Table 2b.1. Evaluation Groups

Evaluation Groups[a]:	Alatrofloxacin ↓ Trovafloxacin	Ceftazidime ↓ Ciprofloxacin
Randomized	135	140
All Treated	135 (100%)	140 (100%)
Completed Treatment	88 (65%)	101 (72%)
Completed Study	86 (64%)	89 (64%)
Evaluated for Efficacy[b]		
Clinical Intent-to-Treat	132 (98%)	139 (>99%)
Clinically Evaluable[c]	103 (76%)	109 (78%)
Bacteriologically Intent-to-Treat	66 (49%)	81 (58%)
Bacteriologically Evaluable	52 (39%)	66 (47%)
Assessed for Safety[d]		
Adverse Events	135 (100%)	140 (100%)
Laboratory Tests	119 (88%)	124 (89%)

a The daily dose of alatrofloxacin was 300 mg and that of trovafloxacin was 200 mg. The daily dose of oral ciprofloxacin was 1500 mg (750 mg administered twice daily) and the daily dose of intravenous ceftazidime was 4000 mg (2000 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 135 alatrofloxacin/trovafloxacin and 140 ceftazidime/ciprofloxacin randomized subjects, 3 alatrofloxacin/trovafloxacin subjects and 1 ceftazidime/ciprofloxacin subject 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 132 alatrofloxacin/trovafloxacin and 139 ceftazidime/ciprofloxacin clinically ITT subjects, 29 in the alatrofloxacin/trovafloxacin group and 30 in the ceftazidime/ ciprofloxacin group were not clinically evaluable; therefore, 103 subjects in the alatrofloxacin/trovafloxacin group and 109 subjects in the ceftazidime/ciprofloxacin group were clinically evaluable. The most common reasons for exclusion from clinical efficacy analyses were insufficient therapy (21/135 [16%], alatrofloxacin/trovafloxacin and 11/140 [8%], ceftazidime/ciprofloxacin), no post-baseline clinical assessments and no post-baseline clinical assessments in evaluable window (18/135 [13%], alatrofloxacin/trovafloxacin and 16/140 [11%], ceftazidime/ciprofloxacin). Other reasons included inappropriate use of optional study antibiotics (no baseline *Pseudomonas*), inappropriate use of optional study antibiotic active against baseline pathogen, concomitant antibiotic for "other" infection during therapy, and chest x-ray negative for nosocomial pneumonia.

Of the 132 alatrofloxacin/trovafloxacin and 139 ceftazidime/ciprofloxacin clinically ITT subjects, 66 subjects in the alatrofloxacin/trovafloxacin group and 58 subjects in the ceftazidime/ciprofloxacin group had negative baseline cultures; therefore, 66 subjects in the alatrofloxacin/trovafloxacin group and 81 subjects in the ceftazidime/ciprofloxacin group were included in the bacteriological ITT analysis.

Of the 103 alatrofloxacin/trovafloxacin and 109 ceftazidime/ciprofloxacin clinically evaluable subjects, 51 subjects in the alatrofloxacin/trovafloxacin group and 43 subjects in the ceftazidime/ciprofloxacin group were not included in the bacteriologically evaluable analyses; therefore, 52 subjects in the alatrofloxacin/trovafloxacin group and 66 subjects in the ceftazidime/ciprofloxacin group were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (50/135 [37%], alatrofloxacin/trovafloxacin and 43/140 [31%], ceftazidime/ciprofloxacin). The other reasons were no post-baseline cultures (the subject [Subject 5800-0581, alatrofloxacin/trovafloxacin] excluded for this reason had no baseline pathogen and baseline culture outside evaluable window). (Subjects may have had more than one reason for exclusion from clinical and bacteriological analyses.)

Discontinuations

Of the 135 alatrofloxacin/trovafloxacin and 140 ceftazidime/ciprofloxacin treated subjects, 47 alatrofloxacin/trovafloxacin and 39 ceftazidime/ciprofloxacin subjects were prematurely discontinued from treatment as summarized in Table 2b.2.

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

	Alatrofloxacin ↓ Trovafloxacin (N=135)		Ceftazidime ↓ Ciprofloxacin (N=140)	
	Number and Percentage (%) of Subjects			
Total Discontinued	47	(35%)	39	(28%)
Discontinuations Related to Study Drug:	19	(14%)	16	(11%)
Adverse Event	7	(5%)	1	(<1%)
Insufficient Response	11	(8%)	15	(11%)
Laboratory Abnormality	1	(<1%)	0	
Discontinuations Unrelated to Study Drug:	28	(21%)	23	(16%)
Adverse Event	8	(6%)	4	(3%)
Does Not Meet Randomization Criteria	1	(<1%)	2	(1%)
Laboratory Abnormality	4	(3%)	2	(1%)
Other	5	(4%)	3	(2%)
Patient Died	9	(7%)	12	(9%)
Protocol Violation	1	(<1%)	0	

Demographics

Eighty-eight (88) of the 135 treated alatrofloxacin/trovafloxacin subjects (65%) were male and 47 (35%) were female. Ninety-nine (99) of the 140 ceftazidime/ciprofloxacin subjects (71%) were male and 41 (29%) were female. The subjects in the alatrofloxacin/trovafloxacin and ceftazidime/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 ceftazidime/ciprofloxacin treatment groups (28% and 36% ex-smoker, 37% and 35% never smoked, and 34% and 29% 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 pneumonia. The median duration (range) since onset of nosocomial pneumonia was 2 days (0-12 days) for subjects in the alatrofloxacin/trovafloxacin group and 2 days (1-19) for subjects in the ceftazidime/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 ceftazidime/ciprofloxacin groups with respect to medical history at baseline.

The mean APACHE II score at baseline for clinically evaluable subjects in the alatrofloxacin/trovafloxacin group and the ceftazidime/ciprofloxacin group was 12.66 and 13.59, respectively. Similar results were noted for clinically intent-to-treat subjects.

Reviewer's Note: The reviewing medical officer, Dr. Regina Alivisatos, felt that the difference in mean APACHE II scores at baseline was clinically relevant. As a result, clinical success rates will be displayed below for subgroups of mild/moderate versus severely ill patients, in addition to the overall analysis.

Clinical Response

A summary of clinical response for clinically evaluable subjects at EOT and EOS is presented by treatment group in Table 2b.3. Clinical response was considered therapeutically equivalent between alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin at both EOT and EOS.

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

	Alatrofloxacin ↓ Trovafloxacin (N=103)		Ceftazidime ↓ Ciprofloxacin (N=109)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	100	(100%)	107	(100%)	
Success (Cure + Improvement)	74	(74%)	75	(70%)	-8.3, 16.1
Distribution of Clinical Response:					
Cure	54	(54%)	52	(49%)	
Improvement	20	(20%)	23	(21%)	
Failure	26	(26%)	32	(30%)	
End of Study:					
Number of Subjects Assessed	85	(100%)	89	(100%)	
Success (Cure + Improvement)	56	(66%)	52	(58%)	-6.9, 21.8
Distribution of Clinical Response:					
Cure	54	(64%)	48	(54%)	
Improvement	2	(2%)	4	(4%)	
Failure	26	(31%)	32	(36%)	
Relapse	3	(4%)	5	(6%)	

The number of clinically evaluable subjects with mild/moderate and severe nosocomial pneumonia at baseline was similar between the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin treatment groups (mild/moderate nosocomial pneumonia at baseline: 47 and 49 subjects, respectively; severe nosocomial pneumonia at baseline: 56 and 60 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 higher for clinically evaluable subjects in the alatrofloxacin/trovafloxacin group compared to the ceftazidime/ciprofloxacin group at the end of treatment (89% and 74%, respectively) and at the end of study (85% and 71%, respectively) for subjects with mild/moderate nosocomial pneumonia at baseline. Among subjects with severe nosocomial pneumonia, sponsor-defined clinical success rates were comparable between the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups at the end of treatment (63% and 67%, respectively) and at the end of study (49% and 47%, 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 2b.4.

Table2b.4. Summary of Clinical Success Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens[a] (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=103)		Ceftazidime ↓ Ciprofloxacin (N=109)		Alatrofloxacin ↓ Trovafloxacin (N=103)	Ceftazidime ↓ Ciprofloxacin (N=109)	
	Number of Subjects						
Pathogen	End of Treatment				End of Study		
S. aureus	14/17	(82%)	12/20	(60%)	10/13	6/15	(40%)
P. aeruginosa	4/8		9/17	(53%)	1/5	5/14	
E. coli	6/6		5/11		5/6	5/11	
H. influenzae	7/7		5/7		4/5	4/6	
S. pneumoniae	5/6		0/3		3/4	0/3	

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 2b.5.

Table 2b.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=52)	Ceftazidime ↓ Ciprofloxacin (N=66)	95% CI	Alatrofloxacin ↓ Trovafloxacin (N=52)	Ceftazidime ↓ Ciprofloxacin (N=66)
	Number and Percentage (%) of Pathogens				
Pathogen	End of Treatment			End of Study	
S. aureus	12/16 (75%)	12/20 (60%)	(-15.2, 45.2)	11/12	6/12
P. aeruginosa	2/8	9/17 (53%)	ND	1/5	7/13
E. coli	6/6	9/11	ND	6/6	9/9
H. influenzae	6/7	6/7	ND	4/5	5/6
S. pneumoniae	5/5	0/3	ND	3/3	0/2
E. cloacae	1/4	6/6	ND	2/4	5/5

ND = Not Determined
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 2b.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 ceftazidime/ciprofloxacin at both EOT and EOS.*

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

	Alatrofloxacin ↓ Trovafloxacin	Ceftazidime ↓ Ciprofloxacin	95% CI
	Number and Percentage (%) of Subjects		
End of Treatment:			
Number of Subjects Assessed	80 (100%)	86 (100%)	
Success (Cure + Improvement)	54 (68%)	54 (63%)	(-11.0, 20.4)
End of Study:			
Number of Subjects Assessed	85 (100%)	89 (100%)	
Success (Cure + Improvement)	54 (64%)	51 (57%)	(-9.4, 21.9)

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 2b.7. Tables 2b.8 and 2b.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 treatment-related adverse events, discontinued treatment due to an adverse event, and discontinued treatment due to a treatment-related adverse event (p=0.01, 0.02 and 0.03, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution for the first two comparisons and Fisher's exact test for the third comparison).

Table 2b.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	Ceftazidime ↓ Ciprofloxacin
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	88/135 (65%)	79/140 (56%)
Treatment-Related Adverse Events	16/135 (12%)	5/140 (4%)
Discontinuations From Treatment Due to an Adverse Event	16/135 (12%)	6/140 (4%)
Discontinuations From Treatment Due to a Treatment-Related Adverse Event	7/135 (5%)	1/140 (<1%)
Clinically Significant Laboratory Values	95/119 (80%)	109/124 (88%)

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

	Alatrofloxacin ↓ Trovafloxacin (N=135)	Ceftazidime ↓ Ciprofloxacin (N=140)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	88 (65%)	79 (56%)
BODY SYSTEM WHO Term		
APPL./INJ./INCISION/INSERTION SITE	2 (1%)	8 (6%)
Insertion Site Infection/Inflammation	1 (<1%)	4 (3%)
Device Complication	1 (<1%)	6 (4%)
CARDIOVASCULAR	23 (17%)	25 (18%)
Cardiac Arrest	6 (4%)	4 (3%)
Circulatory Failure	6 (4%)	3 (2%)
CENTRAL AND PERIPHERAL NERVOUS	17 (13%)	9 (6%)
Headache	4 (3%)	2 (1%)
GASTROINTESTINAL	24 (18%)	25 (18%)
Abdominal Pain	0	6 (4%)
Constipation	4 (3%)	7 (5%)
Diarrhea	5 (4%)	2 (1%)
Vomiting	6 (4%)	2 (1%)
OTHER ADVERSE EVENTS	5 (4%)	7 (5%)
Multi-Organ Failure	3 (2%)	4 (3%)
PSYCHIATRIC	5 (4%)	13 (9%)
Agitation	0	7 (5%)
Anxiety	1 (<1%)	5 (4%)
RESPIRATORY	25 (19%)	22 (16%)
Dyspnea	4 (3%)	3 (2%)
Pneumonia	7 (5%)	6 (4%)
Pulmonary Edema	4 (3%)	0
Sinusitis	4 (3%)	1 (<1%)
SKIN AND APPENDAGES	7 (5%)	6 (4%)
Rash	4 (3%)	4 (3%)

a ≥3% of subjects in either treatment group.
b Includes data up to 7 days after last dose of active study medication

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

	Alatrofloxacin ↓ Trovafloxacin (N=135)		Ceftazidime ↓ Ciprofloxacin (N=140)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	16	(12%)	5	(4%)
BODY SYSTEM WHO Term				
AUTONOMIC NERVOUS	3	(2%)	0	
Flushing	3	(2%)	0	
GASTROINTESTINAL	10	(7%)	1	(<1%)
Vomiting	6	(4%)	0	
SKIN AND APPENDAGES	3	(2%)	1	(<1%)
Rash	3	(2%)	1	(<1%)

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

Thirty-seven (37) subjects in the alatrofloxacin/trovafloxacin and 30 subjects in the ceftazidime/ciprofloxacin died during this study. No death was considered to be treatment-related. Forty-nine (49) subjects in the alatrofloxacin/trovafloxacin group and 47 subjects in the ceftazidime/ciprofloxacin group had serious adverse events. One subject in the ceftazidime/ciprofloxacin group had a serious adverse event (elevated international normalized ratio and bruising) 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, "other" reasons, or concomitant treatment.

Sponsor Summary and Conclusion: Alatrofloxacin (equivalent to 300 mg trovafloxacin 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 was statistically equivalent to intravenous ceftazidime (2000 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 for sponsor-defined clinical success rate at the end of treatment. Sponsor-defined pathogen eradication rates were generally comparable among subjects in the alatrofloxacin/trovafloxacin and ceftazidime/ciprofloxacin groups at the end of treatment and end of study for all pathogens isolated. All isolates of *S. pneumoniae*, including two penicillin-resistant isolates, had pathogen outcomes of eradication in subjects receiving alatrofloxacin/trovafloxacin, while all isolates of *S. pneumoniae* in the ceftazidime/ciprofloxacin group had pathogen outcomes of persistent. The percentage of subjects discontinued from treatment due to adverse events was 12% in the alatrofloxacin/trovafloxacin group and 4% in the ceftazidime/ciprofloxacin group. Seven (7) subjects in the alatrofloxacin/trovafloxacin group and one subject in the ceftazidime/ciprofloxacin group were discontinued from treatment due to treatment-related adverse events. The overall percentage of all causality and treatment-related adverse events was 65% and 12%, respectively, for subjects in the alatrofloxacin/trovafloxacin group and 56% and 4%, respectively, for subjects in the ceftazidime/ciprofloxacin group. The most commonly reported treatment-related adverse event was vomiting in the

alatrofloxacin/trovafloxacin group; all treatment-related adverse events in the ceftazidime/ciprofloxacin were reported by <1% of subjects.

Reviewer's Summary and Conclusion: *Alatrofloxacin/trovafloxacin was found to be therapeutically equivalent to ceftazidime/ciprofloxacin at both EOT and EOS in terms of the 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 gentamycin 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 treatment-related adverse events, 12% versus 4% for ceftazidime/ciprofloxacin patients, discontinued treatment due to an adverse event, 12% versus 4% for ceftazidime/ciprofloxacin patients, and discontinued treatment due to a treatment-related adverse event, 5% versus <1% for ceftazidime/ciprofloxacin patients (p=0.01, 0.02 and 0.03, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution for the first two comparisons and Fisher's exact test for the third comparison).

Table 3d.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=55)	Amoxycillin 500 mg TID (N=52)	95% CI	Trovafloxacin 200 mg (N=53)	Amoxycillin 500 mg TID (N=44)	95% CI
	Number and Percentage (%) of Pathogens					
Pathogen	End of Treatment			End of Study		
H. influenzae	21/21 (100%)	17/20 (85%)	-0.6, 30.6	19/20 (95%)	10/14 (71%)	ND
S. pneumoniae	21/21 (100%)	17/19 (89%)	-3.3, 24.3	20/21 (95%)	15/18 (83%)	-7.6, 31.4
M. catarrhalis	5/5	3/3	ND	4/4	3/3	ND
C. pneumoniae	1/1	4/4	ND	1/1	2/2	ND
M. pneumoniae	4/5	2/3	ND	4/5	1/2	ND

ND = Not Determined

a Includes ≥5 isolates of a given pathogen in any treatment group as well as the atypical pathogens (*C. pneumoniae* and *M. pneumoniae*); percents and CIs 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 from treatment due to adverse events, and clinically significant laboratory values is presented in Table 3d.6. Tables 3d.7 and 3d.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 3d.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)	Amoxycillin (500 mg TID)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	52/150 (35%)	44/152 (29%)
Treatment-Related Adverse Events	24/150 (16%)	22/152 (14%)
Discontinuations From Treatment Due to Adverse Events[a]	9/150 (6%)	7/152 (5%)
Clinically Significant Laboratory Values	49/144 (34%)	44/148 (30%)

a Five (5) and two discontinuations in the trovafloxacin and amoxycillin treatment groups, respectively, were treatment-related.

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

	Trovafloxacin 200 mg (N=150)		Amoxycillin 500 mg TID (N=152)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	52	(35%)	44	(29%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS	15	(10%)	7	(5%)
Confusion	3	(2%)	1	(<1%)
Dizziness	6	(4%)	2	(1%)
Headache	5	(3%)	3	(2%)
GASTROINTESTINAL	18	(12%)	18	(12%)
Constipation	3	(2%)	0	
Diarrhea	3	(2%)	9	(6%)
Nausea	7	(5%)	6	(4%)
Vomiting	4	(3%)	1	(<1%)
GENERAL	2	(1%)	4	(3%)
Back Pain	1	(<1%)	3	(2%)
PSYCHIATRIC	6	(4%)	4	(3%)
Somnolence	3	(2%)	1	(<1%)
RESPIRATORY	8	(5%)	7	(5%)
Pneumonia	3	(2%)	2	(1%)
SKIN AND APPENDAGES	1	(<1%)	5	(3%)
Rash	0		3	(2%)

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

Reviewer's Note: The proportion of trovafloxacin patients experiencing central and peripheral nervous system events (all causalities) was marginally significantly higher than that in the amoxycillin group (p = 0.07 using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 3d.8. Summary of the Most Commonly Reported Treatment-Related Adverse Events[a,b] by Body System (All Treated Subjects)

	Trovafloxacin 200 mg/day (N=150)		Amoxycillin 500 mg TID (N=152)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event	24	(16%)	22	(14%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	9	(6%)	5	(3%)
Dizziness	5	(3%)	2	(1%)
Headache	2	(1%)	2	(1%)
GASTROINTESTINAL	12	(8%)	14	(9%)
Diarrhea	3	(2%)	7	(5%)
Dyspepsia	2	(1%)	1	(<1%)
Nausea	5	(3%)	5	(3%)
Vomiting	3	(2%)	0	
PSYCHIATRIC	4	(3%)	3	(2%)
Somnolence	2	(1%)	1	(<1%)
SKIN AND APPENDAGES	1	(<1%)	3	(2%)
Rash	0		2	(1%)

a ≥1% of subjects in either treatment group.
b Includes data up to 7 days after last dose of active study medication.

Twelve (12) subjects in the trovafloxacin group and 11 subjects in the amoxycillin group had serious adverse events. One subject in the trovafloxacin group had serious adverse events (sweating, faintness, vomiting, loss of consciousness, and allergic conjunctivitis) 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.

Five (5) subjects in the trovafloxacin group and 7 subjects in the amoxycillin group died during this study. None of the deaths was considered to be related to study drug.

Sponsor Summary and Conclusions: Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxycillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were statistically equivalent for the sponsor-defined clinical success rates at the end of treatment for both intent-to-treat and evaluable subjects. Sponsor-defined eradication rates were comparable between the two treatment groups at the end of treatment for baseline isolates of *S. pneumoniae* and *H. influenzae*. All five trovafloxacin subjects who had penicillin-resistant (MIC ≥0.1 µg/mL) *S. pneumoniae* isolated at baseline were clinical cures or improvements at the end of treatment and end of study. One subject in the amoxycillin group had penicillin-resistant *S. pneumoniae* isolated at baseline and was a clinical failure at the end of treatment and end of study. Of the subjects with a clinical response of failure or relapse, none in the trovafloxacin group and two in the amoxycillin group had an outcome of persistence confirmed by microbiology.

The percentage of subjects discontinued from treatment due to adverse events was 6% in the trovafloxacin group and 5% in the amoxycillin group. The overall percentage of all and

treatment-related adverse events in the trovafloxacin group was comparable to that of subjects in the amoxycillin group (35% and 16% versus 29% and 14%, respectively). The most commonly reported treatment-related adverse events were dizziness (3%) and nausea (3%) for subjects in the trovafloxacin group and diarrhea (5%) and nausea (3%) for subjects in the amoxycillin group.

Reviewer's Summary and Conclusions: *Trovafloxacin (200 mg once daily) administered orally for 7 to 10 days and amoxycillin (500 mg three times daily) administered orally for 7 to 10 days with optional erythromycin were considered therapeutically equivalent in terms of clinical response in clinically evaluable patients at both EOT and EOS.*

The proportion of trovafloxacin patients experiencing central and peripheral nervous system events (all causalities) was marginally significantly higher than that in the amoxycillin group ($p = 0.07$ using the test of equal proportions based on the normal approximation to the binomial distribution).

III.E. Protocol 154-134

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

Study Dates: 28 November 1994 to 13 November 1995

Study Objectives: The objective of this study was to compare the safety and efficacy of trovafloxacin and clarithromycin in the treatment of subjects with community-acquired pneumonia appropriate for oral therapy.

Study Design: Study 154-134 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (200 mg once daily) versus clarithromycin (500 mg twice daily), administered orally for 7 or 10 days for the treatment of community-acquired pneumonia.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥16 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 specimens and blood cultures at baseline).

Clinical response was to be determined by the sponsor and was 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 time point. Clinical assessment was to be based upon resolution or

improvement of radiological findings, clinical signs of infection, such as resolution of fever, disappearance or diminution in purulent sputum production, improvement or resolution of dyspnea, cough, 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 and improvement or lack of progression of acute lung infiltration on chest x-ray), 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 therapy (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, or relapse.

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

Table 3e.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (200 mg daily)		Clarithromycin (500 mg BID)	
Entered Study[a]	179		180	
All Treated	178	(>99%)	180	(100%)
Completed Treatment	147	(83%)	154	(86%)
Completed Study	157	(88%)	167	(93%)
Evaluated for Efficacy				
Clinical Intent-to-treat	163	(91%)	172	(96%)
Clinically Evaluable[b]	144	(80%)	156	(87%)
Bacteriologically Intent-to-Treat	64	(36%)	72	(40%)
Bacteriologically Evaluable[b]	59	(33%)	67	(37%)
Assessed for Safety				
Adverse Events	178	(100%)	180	(100%)
Laboratory Tests	173	(97%)	174	(97%)

a Subjects who were randomized.
b Based on End of Treatment assessment.

Reviewer's Note: Somewhat fewer trovafloxacin patients were considered clinically evaluable, however this difference was not statistically significant (p=0.11 using the test of equal proportions based on the normal approximation to the binomial distribution).

Of the 359 randomized subjects, 16 trovafloxacin subjects and 8 clarithromycin 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.

Of the 335 clinical ITT subjects, 35 were not clinically evaluable (19, trovafloxacin and 16, clarithromycin); therefore, 300 subjects (144, trovafloxacin and 156, clarithromycin) were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (15/179 [8%], trovafloxacin and 12/180 [7%], clarithromycin. Other reasons were no post-baseline clinical assessments, no post-baseline assessment in evaluable analysis windows, concomitant antibiotic therapy for intercurrent illness, prior antibiotic therapy, and randomized but not treated.

Of the 335 clinical ITT subjects, 199 had negative baseline cultures (trovafloxacin, 99 subjects and clarithromycin, 100 subjects); therefore, 136 subjects (64, trovafloxacin and 72, clarithromycin) were included in the bacteriological ITT analysis.

Of the 300 clinically evaluable subjects, 174 subjects were not included in the bacteriologically evaluable analyses (trovafloxacin, 85 subjects and clarithromycin, 89 subjects); therefore, 126 subjects (59, trovafloxacin and 67, clarithromycin) were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (trovafloxacin, 85 subjects and clarithromycin, 89 subjects). Other reasons were baseline culture outside specified visit window and no post-baseline cultures. (Subjects may have had more than one reason for exclusion from analysis.)

Discontinuations

Of the 358 treated subjects, 57 subjects were prematurely discontinued from treatment as summarized in Table 3e.2.

Table 3e.2. Summary of Premature Discontinuations From Treatment (All-Treated Subjects)

	Trovafloxacin 200 mg (N=178)	Clarithromycin 500 mg BID (N=180)
	Number and Percentage (%) of Subjects	
Total Discontinued	31 (17%)	(14%)
Discontinuations Related to Study Drug:	15 (8%)	(8%)
Adverse Event	14 (8%)	(5%)
Insufficient Response	1 (<1%)	(2%)
Laboratory Abnormality	0	(<1%)
Discontinuations Unrelated to Study Drug:	16 (9%)	(7%)
Adverse Event	4 (2%)	(<1%)
Did Not Meet Randomization Criteria	10 (6%)	(3%)
Lost To Follow-Up	1 (<1%)	(1%)
Other	0	(1%)
Withdrew Consent	1 (<1%)	(<1%)

Demographics

One hundred nine (109) of the 178 treated trovafloxacin subjects were males (61%) and 69 were females (39%) and 79 of the 180 treated clarithromycin subjects were males (44%) and 101 were females (56%). The males and females in the trovafloxacin and clarithromycin 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 clarithromycin treatment groups (28% and 27% ex-smoker, 41% and 39% never smoked, and 31% and 33% 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 (1-72 days) for subjects in the trovafloxacin group and 5 days (1-45 days) for subjects in the clarithromycin 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 trovafloxacin and clarithromycin groups with respect to medical history at baseline.

Reviewer's Note: Actually, a significantly higher proportion of clinical ITT trovafloxacin patients had ischemic heart disease at baseline (19/178 = 11% of trovafloxacin patients vs. 5/180 = 3% of clarithromycin patients; p = 0.003 using the test of equal proportions based on the normal approximation to the binomial distribution). In addition, the proportion of males in the trovafloxacin group was significantly higher than that in the clarithromycin group (p = 0.001 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 3e.3. Trovafloxacin and clarithromycin were considered therapeutically equivalent at both EOT and EOS.

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

	Trovafloxacin 200 mg (N=144)		Clarithromycin 500 mg BID (N=156)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	143	(100%)	155	(100%)	
Success (Cure + Improvement)	137	(96%)	146	(94%)	(-3.3, 6.5)
Distribution of Clinical Response:					
Cure	56	(39%)	59	(38%)	
Improvement	81	(57%)	87	(56%)	
Failure	6	(4%)	9	(6%)	
End of Study:					
Number of Subjects Assessed	135	(100%)	144	(100%)	
Success (Cure + Improvement)	120	(89%)	124	(86%)	(-5.0, 10.5)
Distribution of Clinical Response:					
Cure	108	(80%)	113	(78%)	
Improvement	12	(9%)	11	(8%)	
Failure	6	(4%)	9	(6%)	
Relapse	9	(7%)	11	(8%)	

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 3e.4.

Table 3e.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=59)		Clarithromycin 500 mg BID (N=67)		Trovafloxacin 200 mg (N=57)		Clarithromycin 500 mg BID (N=59)	
	Number of Subjects							
Pathogen	End of Treatment				End of Study			
M. pneumoniae	17/18	(94%)	18/18	(100%)	16/17	(94%)	17/17	(100%)
H. influenzae	12/12		15/16	(94%)	11/11		14/16	(88%)
S. pneumoniae	12/12		15/16	(94%)	11/12		13/15	(87%)
C. pneumoniae	6/6		10/10		5/6		5/6	

a ≥10 isolates of a given pathogen in any 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 3e.5.

Table 3e.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=59)	Clarithromycin 500 mg BID (N=67)	95% CI	Trovafloxacin 200 mg (N=56)	Clarithromycin 500 mg BID (N=59)	95% CI
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
H. influenzae	12/12	15/16 (94%)	ND	10/10	13/16 (81%)	ND
S. pneumoniae	10/11	14/15 (93%)	ND	11/12	13/15 (87%)	ND
C. pneumoniae	6/6	10/10	ND	5/6	5/6	ND
M. pneumoniae	17/18 (94%)	18/18 (100%)	-16.1, 5.0	16/17 (94%)	17/17 (100%)	-17.1, 5.3

ND = Not Determined
a ≥10 isolates of a given pathogen in any treatment group; 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 3e.6. Tables 3e.7 and 3e.8 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 3e.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	Clarithromycin 500 mg BID
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	100/178 (56%)	120/180 (67%)
Treatment-Related Adverse Events	57/178 (32%)	71/180 (39%)
Discontinuations Due to an Adverse Event[a]	18/178 (10%)	12/180 (7%)
Clinically Significant Laboratory Values	39/173 (23%)	48/174 (28%)

a For two subjects in the clarithromycin group, the investigator indicated study drug discontinuation on the adverse event page of the CRF; however, study drug discontinuation was not checked off on the subject summary page of the CRF.

Reviewer's Note: A higher proportion of clarithromycin patients experienced adverse events (all causalities); p = 0.04 using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 3e.7. A Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 200 mg (N=178)		Clarithromycin 500 mg BID (N=180)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event[c]	100	(56%)	120	(67%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	47	(26%)	28	(16%)
Dizziness	24	(13%)	8	(4%)
Headache	23	(13%)	21	(12%)
GASTROINTESTINAL SYSTEM	40	(22%)	56	(31%)
Diarrhea	5	(3%)	17	(9%)
Nausea	25	(14%)	28	(16%)
Vomiting	12	(7%)	14	(8%)
GENERAL	15	(8%)	18	(10%)
Back Pain	3	(2%)	5	(3%)
Moniliasis	2	(1%)	6	(3%)
REPRODUCTIVE	1	(<1%)	5	(3%)
Vaginitis[d]	1	(1%)	4	(4%)
RESPIRATORY SYSTEM	16	(9%)	18	(10%)
Sinusitis	3	(2%)	7	(4%)
SKIN/APPENDAGES	13	(7%)	9	(5%)
Rash	5	(3%)	2	(1%)
SPECIAL SENSES	10	(6%)	39	(22%)
Taste Perversion	7	(4%)	34	(19%)

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 females.

Reviewer's Note: A higher proportion of trovafloxacin patients experienced dizziness ($p=0.003$ using the test of equal proportions based on the normal approximation to the binomial distribution). A higher proportion of clarithromycin patients experienced diarrhea and taste perversion ($p=0.01$ and $p<0.001$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 3e.8. A Summary of the Most Commonly Reported Treatment-Related Adverse Events[a,b] by Body System (All Treated Subjects)

	Trovafloxacin 200 mg (N=178)		Clarithromycin 500 mg BID (N=180)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event[c]	57	(32%)	71	(39%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	26	(15%)	7	(4%)
Dizziness	18	(10%)	3	(2%)
Headache	6	(3%)	5	(3%)
GASTROINTESTINAL SYSTEM	27	(15%)	36	(20%)
Abdominal Pain	3	(2%)	2	(1%)
Diarrhea	2	(1%)	13	(7%)
Nausea	21	(12%)	15	(8%)
Vomiting	8	(4%)	8	(4%)
GENERAL	4	(2%)	7	(4%)
Moniliasis	2	(1%)	6	(3%)
REPRODUCTIVE	1	(<1%)	3	(2%)
Vaginitis[d]	1	(1%)	3	(3%)
SKIN AND APPENDAGES	8	(4%)	2	(1%)
Pruritus	4	(2%)	1	(<1%)
SPECIAL SENSES	7	(4%)	35	(19%)
Taste Perversion	7	(4%)	34	(19%)

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; therefore, the percentages are based on the number of males or females appropriately.

Eleven subjects in the trovafloxacin group and 13 subjects in the clarithromycin group had serious adverse events. With the exception of the one subject in the clarithromycin group who had a serious adverse event that was considered to be related to study drug, all serious adverse events were attributed to other illnesses or to the disease under study.

There were three deaths (2 trovafloxacin patients and 1 clarithromycin patient) that occurred greater than 30 days after the last treatment dose; all deaths were considered unrelated to study drug.

Sponsor Summary and Conclusion: Trovafloxacin 200 mg once daily for 7 or 10 days was statistically equivalent to clarithromycin 500 mg BID for 7 or 10 days for the treatment of community-acquired pneumonia.

The percentage of subjects discontinued from treatment due to adverse events was 10% in the trovafloxacin group and 7% in the clarithromycin group. The overall percentage of adverse events was lower (56%) in the trovafloxacin group compared to the clarithromycin group (67%); treatment-related adverse events were reported in 32% and 39% of subjects,

respectively. The most commonly reported treatment-related adverse events in the trovafloxacin group were nausea (12%) and dizziness (10%). The most commonly reported treatment-related adverse events in the clarithromycin group were taste perversion (19%), nausea (8%) and diarrhea (7%).

Reviewer's Summary and Conclusions: *Trovafloxacin 200 mg once daily for 7 or 10 days and clarithromycin 500 mg BID for 7 or 10 days were considered therapeutically equivalent in terms of clinical response at both EOT and EOS.*

Overall, a higher proportion of clarithromycin patients experienced adverse events ($p=0.04$ using the test of equal proportions based on the normal approximation to the binomial distribution). In terms of individual adverse events, a higher proportion of trovafloxacin patients experienced dizziness ($p=0.003$ using the test of equal proportions based on the normal approximation to the binomial distribution), while a higher proportion of clarithromycin patients experienced diarrhea and taste perversion ($p=0.01$ and $p<0.001$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

IV. ACUTE EXACERBATION OF CHRONIC BRONCHITIS

The efficacy and safety of oral trovafloxacin for the treatment of acute bacterial exacerbation of chronic bronchitis was assessed in three double-blind, comparative trials (154-101, 154-109, and 154-141) and in a supportive study (154-108). The comparator agents were ofloxacin (154-101), clarithromycin (154-109), ciprofloxacin (154-141), and amoxicillin (154-108).

Reviewer's Note: The sponsor assessed whether efficacy differed in various subgroups in the bronchitis 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 response rate was observed in elderly patients (≥75 versus <75 years of age) in both the trovafloxacin and comparator arms at EOT and EOS.

IV.A. Protocol 154-101

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 10 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG OR 300 MG DAILY) OR OFLOXACIN (800 MG DAILY) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study Dates: 24 November 1993 - 11 July 1994

Study Objectives: The objective of this study was to compare the safety and efficacy of two doses of trovafloxacin and ofloxacin in the treatment of subjects with acute exacerbation of chronic bronchitis.

Reviewer's Note: This was a Phase II study to examine the efficacy and safety of two different doses of trovafloxacin. The study was not adequately powered to demonstrate equivalence of either trovafloxacin regimen to ofloxacin. The study was also not adequately powered to detect significant treatment differences. As a result, any findings from this study should be interpreted with caution.

Study Design: Study 154-101 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg or 300 mg daily as a single dose in the morning) versus ofloxacin (800 mg daily as 400 mg in the morning and evening), administered orally for 10 days for the treatment of acute exacerbation of chronic bronchitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, between the ages of 18 and 72 at the baseline assessment, with clinically documented acute exacerbation of chronic bronchitis were eligible to participate in the study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment of signs and symptoms) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens).

Clinical response was to be determined by the investigator and evaluated at the end of therapy (Day 11) and at the end of study (Day 25), or at the time of discontinuation from study. Clinical response was to be based primarily on the global assessment of the clinical

presentation of the subject made by the investigator at the evaluation time point. Clinical assessment was to be based upon resolution or improvement of clinical laboratory signs of infection such as defervescence, disappearance or diminution in purulent sputum production, changes in dyspnea and cough, and stabilization in general physical condition. Additional supporting data to evaluate clinical response was to include reduction in leukocytosis. Clinical response was to be classified as cure, improvement, failure, or indeterminate.

Bacteriological response was to be determined by the sponsor and evaluated at the end of therapy (Day 11) and at the end of study (Day 25), or at the time of discontinuation from the study. Bacteriologic response was to be classified by the sponsor as indeterminate (unevaluable), eradication, presumptive eradication, persistence, relapse, superinfection, colonization, eradication with reinfection, or presumed persistence.

Reviewer's Note: Please see the medical officer's review for a more detailed definition of clinical and bacteriologic response.

The primary efficacy endpoint was the sponsor-defined clinical response at EOT.

Secondary efficacy endpoints were:

- Pathogen eradication rates at EOT and EOS,
- Investigator-defined clinical response at EOT, and sponsor- 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, including serious adverse events, clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis), physical examinations, concomitant medication use, and vital signs (blood pressure, pulse rate, body temperature, and respiratory rate).

Sponsor Efficacy Results: One planned and two unplanned interim analyses were done during the course of this study. These were done for administrative reasons only and resulted in no unblinding of individual subject data or modification of the design of the study. No adjustments were made to the nominal p-values to account for these analyses.

Reviewer's Note: As this study is underpowered to begin with, this reviewer also did not make any adjustments to the final analysis.

Analysis Groups

Table 4a.1 summarizes the number of patients enrolled, treated, and included in each of the sponsor analysis groups.

Table 4a.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg/day)	Trovafloxacin (300 mg/day)	Ofloxacin (400 mg BID)
Entered Study[a]	74	76	73
All Treated	73 (100%)	75 (100%)	73 (100%)
Completed Study	66 (90%)	55 (73%)	63 (86%)
Completed Treatment	67 (92%)	56 (75%)	64 (88%)
Evaluated for Efficacy			
Clinical Intent-to-treat	74 (100%)	76 (100%)	73 (100%)
Clinically Evaluable	65 (88%)	58 (76%)	62 (85%)
Assessed for Safety			
Adverse Events	73 (100%)	75 (100%)	73 (100%)
Laboratory Tests	72 (99%)	72 (96%)	69 (95%)

a Subjects who were randomized.

Reviewer's Note: The percent of patients completing study, completing treatment, and evaluable for efficacy was lower in the trovafloxacin 300 mg arm. For patients completing study and completing treatment, the difference was significant ($p=0.01$ using the chi-square test in both cases). For patients evaluable for efficacy, this difference was not statistically significant ($p=0.15$ using the chi-square test).

Thirty-eight (38) of 223 randomized subjects were not clinically evaluable (9/74 [12%] subjects in the trovafloxacin 100 mg group; 18/76 [24%] subjects in the trovafloxacin 300 mg group; and 11/73 [15%] subjects in the ofloxacin group). The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (4/74 [5%], trovafloxacin 100 mg; 14/76 [18%], trovafloxacin 300 mg; and 7/73 [10%], ofloxacin). Other reasons were noncompliance, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, and lost to follow-up.

Reviewer's Note: The difference among the three treatment arms with respect to percent of patients excluded from clinical efficacy analyses due to insufficient therapy / early discontinuation is statistically significant ($p=0.04$ using the chi-square test).

One hundred fifty-eight (158) of 223 randomized subjects were not bacteriologically evaluable (49/74 [66%] subjects in the trovafloxacin 100 mg group; 57/76 [75%] subjects in the trovafloxacin 300 mg group; and 52/73 [71%] subjects in the ofloxacin group). The most common reason for exclusion from bacteriological efficacy analyses was no baseline pathogen (39/74 [53%], trovafloxacin 100 mg; 43/76 [57%], trovafloxacin 300 mg; and 42/73 [58%], ofloxacin). Other reasons were baseline culture outside (specified visit) window, outcome not assessable at end of treatment, and not clinically evaluable.

Discontinuations

Of the 221 treated subjects, 34 subjects were prematurely discontinued from treatment as summarized in Table 4a.2.

Reviewer's Note: The percent of patients discontinuing due to an adverse event is higher for the trovafloxacin 300 mg arm ($p<0.001$ using the chi-square test).

Table 4a.2. A Summary of Premature Discontinuations From Treatment (All-Treated Subjects)

	Trovafloxacin 100 mg (N=73)	Trovafloxacin 300 mg (N=75)	Ofloxacin. 400 mg BID (N=73)	Total (N=221)
	Number and Percentage (%) of Subjects			
Total Discontinued	6 (8%)	19 (25%)	9 (12%)	34 (15%)
Discontinuations Related to Study Drug:	5 (7%)	19 (25%)	6 (8%)	30 (14%)
Adverse Event	4 (5%)	19 (25%)	6 (8%)	29 (13%)
Insufficient Clinical Response	1 (1%)	0	0	1 (<1%)
Discontinuations Unrelated to Study Drug:	1 (1%)	0	3 (4%)	4 (2%)
Adverse Event	0	0	1 (1%)	1 (<1%)
Did Not Meet Randomization Criteria	1 (1%)	0	0	1 (<1%)
Lost to Follow-up	0	0	2 (3%)	2 (<1%)

Demographics

The three treatment groups were comparable with respect to age, race, weight, smoking classification and sex distribution. The distribution of subjects according to smoking classification was similar for the three treatment groups (33-39% ex smoker, 28-32% never smoked, and 33-36% smoker). Demographic characteristics of clinically evaluable subjects were similar to those of all treated subjects.

The primary diagnosis for all treated subjects was acute exacerbation of chronic bronchitis. The median (range) duration since onset of the exacerbation was 7 days (1-115 days) for subjects in the trovafloxacin 100 mg group, 7 days (1-212 days) for subjects in the trovafloxacin 300 mg group and 6 days (1-110 days) for subjects in the ofloxacin group. Similar results were observed for clinically evaluable subjects. There were no marked differences among subjects in the three treatment groups with respect to medical history or physical examination findings at baseline.

Clinical Response

Sponsor-defined clinical response rates at EOT and EOS are shown for clinically evaluable subjects in Table 4a.3. Pairwise comparisons of the difference between treatment groups at EOT and EOS showed that the three treatments were similar. However, since this study was not powered to demonstrate equivalence, no definitive conclusions regarding equivalency of the three treatments can be drawn.

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.

Table 4a.3. A Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)

	Trovafloxacin 100 mg (N=65)	Trovafloxacin 300 mg (N=58)	Ofloxacin 400 mg BID (N=62)	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	61 (100%)	53 (100%)	58 (100%)	
Success (Cure + Improvement)	59 (97%)	52 (98%)	56 (97%)	
Trova 100 mg vs Trova 300 mg				(-7.2, 4.4)
Trova 100 mg vs Ofloxacin				(-6.3, 6.7)
Trova 300 mg vs Ofloxacin				(-4.4, 7.5)
Distribution of Clinical Response:				
Cure	43 (70%)	34 (64%)	39 (67%)	
Improvement	16 (26%)	18 (34%)	17 (29%)	
Failure	2 (3%)	1 (2%)	2 (3%)	
End of Study:				
Number of Subjects Assessed	64 (100%)	55 (100%)	61 (100%)	
Success (Cure + Improvement)	58 (91%)	54 (98%)	57 (93%)	
Trova 100 mg vs Trova 300 mg				(-15.5, 0.4)
Trova 100 mg vs Ofloxacin				(-12.3, 6.6)
Trova 300 mg vs Ofloxacin				(-2.4, 11.9)
Distribution of Clinical Response:				
Cure	55 (86%)	47 (85%)	50 (82%)	
Improvement	3 (5%)	7 (13%)	7 (11%)	
Failure	3 (5%)	1 (2%)	2 (3%)	
Relapse	3 (5%)	0	2 (3%)	

a Trova=trovafloxacin; CI=confidence interval

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

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

	Trovafloxacin 100 mg (N=25)	Trovafloxacin 300 mg (N=20)	Ofloxacin 400 mg BID (N=23)	Trovafloxacin 100 mg (N=27)	Trovafloxacin 300 mg (N=22)	Ofloxacin 400 mg BID (N=23)
	Number of Subjects					
Pathogen	End of Treatment			End of Study		
H. influenzae	12/12	7/7	6/6	12/13	9/9	4/6
M. catarrhalis	6/6	3/3	9/9	5/6	2/2	9/9
S. pneumoniae	3/3	3/4	3/3	2/3	4/5	3/3
H. parainfluenzae	2/2	4/4	3/3	2/2	4/4	3/3
K. pneumoniae	3/3	-	-	4/4	-	-
P. aeruginosa	1/1	1/1	2/3	1/1	1/1	2/3
C. pneumoniae[b]	3/3	2/2	3/3	3/4	2/2	3/3

a ≥3 isolates of a given pathogen in any treatment group.
b Bacteriological results obtained 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 assessed clinically at the end of treatment.