(1%)	1	(<1%)
Other	11	(6%)	9	(5%)
Subject Died	1	(<1%)	1	(<1%)
Protocol Violation	2	(1%)	0	
Withdrew Consent	1	(<1%)	0	
a Subject 5462-0267 entered the study pending results from an HIV test, which subsequently were positive. This subject had received study drug prior to confirmation of the test results.				

Reviewer's Note: As noted above, a significantly lower proportion of alatrofloxacin/trovafloxacin patients completed treatment, i.e., a significantly higher proportion of alatrofloxacin/trovafloxacin patients discontinued study drug (p = 0.026 using the test of equal proportions based on the normal approximation to the binomial distribution).

Demographics

One hundred-twenty (120) of the 196 treated alatrofloxacin/trovafloxacin subjects (61%) were males and 76 (39%) were females and 118 of the 200 treated ciprofloxacin/ampicillin/amoxicillin subjects (59%) were males and 82 (41%) were females. The males and females in the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin treatment groups were generally comparable with respect

to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin treatment groups (36% and 35% ex-smoker, 26% and 23% never smoked, and 38% and 42% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinical ITT subjects was community-acquired pneumonia. The median (range) duration since onset of pneumonia was 5 days (1-32 days) for subjects in the alatrofloxacin/trovafloxacin group and 4 days (1-30 days) for subjects in the ciprofloxacin/ampicillin/amoxicillin 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/ampicillin/amoxicillin groups with respect to medical history at baseline.

Although the two treatment groups were similar overall with respect to baseline characteristics, the subjects with baseline *S. pneumoniae* in the alatrofloxacin/trovafloxacin group were more elderly and had more severe pneumonias (requiring mechanical ventilation, high fractional oxygen, or bacteremic) compared to subjects in the ciprofloxacin/ampicillin/amoxicillin group. Forty-nine percent (49%) of the 45 subjects in the alatrofloxacin/trovafloxacin group with *S. pneumoniae* were ≥ 65 years of age or had a severe pneumonia versus 33% of the 42 subjects in the ciprofloxacin/ampicillin/amoxicillin group with *S. pneumoniae*. Of the alatrofloxacin/trovafloxacin subjects with *S. pneumoniae*, 24% (11/45) were ≥ 65 years of age, 27% (12/45) were bacteremic, and 13% (6/45) required high fractional oxygen or mechanical ventilation versus 14% (6/42), 16% (7/42), and 5% (2/42), respectively, of subjects in the ciprofloxacin/ampicillin/amoxicillin group.

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 3b.3. Response rates for alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin were considered therapeutically equivalent at both EOT and EOS.

Table 3b.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafoxacin (N=169)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=181)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	168	(100%)	179	(100%)	
Success (Cure + Improvement)	151	(90%)	165	(92%)	(-8.3, 3.7)
Distribution of Clinical Response:					
Cure	75	(45%)	74	(41%)	
Improvement	76	(45%)	91	(51%)	
Failure	17	(10%)	14	(8%)	
End of Study:					
Number of Subjects Assessed	140	(100%)	165	(100%)	
Success (Cure + Improvement)	120	(86%)	145	(88%)	(-9.8, 5.5)
Distribution of Clinical Response:					
Cure	106	(76%)	130	(79%)	
Improvement	14	(10%)	15	(9%)	
Failure	17	(12%)	14	(8%)	
Relapse	3	(2%)	6	(4%)	

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 3b.4.

Table 3b.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)								
	Alatrofloxacin ↓ Trovafoxacin (N=77)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=89)		Alatrofloxacin ↓ Trovafoxacin (N=66)		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=75)	
Number of Subjects								
Pathogen	End of Treatment				End of Study			
<i>S. pneumoniae</i>	35/39	(90%)	41/42	(98%)	31/35	(89%)	31/34	(91%)
<i>H. influenzae</i>	19/20	(95%)	21/22	(95%)	15/16	(94%)	20/21	(95%)
<i>S. aureus</i>	4/4		6/6		3/3		4/4	
<i>K. pneumoniae</i>	1/1		6/7		1/1		5/6	
<i>C. pneumoniae</i>	2/4		9/9		2/4		9/9	
<i>L. pneumophila</i>	2/2		4/4		2/2		4/4	
<i>M. pneumoniae</i>	8/8		8/9		8/8		7/8	

a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); 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 3b.5.

Table 3b.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens ^a (Bacteriologically Evaluable Subjects)								
	Alatrofloxacin ↓ Trovafoxacin (N=76)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=88)		Alatrofloxacin ↓ Trovafoxacin (N=64)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=75)	
			95% CI				95% CI	
Number and Percentage (%) of Pathogens								
Pathogen	End of Treatment				End of Study			
<i>S. pneumoniae</i>	35/39 (90%)	38/39 (97%)	-18.4, 3.0	30/33 (91%)	32/34 (94%)	-15.8, 9.4		
<i>H. influenzae</i>	18/19 (95%)	20/21 (95%)	-14.1, 13.1	14/16 (88%)	20/21 (95%)	-26.3, 10.9		
<i>S. aureus</i>	4/4	6/6	ND	3/3	4/4	ND		
<i>K. pneumoniae</i>	1/1	7/7	ND	1/1	6/6	ND		
<i>C. pneumoniae</i>	2/4	9/9	ND	2/4	9/9	ND		
<i>L. pneumophila</i>	2/2	4/4	ND	2/2	4/4	ND		
<i>M. pneumoniae</i>	8/8	8/9	ND	8/8	7/8	ND		

ND = Not Determined

a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15.

A subject could have had more than one pathogen isolated at baseline.

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 3b.6. Tables 3b.7 and 3b.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 3b.6. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values				
	Alatrofloxacin ↓ Trovafoxacin		Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin	
Number and Percentage (%) of Subjects				
Adverse Events: All Causalities	140/196	(71%)	133/200	(67%)
Treatment-Related Adverse Events	53/196	(27%)	47/200	(24%)
Discontinuations Due to an Adverse Event	26/196	(13%)	19/200	(10%)
Clinically Significant Laboratory Values	101/192	(53%)	108/197	(55%)

a For five subjects in the alatrofloxacin/trovafoxacin group and four subjects in the ciprofloxacin/ampicillin/amoxicillin group, the investigator indicated the study drug discontinuation on the adverse event page on the CRF; however, study drug discontinuation was not checked off on the subject summary page of the CRF.

Table 3b.7. A Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causalities (All Treated Subjects)			
	Alatrofloxacin ↓ Trovafloxacin (N=196)	Ciprofloxacin/Ampicillin ↓ Ciprofloxacin/Amoxicillin (N=200)	
Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	140	(71%)	133 (67%)
BODY SYSTEM			
WHO Term			
APPL./INJ./INCISION/INSERTION SITE	24	(12%)	27 (14%)
Appl./Inj./Incision/Insertion Site Pain	7	(4%)	9 (5%)
Appl./Inj./Incision/Insertion Site Reaction	14	(7%)	11 (6%)
Appl./Inj./Incision/Insertion/Device Complication	3	(2%)	6 (3%)
CARDIOVASCULAR	26	(13%)	26 (13%)
Chest Pain	9	(5%)	4 (2%)
Edema Peripheral	8	(4%)	6 (3%)
Hypotension	6	(3%)	0
Phlebitis	1	(<1%)	5 (3%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	53	(27%)	33 (17%)
Dizziness	12	(6%)	3 (2%)
Headache	31	(16%)	21 (11%)
GASTROINTESTINAL SYSTEM	59	(30%)	63 (32%)
Abdominal Pain	8	(4%)	11 (6%)
Constipation	17	(9%)	19 (10%)
Diarrhea	5	(3%)	9 (5%)
Dyspepsia	8	(4%)	7 (4%)
Nausea	18	(9%)	19 (10%)
Vomiting	10	(5%)	9 (5%)
GENERAL	31	(16%)	32 (16%)
Back Pain	8	(4%)	6 (3%)
Pain	4	(2%)	7 (4%)
PSYCHIATRIC	32	(16%)	32 (16%)
Anxiety	5	(3%)	4 (2%)
Insomnia	21	(11%)	24 (12%)
REPRODUCTIVE SYSTEM	1	(<1%)	3 (2%)
Vaginitis ^d	1	(<1%)	3 (4%)
RESPIRATORY SYSTEM	30	(15%)	28 (14%)
Dyspnea	6	(3%)	2 (1%)
Pleural Effusion	8	(4%)	7 (4%)
Pneumonia	5	(3%)	6 (3%)
Respiratory Insufficiency	5	(3%)	2 (1%)
SKIN/APPENDAGES	22	(11%)	17 (9%)
Pruritus	5	(3%)	1 (<1%)
Rash	5	(3%)	5 (3%)

APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion/Site
a ≥3 % of subjects in either treatment group.
b Includes data up to 7 days after last dose of active study medication.
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.
d Preferred term is gender-specific, and the percentages are based on the number of males and females appropriately.

BEST POSSIBLE COPY

Table 3b.8. A Summary of the Most Commonly Reported Treatment-Related Adverse Events ^{a,b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovafoxacin (N=196)		Ciprofloxacin/ Ampicillin ↓ Ciprofloxacin/ Amoxicillin (N=200)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	53	(27%)	47	(24%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	12	(6%)	16	(8%)
Appl./inj./Incision/Insertion Site Pain	1	(<1%)	8	(4%)
Appl./inj./Incision/Insertion Site Reaction	10	(5%)	10	(5%)
CARDIOVASCULAR SYSTEM	1	(<1%)	5	(3%)
Phlebitis	0		4	(2%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	18	(9%)	3	(2%)
Dizziness	3	(2%)	0	
Headache	12	(6%)	2	(1%)
GASTROINTESTINAL SYSTEM	12	(6%)	19	(10%)
Constipation	1	(<1%)	3	(2%)
Diarrhea	3	(2%)	5	(3%)
Dyspepsia	0		5	(3%)
Nausea	6	(3%)	4	(2%)
GENERAL	5	(3%)	6	(3%)
Moniliasis	2	(1%)	4	(2%)
PSYCHIATRIC	6	(3%)	4	(2%)
Anxiety	3	(2%)	0	
Insomnia	1	(<1%)	4	(2%)
REPRODUCTIVE SYSTEM	1	(<1%)	3	(4%)
Vaginitis ^d	1	(<1%)	3	(4%)
SKIN/APPENDAGES	12	(6%)	8	(4%)
Pruritus	3	(2%)	1	(<1%)
Rash	3	(2%)	2	(1%)
Rash Erythematous	3	(2%)	0	
Rash Maculo-Papular	3	(2%)	1	(<1%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion/Site				
a ≥ 2 % of subjects in either treatment group.				
b Includes data up to 7 days after last dose of active study medication.				
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.				
d Preferred term is gender-specific, and the percentages are based on the number of males and females appropriately.				

BEST POSSIBLE COPY

Six (6) subjects in the alatrofloxacin/trovafoxacin group and 14 subjects in the ciprofloxacin/ampicillin/amoxicillin group died during this study, of which two in the alatrofloxacin/trovafoxacin group and 10 in the ciprofloxacin/ampicillin/amoxicillin group occurred in the first 35 days. All deaths were considered by the investigator to be unrelated to study drug.

Thirty-six (36) subjects in the alatrofloxacin/trovafloxacin group and 29 subjects in the ciprofloxacin/ampicillin/amoxicillin group had serious adverse events. With the exception of one subject in the alatrofloxacin/trovafloxacin group who had serious adverse events (nausea/vomiting) that were considered by the investigator to be related to study drug, all serious adverse events were attributed to other events or illnesses or to the disease under study.

Sponsor's Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy were statistically equivalent for clinical success rate at the end of treatment and at the end of study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable for the most frequently isolated baseline pathogens (*S. pneumoniae* and *H. influenzae*) between the two treatment groups at the end of treatment and at the end of study.

The percentage of subjects discontinued from treatment due to adverse events was 13% in the alatrofloxacin/trovafloxacin group and 10% in the ciprofloxacin/ampicillin/amoxicillin group. The overall percentage of all and treatment-related adverse events for subjects in the alatrofloxacin/trovafloxacin group was comparable to that of subjects in the ciprofloxacin/ampicillin/amoxicillin group (71% and 27% versus 67% and 24%, respectively). The most commonly reported treatment-related adverse events were headache in the alatrofloxacin/trovafloxacin group and diarrhea and dyspepsia in the ciprofloxacin/ampicillin/amoxicillin group. Injection site reactions were comparable between the alatrofloxacin/trovafloxacin and ciprofloxacin/ampicillin/amoxicillin groups (6% and 8%, respectively). Mortality (Day 1 - 35) was lower in the alatrofloxacin/trovafloxacin group compared to the ciprofloxacin/ampicillin/amoxicillin group (1% and 5%, respectively).

Reviewer's Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy was considered therapeutically equivalent to intravenous ciprofloxacin (400 mg twice daily) / ampicillin (500 mg every 6 hours) for 2 to 7 days followed by oral ciprofloxacin (500 mg twice daily) / amoxicillin (500 mg three times daily) for 7 to 10 days of total therapy at both EOT and EOS.

The most common adverse events in the alatrofloxacin/trovafloxacin arm were headache (16%), insomnia (11%), constipation (9%), and nausea (9%). The most common adverse events in the ciprofloxacin/ampicillin/amoxicillin arm were insomnia (12%), headache (11%), constipation (10%), and nausea (10%).

BEST POSSIBLE COPY

III.C. Protocol 154-111

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING INTRAVENOUS ALATROFLOXACIN FOLLOWED BY ORAL TROVAFLOXACIN WITH INTRAVENOUS CEFTRIAZONE FOLLOWED BY ORAL CEFPODOXIME WITH OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Study Dates: 8 February 1995 - 22 March 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of intravenous alatrofloxacin followed by oral trovafloxacin, as empiric monotherapy, compared to intravenous ceftriazone followed by oral cefpodoxime, with optional erythromycin, for the treatment of subjects with community acquired pneumonia requiring hospitalization and initial intravenous therapy.

Study Design: Study 154-111 was a randomized, multicenter, double-blind, double-dummy trial of alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) to complete 7 to 10 days of total treatment versus intravenous ceftriazone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg administered twice daily) to complete 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. The total duration of therapy could have been extended to 14 days for subjects presenting with more severe pneumonias or bacteremia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia requiring hospitalization and 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 11) 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 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 11) 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.

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).

Efficacy Results:

Analysis Groups

Table 3c.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3c.1. Evaluation Groups

Evaluation Groups ^a :	Alatrofloxacin	Ceftriaxone
	↓ Trovfloxacin	↓ Cefpodoxime
Entered Study ^b	218	225
All Treated	215 (100%)	222 (100%)
Completed Treatment	170 (79%)	172 (77%)
Completed Study	182 (85%)	183 (82%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	212 (97%)	221 (98%)
Clinically Evaluable	180 (83%)	187 (83%)
Bacteriologically Intent-to-Treat	92 (42%)	102 (45%)
Bacteriologically Evaluable	80 (37%)	85 (38%)
Assessed for Safety		
Adverse Events	215 (100%)	222 (100%)
Laboratory Tests	203 (94%)	205 (92%)

a The daily doses of alatrofloxacin and trovfloxacin were each 200 mg. The daily dose of ceftriaxone was 1000 mg and the daily dose of cefpodoxime was 400 mg (200 mg administered twice daily).

b Subjects who were randomized.

Of the 218 alatrofloxacin/trovfloxacin and 225 ceftriaxone/cefpodoxime randomized subjects, six alatrofloxacin/trovfloxacin subjects and four ceftriaxone/cefpodoxime subjects

had an inappropriate baseline diagnosis (i.e., no community-acquired pneumonia at baseline) and were excluded from all clinical and bacteriological intent-to-treat and evaluable analyses. Among the subjects with an inappropriate baseline diagnosis, two had a baseline diagnosis of *P. carinii* pneumonia, one had tuberculosis, one had a negative baseline chest X-ray and the remaining subjects did not meet the protocol specific inclusion criteria.

Of the 212 alatrofloxacin/trovafloxacin and 221 ceftriaxone/cefpodoxime clinically ITT subjects, 32 in the alatrofloxacin/trovafloxacin group and 34 in the ceftriaxone/cefpodoxime were not clinically evaluable; therefore, 180 subjects in the alatrofloxacin/trovafloxacin group and 187 subjects in the ceftriaxone/cefpodoxime group were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (17/218 [8%], alatrofloxacin/trovafloxacin and 21/225 [9%], ceftriaxone/cefpodoxime). Other reasons were randomized but not treated, no post-baseline clinical assessments, no post-baseline clinical response in evaluable window, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, and other reasons (subjects who were unable to take oral therapy at 7 days and subjects who received incorrect IV drugs).

Of the 212 alatrofloxacin/trovafloxacin and 221 ceftriaxone/cefpodoxime clinical ITT subjects, 119 subjects in each treatment group had negative baseline cultures. Ninety-two (92) subjects in the alatrofloxacin/trovafloxacin group and 102 subjects in the ceftriaxone/cefpodoxime group were included in the bacteriological ITT analysis.

Of the 180 alatrofloxacin/trovafloxacin and 187 ceftriaxone/cefpodoxime clinically evaluable subjects, 100 subjects in the alatrofloxacin/trovafloxacin group and 102 subjects in the ceftriaxone/cefpodoxime group were not included in the bacteriologically evaluable analyses; therefore, 80 subjects in the alatrofloxacin/trovafloxacin and 85 subjects in the ceftriaxone/cefpodoxime group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (99 subjects, each group). Other reasons were baseline culture outside window, no post-baseline cultures (of the 3 subjects in the alatrofloxacin/trovafloxacin group and 19 subjects in the ceftriaxone/cefpodoxime group excluded for this reason, only 1 and 2 subjects, respectively, had baseline pathogens) and *N. meningitidis* in sputum (1 subject). (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 215 alatrofloxacin/trovafloxacin and 222 ceftriaxone/cefpodoxime treated subjects, 45 alatrofloxacin/trovafloxacin and 50 ceftriaxone/cefpodoxime subjects were prematurely discontinued from treatment as summarized in Table 3c.2.

BEST POSSIBLE COPY

Table 3c.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Alatrofloxacin ↓ Trovfloxacin (N=215)	Ceftriaxone ↓ Cefpodoxime (N=222)
	Number and Percentage (%) of Subjects	
Total Discontinued	45 (21%)	50 (23%)
Discontinuations Related to Study Drug:		
Adverse Event	19 (9%)	18 (8%)
Insufficient Response	9 (4%)	2 (<1%)
Laboratory Abnormality	10 (5%)	15 (7%)
Laboratory Abnormality	0	1 (<1%)
Discontinuations Unrelated to Study Drug:		
Adverse Event	26 (12%)	32 (14%)
Did not meet Randomization Criteria	8 (4%)	8 (4%)
Lost to Follow-up	5 (2%)	1 (<1%)
Other	4 (2%)	0
Subject Died	4 (2%)	10 (5%)
Protocol Violation	4 (2%)	5 (2%)
Withdrawn Consent	0	1 (<1%)
Withdrawn Consent	1 (<1%)	7 (3%)

Reviewer’s Note: Patients receiving alatrofloxacin/trovfloxacin experienced a significantly higher number of discontinuations due to adverse events considered related to study drug (4% compared to < 1% for ceftriaxone/cefpodoxime patients; $p = 0.03$ using Fisher’s exact test).

Demographics

One hundred twenty-three (123) of the 215 treated alatrofloxacin/trovfloxacin subjects (57%) were male and 92 (43%) were female, and 147 of the 222 treated ceftriaxone/cefpodoxime subjects (66%) were male and 75 (34%) were female. The males and females in the alatrofloxacin/trovfloxacin and ceftriaxone/cefpodoxime treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the alatrofloxacin/trovfloxacin and ceftriaxone/cefpodoxime treatment groups (36% and 40% ex-smoker, 29% and 24% never smoked, and 35% and 36% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinical ITT and evaluable subjects was community-acquired pneumonia. The median duration (range) since onset of pneumonia was 4 days (1-151 days) for subjects in the alatrofloxacin/trovfloxacin group and 4 days (1-31 days) for subjects in the ceftriaxone/cefpodoxime group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Of the clinical ITT subjects, 81 subjects in both treatment groups were initially suspected by the investigator to have atypical pneumonia and seven subjects in the alatrofloxacin/trovfloxacin group and nine subjects in the ceftriaxone/cefpodoxime group had suspected *Legionella* pneumonia. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the alatrofloxacin/trovfloxacin and ceftriaxone/cefpodoxime groups with respect to medical history at baseline.

Reviewer's Note: In fact, a significantly higher proportion of ceftriaxone/cefpodoxime patients had chronic obstructive lung disease (90/222 = 41% of ceftriaxone/cefpodoxime patients compared to 67/215 = 31% alatrofloxacin/trovafloxacin patients; $p=0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution). In addition, a higher proportion of alatrofloxacin/trovafloxacin patients had diabetes mellitus (41/215 = 19% alatrofloxacin/trovafloxacin patients compared to 24/222 = 11% of ceftriaxone/cefpodoxime patients; $p=0.02$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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 3c.3. Alatrofloxacin/trovafloxacin and ceftriaxone/cefpodoxime were considered therapeutically equivalent at both EOT and EOS.

Table 3c.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Alatrofloxacin ↓ Trovafloxacin (N=180)		Ceftriaxone ↓ Cefpodoxime (N=187)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	178	(100%)	184	(100%)	
Success (Cure + Improvement)	160	(90%)	160	(87%)	(-3.6, 9.5)
Distribution of Clinical Response:					
Cure	102	(57%)	108	(59%)	
Improvement	58	(33%)	52	(28%)	
Failure	18	(10%)	24	(13%)	
End of Study:					
Number of Subjects Assessed	159	(100%)	169	(100%)	
Success (Cure + Improvement)	136	(86%)	138	(82%)	(-4.1, 11.9)
Distribution of Clinical Response:					
Cure	128	(81%)	128	(76%)	
Improvement	8	(5%)	10	(6%)	
Failure	19	(12%)	25	(15%)	
Relapse	4	(3%)	6	(4%)	

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 3c.4.

Table 3c.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=180)	Ceftriaxone ↓ Cefpodoxime (N=187)	Alatrofloxacin ↓ Trovafoxacin (N=159)	Ceftriaxone ↓ Cefpodoxime (N=169)
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
<i>S. pneumoniae</i>	28/32 (88%)	21/23 (91%)	24/28 (86%)	19/21 (90%)
<i>H. influenzae</i>	16/16 (100%)	25/27 (93%)	13/15 (87%)	24/26 (92%)
<i>S. aureus</i>	4/4	7/8	3/3	6/7
<i>M. catarrhalis</i>	5/5	3/3	3/3	3/3
<i>E. coli</i>	4/5	1/3	3/4	0/2
<i>P. aeruginosa</i>	5/5	1/2	2/2	1/2
<i>C. pneumoniae</i>	4/4	9/9	2/2	7/8
<i>L. pneumophila</i>	7/11	8/10	6/10	8/10
<i>M. pneumoniae</i>	12/12	5/6	9/10	4/6

^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); 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 3c.5.

Table 3c.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Bacteriologically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafoxacin (N=80)	Ceftriaxone ↓ Cefpodoxime (N=85)	95% CI	Alatrofloxacin ↓ Trovafoxacin (N=68)	Ceftriaxone ↓ Cefpodoxime (N=79)	95% CI
	Number and Percentage (%) of Pathogens					
Pathogen	End of Treatment			End of Study		
<i>S. pneumoniae</i>	28/31 (90%)	22/23 (96%)	-18.7, 8.0	25/27 (93%)	19/20 (95%)	-16.1, 11.3
<i>H. influenzae</i>	16/16 (100%)	23/26 (88%)	-0.7, 23.8	13/15 (87%)	22/24 (92%)	-25.5, 15.5
<i>S. aureus</i>	4/4	7/8	ND	3/3	6/7	ND
<i>M. catarrhalis</i>	5/5	3/3	ND	3/3	3/3	ND
<i>P. aeruginosa</i>	5/5	1/2	ND	2/2	0/2	ND
<i>C. pneumoniae</i>	4/4	9/9	ND	2/2	7/8	ND
<i>L. pneumophila</i>	8/11	8/10	ND	7/10	8/10	ND
<i>M. pneumoniae</i>	12/12	5/6	ND	9/10	4/6	ND

ND = Not Determined

^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*); percents displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

BEST POSSIBLE COPY

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuation due to adverse events and clinically significant laboratory values is presented in Table 3c.6. Tables 3c.7 and 3c.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

BEST POSSIBLE COPY

Table 3c.6 A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values		
	Alatrofloxacin ↓ Trovafoxacin (N=215)	Ceftriaxone ↓ Cefpodoxime (N=222)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	177/215 (82%)	172/222 (77%)
Treatment-Related Adverse Events	70/215 (33%)	57/222 (26%)
Discontinuations From Treatment Due to an Adverse Event^a	22/215 (10%)	18/222 (8%)
Clinically Significant Laboratory Values	121/203 (60%)	114/205 (56%)

^a With the exception of eight subjects in the alatrofloxacin/trovafoxacin group and eight subjects in the ceftriaxone/cefpodoxime group who were discontinued due to unrelated adverse events, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related.

BEST POSSIBLE COPY

BEST POSSIBLE COPY

Table 3c.7. Summary of the Most Commonly Reported Adverse Events^{a,b} by Body System - All Causality (All Treated Subjects)				
	Alatrofloxacin ↓ Trovfloxacin (N=215)		Ceftriaxone ↓ Cefpodoxime (N=222)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event ^c	177	(82%)	172	(77%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	43	(20%)	36	(16%)
Appl./Inj./Incision/Insertion Site Pain	15	(7%)	10	(5%)
Appl./Inj./Incision/Insertion Site Reaction	20	(9%)	10	(5%)
Appl./Inj./Incision/Insertion/Device Complication	14	(7%)	18	(8%)
CARDIOVASCULAR	44	(20%)	46	(21%)
Edema Peripheral	14	(7%)	10	(5%)
CENTRAL AND PERIPHERAL NERVOUS	74	(34%)	44	(20%)
Confusion	11	(5%)	8	(4%)
Dizziness	21	(10%)	3	(1%)
Headache	41	(19%)	27	(12%)
GASTROINTESTINAL	85	(40%)	82	(37%)
Abdominal Pain	13	(6%)	7	(3%)
Constipation	23	(11%)	10	(5%)
Diarrhea	20	(9%)	25	(11%)
Dyspepsia	11	(5%)	12	(5%)
Nausea	27	(13%)	27	(12%)
Vomiting	17	(8%)	17	(8%)
GENERAL	39	(18%)	36	(16%)
Moniliasis	7	(3%)	12	(5%)
PSYCHIATRIC	47	(22%)	45	(20%)
Anxiety	13	(6%)	16	(7%)
Insomnia	16	(7%)	18	(8%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site				
a ≥5 % of subjects in any treatment group.				
b Includes data up to 7 days after last dose of active study medication				
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.				

Reviewer's Note: Alatrofloxacin/trovfloxacin patients experienced a significantly higher percentage of the following adverse events than did ceftriaxone/cefpodoxime patients: central and peripheral nervous system events (overall), dizziness, headache, and constipation ($p < 0.001$, $p < 0.001$, $p = 0.046$, and $p = 0.01$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

BEST POSSIBLE COPY

Table 3c.8. Summary of the Most Commonly Reported Treatment-Related Adverse Events^{a,b} by Body System (All Treated Subjects)				
	Alatrofloxacin ↓ Trovfloxacin (N=215)		Ceftriaxone ↓ Cefpodoxime (N=222)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event^c	70	(33%)	57	(26%)
BODY SYSTEM				
WHO Term				
APPL./INJ./INCISION/INSERTION SITE	18	(8%)	9	(4%)
Appl./Inj./Incision/Insertion Site Pain	7	(3%)	5	(2%)
Appl./Inj./Incision/Insertion Site Reaction	13	(6%)	2	(<1%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	21	(10%)	9	(4%)
Dizziness	11	(5%)	2	(<1%)
Headache	9	(4%)	6	(3%)
GASTROINTESTINAL	22	(10%)	30	(14%)
Diarrhea	7	(3%)	15	(7%)
Nausea	11	(5%)	9	(4%)
Vomiting	1	(<1%)	6	(3%)
GENERAL	11	(5%)	10	(5%)
Moniliasis	6	(3%)	9	(4%)
REPRODUCTIVE	1	(<1%)	2	(<1%)
Vaginitis ^d	1	(1%)	2	(3%)
APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site				
a ≥3 % of subjects in any treatment group.				
b Includes data up to 7 days after last dose of active study medication.				
c Although a subject may have had two or more adverse events in a body system category, the subject was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of subjects with any adverse events. If an individual adverse event was reported by the same subject more than once, the adverse event was counted only once.				
d Preferred term is gender specific; therefore, the percentages are based on the number of males or females appropriately.				

Eleven (11) subjects in the alatrofloxacin/trovfloxacin group and 20 subjects in the ceftriaxone/cefpodoxime group died during this study. With the exception of one death in the ceftriaxone/cefpodoxime group that occurred > 30 days post-therapy and was considered by the investigator to be treatment related (upper gastrointestinal bleeding and pneumonia), all deaths were considered by the investigator to be unrelated to study drug.

Thirty-four (34) subjects in the alatrofloxacin/trovfloxacin group and 47 subjects in the ceftriaxone/cefpodoxime group had serious adverse events. Two subjects in the alatrofloxacin/trovfloxacin group and two subjects in the ceftriaxone/cefpodoxime group who had serious adverse events that were 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 concomitant treatment.

BEST POSSIBLE COPY

Sponsor Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were statistically equivalent 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 were comparable between the two treatment groups at the end of treatment and at the end of study for baseline isolates of *S. pneumoniae* and *H. influenzae*. All subjects who had penicillin-resistant (MIC ≥ 0.1 $\mu\text{g/mL}$) *S. pneumoniae* isolated at baseline (10 in the alatrofloxacin/trovafloxacin group and one in the ceftriaxone/cefpodoxime group) were clinical cures or improvements at the end of treatment and the end of study. No subject in the alatrofloxacin/trovafloxacin group with a clinical outcome of failure had a microbiologically confirmed persistent pathogen.

The percentage of subjects discontinued from treatment due to adverse events was 10% in the alatrofloxacin/trovafloxacin group and 8% in the ceftriaxone/cefpodoxime group. Nine (9) subjects in the alatrofloxacin/trovafloxacin group and two subjects in the ceftriaxone/cefpodoxime group were discontinued from treatment due to treatment-related adverse events. The most frequently occurring treatment-related adverse events that lead to discontinuation were those related to the intravenous insertion site (insertion site reaction, paresthesia, pruritus, thrombophlebitis, phlebitis) among subjects in the alatrofloxacin/trovafloxacin group and colitis and diarrhea among subjects in the ceftriaxone/cefpodoxime group. The overall percentage of all and treatment-related adverse events in the alatrofloxacin/trovafloxacin group was comparable to that of subjects in the ceftriaxone/cefpodoxime group (82% and 33% versus 77% and 26%, respectively). The most commonly reported treatment-related adverse events were dizziness (5%) and nausea (5%) for subjects in the alatrofloxacin/trovafloxacin group and diarrhea (7%) for subjects in the ceftriaxone/cefpodoxime group.

Reviewer's Summary and Conclusion: Alatrofloxacin (200 mg once daily) administered intravenously for 2 to 7 days followed by oral trovafloxacin (200 mg once daily) for 7 to 10 days of total therapy and intravenous ceftriaxone (1000 mg once daily) for 2 to 7 days followed by oral cefpodoxime (200 mg twice daily) for 7 to 10 days of total therapy were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.

Alatrofloxacin/trovafloxacin patients experienced a significantly higher percentage of the following adverse events than did ceftriaxone/cefpodoxime patients: central and peripheral nervous system events (overall), dizziness, headache, and constipation ($p < 0.001$, $p < 0.001$, $p = 0.046$, and $p = 0.01$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

BEST POSSIBLE COPY

III.D. Protocol 154-112

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN WITH AMOXYCILLIN AND OPTIONAL ERYTHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA.

Study Dates: 9 December 1994 - 12 June 1996

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin to amoxicillin, with optional erythromycin, for the treatment of subjects with community acquired pneumonia.

Study Design: Study 154-112 was a randomized, multicenter, double-blind, double-dummy trial of trovafloxacin (200 mg once daily) administered orally for 7 to 10 days of total treatment versus amoxicillin (500 mg t.i.d.) administered orally for 7 to 10 days of total treatment, for the treatment of community acquired pneumonia. In addition, erythromycin may have been added to the comparative regimen on suspicion of an atypical pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Men or women, ≥ 18 years of age at the baseline assessment, with clinically and radiologically documented community acquired pneumonia 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 11) 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 11) 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.

BEST POSSIBLE COPY

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.

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

Efficacy Results:

Analysis Groups

Table 3d.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 3d.1. Evaluation Groups

Evaluation Groups:	Trovfloxacin (200 mg/day)	Amoxycillin (500 mg TID)
Entered Study ^a	151	152
All Treated	150 (100%)	152 (100%)
Completed Treatment	136 (91%)	139 (91%)
Completed Study	140 (93%)	136 (89%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	148 (98%)	149 (98%)
Clinically Evaluable ^b	138 (91%)	141 (93%)
Bacteriologically Intent-to-Treat	60 (40%)	55 (36%)
Bacteriologically Evaluable	55 (36%)	52 (34%)
Assessed for Safety		
Adverse Events	150 (100%)	152 (100%)
Laboratory Tests	144 (96%)	148 (97%)

a Subjects who were randomized.

b Clinically evaluable at end of treatment.

Of the 151 trovafloxacin and 152 amoxycillin randomized subjects, three trovafloxacin subjects and three amoxycillin subjects had an inappropriate baseline diagnosis (i.e., no clinical signs and symptoms of community-acquired pneumonia at baseline as defined by protocol) and were excluded from all intent-to-treat and evaluable analyses. Among the subjects with an inappropriate baseline diagnosis, two in each treatment group had tuberculosis at baseline and one in each treatment group did not meet the protocol-specific inclusion criteria.

Of the 148 trovafloxacin and 149 amoxycillin clinical ITT subjects, 10 in the trovafloxacin group and 8 in the amoxycillin were not clinically evaluable; therefore, 138 subjects in the trovafloxacin group and 141 subjects in the amoxycillin group were clinically evaluable. The

most common reasons for exclusion from clinical efficacy analyses were no post-baseline clinical assessments (4/151 [3%], trovafloxacin and 6/152 [4%], amoxicillin), no post-baseline clinical response in evaluable window (4/151 [3%], trovafloxacin and 6/152 [4%], amoxicillin), and insufficient therapy due to early discontinuation from treatment or study (7/151 [5%], trovafloxacin and 3/152 [2%], amoxicillin). Other reasons were randomized but not treated, prior antibiotic therapy, and concomitant antibiotic therapy for intercurrent illness.

Of the 148 trovafloxacin and 149 amoxicillin clinical ITT subjects, 88 subjects in the trovafloxacin group and 94 subjects in the amoxicillin group had negative baseline cultures; therefore, 60 subjects in the trovafloxacin group and 55 subjects in the amoxicillin group were included in the bacteriological ITT analysis.

Of the 138 trovafloxacin and 141 amoxicillin clinically evaluable subjects, 83 subjects in the trovafloxacin group and 89 subjects in the amoxicillin group were not included in the bacteriologically evaluable analyses; therefore, 55 subjects in the trovafloxacin and 52 subjects in the amoxicillin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (82/151 [54%], trovafloxacin and 89/152 [59%], amoxicillin). Other reasons were baseline culture outside window and no post-baseline cultures (the subject [Subject 5809-0279] in the trovafloxacin group excluded for this reason had a baseline pathogen). (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 150 trovafloxacin and 152 amoxicillin treated subjects, 14 trovafloxacin and 13 amoxicillin subjects were prematurely discontinued from treatment as summarized in Table 3d.2.

Table 3d.2. Summary of Premature Discontinuations From Treatment (All Treated Subjects)				
	Trovafloxacin 200 mg (N=150)		Amoxicillin 500 mg TID (N=152)	
	Number and Percentage (%) of Subjects			
Total Discontinued	14	(9%)	13	(9%)
Discontinuations Related to Study Drug:	8	(5%)	7	(5%)
Adverse Event	5	(3%)	2	(1%)
Insufficient Response	3	(2%)	5	(3%)
Discontinuations Unrelated to Study Drug:	6	(4%)	6	(4%)
Adverse Event	2	(1%)	3	(2%)
Lost to Follow-up	0		1	(<1%)
Other	1	(<1%)	0	
Subject Died	2	(1%)	0	
Protocol Violation	0		2	(1%)
Withdrawn Consent	1	(<1%)	0	

APPROB THIS WAY
TO ORIGINAL

Demographics

Eight-four (84) of the 150 treated trovafloxacin subjects (56%) were male and 66 (44%) were female and 93 of the 152 treated amoxicillin subjects (61%) were male and 59 (39%) were female. The males and females in the trovafloxacin and amoxicillin treatment groups were generally comparable with respect to age, race, and weight. The distribution of subjects according to smoking classification was also similar between the trovafloxacin and amoxicillin treatment groups (31% and 33% ex-smoker, 33% and 34% never smoked, and 37% and 34% smoker, respectively). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for clinical ITT subjects was community-acquired pneumonia. The median duration (range) since onset of pneumonia was 5 days (1-69 days) for subjects in the trovafloxacin group and 5 days (1-42 days) for subjects in the amoxicillin group. In some cases investigators reported the onset of any respiratory symptoms, so prolonged episodes of cough and sputum production are included. Of the clinical ITT subjects, 23 subjects in the trovafloxacin group and 28 subjects in the amoxicillin group were initially suspected by the investigator to have atypical pneumonia. Similar results were observed for clinically evaluable subjects. There were no marked differences between subjects in the trovafloxacin and amoxicillin groups with respect to medical history at baseline.

Reviewer's Note: The proportion of clinical ITT trovafloxacin patients with bilateral pneumonia (as diagnosed by x-ray) was somewhat higher than that for clinical ITT amoxicillin patients; this difference was marginally statistically significant (35/148 = 24% trovafloxacin patients vs. 23/149 = 15% amoxicillin patients; $p = 0.07$ using the test of equal proportions based on the normal approximation to the binomial distribution).

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 3d.3. Trovafloxacin and amoxicillin were considered therapeutically equivalent at both EOT and EOS.

BEST POSSIBLE COPY

Table 3d.3. Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)					
	Trovafloracin 200 mg (N=138)		Amoxicillin 500 mg TID (N=141)		95% CI
Number and Percentage (%) of Subjects					
End of Treatment:					
Number of Subjects Assessed	137	(100%)	140	(100%)	
Success (Cure + Improvement)	128	(93%)	128	(91%)	(-4.2, 8.2)
Distribution of Clinical Response:					
Cure	71	(52%)	75	(54%)	
Improvement	57	(42%)	53	(38%)	
Failure	9	(7%)	12	(9%)	
End of Study:					
Number of Subjects Assessed	122	(100%)	127	(100%)	
Success (Cure + Improvement)	107	(88%)	110	(87%)	(-7.2, 9.4)
Distribution of Clinical Response:					
Cure	98	(80%)	97	(76%)	
Improvement	9	(7%)	13	(10%)	
Failure	9	(7%)	12	(9%)	
Relapse	6	(5%)	5	(4%)	

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 3d.4.

Table 3d.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens^a (Clinically Evaluable Subjects)								
	Trovafloracin 200 mg (N=56)		Amoxicillin 500 mg TID (N=52)		Trovafloracin 200 mg (N=53)		Amoxicillin 500 mg TID (N=44)	
Number and Percentage (%) of Subjects								
Pathogen	End of Treatment				End of Study			
<i>H. influenzae</i>	21/22	(95%)	19/20	(95%)	18/20	(90%)	11/15	(73%)
<i>M. catarrhalis</i>	5/5		3/3		4/4		3/3	
<i>S. pneumoniae</i>	21/21	(100%)	16/19	(84%)	20/21	(95%)	14/18	(78%)
<i>M. pneumoniae</i>	4/5		2/3		4/5		1/2	
<i>C. pneumoniae</i>	1/1		4/4		1/1		2/2	

^a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae* and *M. pneumoniae*); percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

BEST POSSIBLE COPY

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 3d.5.