Bacteriologic Response

A summary of sponsor-defined pathogen eradication rates at EOT and EOS for the most frequently isolated baseline pathogens is presented for bacteriologically evaluable subjects in Table 4a.5.

Table 4a.5 A Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens[a] (Bacteriologically Evaluable Subjects)

	Trovafloxacin 100 mg (N=25)	Trovafloxacin 300 mg (N=19)	Ofloxacin 400 mg BID (N=21)	Trovafloxacin 100 mg (N=24)	Trovafloxacin 300 mg (N=15)	Ofloxacin 400 mg BID (N=20)
	Number of Pathogens					
Pathogen[b]	End of Treatment			End of Study		
H. influenzae	12/12	6/6	5/5	10/12	5/5	5/5
M. catarrhalis	6/6	3/3	8/8	5/5	2/2	8/8
S. pneumoniae	3/3	4/4	3/3	2/3	3/3	3/3
H. parainfluenzae	2/2	4/4	3/3	2/2	3/3	3/3
K. pneumoniae	3/3	-	-	3/3	-	-
P. aeruginosa	1/1	1/1	2/3	0/1	1/1	2/2

a ≥3 isolates of a given pathogen in any treatment group.
b All pathogens were isolated from sputum.
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 4a.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, results for the three treatment groups appeared similar but sample sizes were too small to allow for any definitive conclusions about equivalence.*

Table 4a.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)

	Trovafloxacin 100 mg	Trovafloxacin 300 mg	Ofloxacin 400 mg BID	95% CI
	Number and Percentage (%) of Subjects			
End of Treatment:				
Number of Subjects Assessed	61 (100%)	49 (100%)	57 (100%)	
Success (Cure + Improvement)	58 (95%)	48 (98%)	55 (97%)	
Trova 100 mg vs Trova 300 mg				(-16.4, 10.1)
Trova 100 mg vs Ofloxacin				(-15.2, 10.7)
Trova 300 mg vs Ofloxacin				(-11.4, 15.0)
End of Study:				
Number of Subjects Assessed	65 (100%)	54 (100%)	61 (100%)	
Success (Cure + Improvement)	57 (88%)	52 (96%)	57 (93%)	
Trova 100 mg vs Trova 300 mg				(-23.8, 5.1)
Trova 100 mg vs Ofloxacin				(-21.1, 7.9)
Trova 300 mg vs Ofloxacin				(-10.3, 17.1)

a Trova=trovafloxacin

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 4a.7. Tables 4a.8 and 4a.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: The percent of patients experiencing adverse events regardless of relationship to study drug, treatment-related adverse events, and discontinuations due to an adverse event were all significantly higher in the trovafloxacin 300 mg arm (p-values <0.0001, <0.0001, and =0.001, respectively, using the chi-square test). In addition, the rate of dizziness in the trovafloxacin 300 mg arm was rather high (40% of patients experienced dizziness; 37% of patients experienced dizziness that was considered treatment related).

Table 4a.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 100 mg (N=73)	Trovafloxacin 300 mg (N=75)	Ofloxacin 400 mg BID (N=73)
	Number and Percentage (%) of Subjects		
Adverse Events: All Causalities	22 (30%)	52 (69%)	26 (36%)
Treatment-Related Adverse Events	10 (14%)	46 (61%)	21 (29%)
Discontinuations Due to an Adverse Event[a]	4 (5%)	19 (25%)	7 (10%)
Clinically Significant Laboratory Values	27/72 (38%)	33/72 (46%)	32/69 (46%)

a With the exception of one ofloxacin subject who was discontinued due to an unrelated adverse event, all subjects were discontinued due to adverse events that were considered by the investigator to be study drug-related.

Table 4a.8. A Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 100 mg (N=73)		Trovafloxacin 300 mg (N=75)		Ofloxacin 400 mg BID (N=73)	
	Number and Percentage (%) of Subjects					
Number of Subjects With at Least One Adverse Event[c]	22	(30%)	52	(69%)	26	(36%)
BODY SYSTEM WHO Term						
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	8	(11%)	38	(51%)	10	(14%)
Dizziness	4	(5%)	30	(40%)	7	(10%)
Headache	4	(5%)	9	(12%)	2	(3%)
Confusion	0		4	(5%)	0	
GASTROINTESTINAL SYSTEM	9	(12%)	27	(36%)	10	(14%)
Nausea	4	(5%)	13	(17%)	3	(4%)
Vomiting	2	(3%)	7	(9%)	3	(4%)
Abdominal Pain	1	(1%)	5	(7%)	2	(3%)
PSYCHIATRIC SYSTEM	2	(3%)	4	(5%)	9	(12%)
Insomnia	1	(1%)	1	(1%)	7	(10%)

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.

Table 4a.9. A Summary of the Most Commonly Reported Treatment-Related Adverse Events[a,b] by Body System (All Treated Subjects)

	Trovafloxacin 100 mg (N=73)		Trovafloxacin 300 mg (N=75)		Ofloxacin 400 mg BID (N=73)	
	Number and Percentage (%) of Subjects					
Number of Subjects With at Least One Adverse Event[c]	10	(14%)	46	(61%)	21	(29%)
BODY SYSTEM WHO Term						
AUTONOMIC NERVOUS SYSTEM	1	(1%)	7	(9%)	0	
Flushing	0		3	(4%)	0	
Sweating Increased	1	(1%)	3	(4%)	0	
CARDIOVASCULAR SYSTEM	0		3	(4%)	0	
Edema Periorbital	0		2	(3%)	0	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	3	(4%)	34	(45%)	9	(12%)
Dizziness	3	(4%)	28	(37%)	7	(10%)
Headache	2	(3%)	7	(9%)	1	(1%)
Confusion	0		4	(5%)	0	
Gait Abnormal	0		2	(3%)	0	
Vertigo	0		2	(3%)	0	
GASTROINTESTINAL SYSTEM	4	(5%)	24	(32%)	8	(11%)
Nausea	2	(3%)	11	(15%)	3	(4%)
Vomiting	1	(1%)	7	(9%)	2	(3%)
Abdominal Pain	0		4	(5%)	2	(3%)
Dyspepsia	1	(1%)	3	(4%)	1	(1%)
Diarrhea	2	(3%)	1	(1%)	0	
Appetite Increased	0		2	(3%)	0	
GENERAL	0		5	(7%)	0	
Fatigue	0		2	(3%)	0	
Hot Flushes	0		2	(3%)	0	
PSYCHIATRIC SYSTEM	1	(1%)	2	(3%)	9	(12%)
Insomnia	0		0		7	(10%)
Impotence[d]	0		1	(3%)	0	
REPRODUCTIVE SYSTEM	0		0		1	(1%)
Vaginitis[d]	0		0		1	(3%)
SKIN/APPENDAGES	1	(1%)	4	(5%)	1	(1%)
Pruritus	0		3	(4%)	0	
SPECIAL SENSES	2	(3%)	7	(9%)	2	(3%)
Tinnitus	1	(1%)	2	(3%)	0	
Vision Abnormal	1	(1%)	3	(4%)	1	(1%)

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.

One subject in the trovafloxacin 300 mg group and two subjects in the ofloxacin group experienced serious adverse events that were considered to be unrelated to study drug. No subjects in any of the three treatment groups died during this study.

Sponsor's Summary and Conclusions: Trovafloxacin 100 mg or 300 mg and ofloxacin 400 mg BID were similar with respect to clinical response rates at the end of treatment and at the end of the study for both intent-to-treat and evaluable subjects. Pathogen eradication rates were comparable among the three treatment groups at the end of treatment. At the end of study, bacteriologic relapses were observed in four subjects in the trovafloxacin 100 mg group. However, because of the small number of bacteriologically evaluable subjects in this treatment group (N=24), no definitive conclusions could be drawn. Both trovafloxacin 100 mg and 300 mg once daily were generally well tolerated; however, the incidence of adverse events in the 100 mg group was lower than that observed in the 300 mg group.

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 100 mg, trovafloxacin 300 mg, and ofloxacin appeared similar at both EOT and EOS (perhaps more similar at EOT), but sample sizes were too small to allow for any definitive conclusions about equivalence.*

The percent of patients experiencing adverse events regardless of relationship to study drug, treatment-related adverse events, and discontinuations due to an adverse event were all significantly different across treatment groups (rates were higher in the trovafloxacin 300 mg arm; p-values <0.0001, <0.0001, and =0.001, respectively, using the chi-square test). In addition, the rate of dizziness in the trovafloxacin 300 mg arm was rather high (40% of patients experienced dizziness; 37% of patients experienced dizziness that was considered treatment related).

IV.B. Protocol 154-109

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) OR CLARITHROMYCIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study Dates: 16 November 1994 - 22 June 1995

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

Study Design: Study 154-109 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily) versus clarithromycin (500 mg twice daily) administered orally for 7 days for the treatment of acute bacterial exacerbation of chronic bronchitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥40 years of age at the baseline visit, with clinically documented acute bacterial exacerbation of chronic bronchitis were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical and laboratory signs of

infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens).

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the 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 signs of infection such as disappearance or diminution in purulent sputum production, changes in dyspnea and cough 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 acute bacterial exacerbation chronic bronchitis to the baseline level that existed prior to the occurrence of acute exacerbation), improvement (resolution of sputum purulence but incomplete resolution of the other signs and symptoms of acute bacterial exacerbation of chronic bronchitis and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of acute bacterial exacerbation of chronic bronchitis or a need for additional antibiotic for inadequate response).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the 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 and;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

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

<u>Reviewer's Note:</u> As with study 154-101, the reviewing medical officer, Dr. Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.

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

Sponsor Efficacy Results:

Analysis Groups

Table 4b.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Table 4b.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg daily)	Clarithromycin (500 mg BID)
Entered Study[a]	210 (100%)	200 (100%)
All Treated	210 (100%)	200 (100%)
Completed Treatment	201 (96%)	183 (92%)
Completed Study	206 (98%)	188 (94%)
Evaluated for Efficacy		
Clinical ITT	208 (>99%)	199 (>99%)
Clinically Evaluable[b]	203 (97%)	188 (94%)
Bacteriologically ITT	96 (46%)	86 (43%)
Bacteriologically Evaluable[b]	93 (44%)	81 (41%)
Assessed for Safety		
Adverse Events	210 (100%)	200 (100%)
Laboratory Tests	204 (97%)	189 (95%)

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

Of the 410 randomized subjects, two trovafloxacin subjects and one clarithromycin subject had an inappropriate baseline diagnosis due to insufficient symptoms or inappropriate sputum histology and were excluded from all clinical and bacteriological ITT and evaluable analyses.

Of the 407 clinical ITT subjects, 16 were not clinically evaluable (5 subjects in the trovafloxacin group and 11 subjects in the clarithromycin group); therefore 391 (203 trovafloxacin and 188 clarithromycin) subjects were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was prior antibiotic therapy (4 trovafloxacin and 3 clarithromycin subjects). Other reasons were no post-baseline clinical assessment, insufficient therapy, and concomitant antibiotic therapy for intercurrent illness.

Of the 407 clinical ITT subjects, 225 were not included in the bacteriologically ITT analysis due to negative baseline cultures (trovafloxacin, 112 subjects and clarithromycin, 113 subjects); therefore, 182 (96 trovafloxacin and 86 clarithromycin) subjects were included in the bacteriological ITT analysis.

Of the 391 clinically evaluable subjects, 217 subjects were not included in the bacteriologically evaluable analyses (trovafloxacin, 110 subjects and clarithromycin, 107 subjects); therefore 174 subjects (93 trovafloxacin and 81 clarithromycin) were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (trovafloxacin, 108 subjects and clarithromycin, 105 subjects). Other reasons were baseline culture outside specified visit window and no post-baseline cultures.

Discontinuations

Of the 410 treated subjects, 26 subjects were prematurely discontinued from treatment as summarized in Table 4b.2.

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

	Trovafloxacin 100 mg (N=210)		Clarithromycin 500 mg BID (N=200)		Total (N=410)	
	Number and Percentage (%) of Subjects					
Total Discontinued	9	(4%)	17	(9%)	26	(6%)
Discontinuations Related to Study Drug:	6	(3%)	10	(5%)	16	(4%)
Adverse Event	3	(1%)	6	(3%)	9	(2%)
Insufficient Response	3	(1%)	4	(2%)	7	(2%)
Discontinuations Unrelated to Study Drug:	3	(1%)	7	(4%)	10	(2%)
Adverse Event	1	(<1%)	3	(2%)	4	(<1%)
Did Not Meet Randomization Criteria	1	(<1%)	1	(<1%)	2	(<1%)
Laboratory Abnormality	1	(<1%)	1	(<1%)	2	(<1%)
Protocol Violation	0		2	(1%)	2	(<1%)

Demographics

One hundred eighty-nine (189) of the 410 treated subjects were male (102, trovafloxacin; 87, clarithromycin) and 221 were female (108, trovafloxacin; 113, clarithromycin). 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 groups (33% and 37% ex-smoker, 30% and 26% never smoked, and 36% and 38% 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 acute bacterial exacerbation of chronic bronchitis. The median duration since onset of acute bacterial exacerbation of chronic bronchitis was 7 days for subjects in both the trovafloxacin and clarithromycin groups (range of 1 to 182 days for trovafloxacin, 1 to 69 days for clarithromycin). Similar results were observed for clinically evaluable subjects.

Clinical Response

A summary of clinical response for clinically evaluable subjects at the end of treatment and at the end of study is presented by treatment group in Table 4b.3. Trovafloxacin was considered therapeutically equivalent to clarithromycin at both EOT and EOS.

Reviewer's Note: One of the investigators involved in this study, Dr. Fiddes, has plead guilty to several violations of FDA regulations. Dr. Fiddes enrolled a small number of patients in this study, 12 total (6 trovafloxacin and 6 clarithromycin patients), thus the exclusion of data from his center does not effect conclusions about efficacy.

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

	Trovafloxacin 100 mg (N=203)		Clarithromycin 500 mg BID (N=188)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	203	(100%)	188	(100%)	
Success (Cure + Improvement)	181	(89%)	160	(85%)	(-2.6, 10.7)
Distribution of Clinical Response:					
Cure	87	(43%)	75	(40%)	
Improvement	94	(46%)	85	(45%)	
Failure	22	(11%)	28	(15%)	
End of Study:					
Number of Subjects Assessed	197	(100%)	178	(100%)	
Success (Cure + Improvement)	158	(80%)	131	(74%)	(-1.9, 15.1)
Distribution of Clinical Response:					
Cure	140	(71%)	110	(62%)	
Improvement	18	(9%)	21	(12%)	
Failure	22	(11%)	28	(16%)	
Relapse	17	(9%)	19	(11%)	

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 4b.4.

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

	Trovafloxacin 100 mg (N=93)		Clarithromycin 500 mg BID (N=83)		Trovafloxacin 100 mg (N=91)		Clarithromycin 500 mg BID (N=80)	
	Number and Percentage (%) of Subjects							
Pathogen	End of Treatment				End of Study			
H. influenzae	24/26	(92%)	16/18	(89%)	24/26	(92%)	7/16	(44%)
M. catarrhalis	14/18	(78%)	16/20	(80%)	12/17	(71%)	14/19	(74%)
S. aureus	13/14		10/12		11/13		9/12	
P. aeruginosa	13/14		8/8		10/14		7/8	
S. pneumoniae	7/7		10/11		6/7		10/11	

a ≥10 isolates of a given pathogen in any treatment group.
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 4b.5.

Table 4b.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens[a] (Bacteriologically Evaluable Subjects)

	Trovafloxacin 100 mg (N=93)	Clarithromycin 500 mg BID (N=81)	95% CI	Trovafloxacin 100 mg (N=87)	Clarithromycin 500 mg BID (N=77)	95% CI
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
H. influenzae	24/26 (92%)	12/16 (75%)	-6.3, 40.9	22/24 (92%)	10/16 (63%)	3.0, 55.3
M. catarrhalis	13/17 (76%)	17/18 (94%)	-40.7, 4.8	13/16 (81%)	16/18 (89%)	-31.7, 16.4
S. aureus	14/14	12/12	ND	13/13	11/12	ND
P. aeruginosa	9/13	6/8	ND	9/14	6/8	ND
S. pneumoniae	6/7	11/11	ND	7/7	11/11	ND

ND = Not Determined
a ≥10 isolates of a given pathogen in any treatment group. Percents are 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 4b.6 presents clinical response for the MO clinically evaluable patient group at both EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, trovafloxacin was considered therapeutically equivalent to clarithromycin at both EOT and EOS.*

Table 4b.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)

	Trovafloxacin 100 mg	Clarithromycin 500 mg BID	95% CI
	Number and Percentage (%) of Subjects		
End of Treatment:			
Number of Subjects Assessed	196 (100%)	176 (100%)	
Success (Cure + Improvement)	174 (89%)	148 (84%)	(-2.8, 12.2)
End of Study:			
Number of Subjects Assessed	196 (100%)	176 (100%)	
Success (Cure + Improvement)	157 (80%)	129 (73%)	(-2.3, 15.9)

Reviewer's Note: One of the investigators involved in this study, Dr. Fiddes, has plead guilty to several violations of FDA regulations. Dr. Fiddes enrolled a small number of patients in this study, 12 total (6 trovafloxacin and 6 clarithromycin patients), thus the exclusion of data from his center does not effect conclusions about efficacy.

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 4b.7. Tables 4b.8 and 4b.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Reviewer's Note: There was a higher incidence of both adverse events, regardless of relationship to study drug, and treatment-related adverse events in the clarithromycin arm ($p = 0.04$ and $p < 0.0001$, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 4b.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 100 mg daily (N=210)	Clarithromycin 500 mg BID (N=200)
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	85/210 (40%)	101/200 (51%)
Treatment-Related Adverse Events	42/210 (20%)	76/200 (38%)
Discontinuations Due to an Adverse Event[a]	4/210 (2%)	8/200 (4%)
Clinically Significant Laboratory Values	28/204 (14%)	25/189 (13%)

a With the exception of one subject in the trovafloxacin group and two subjects in the clarithromycin group, all of whom were discontinued due to adverse events that were attributed to other illnesses or to the disease under study, all subjects who were discontinued from treatment had adverse events that were considered by the investigator to be study drug-related.

Table 4b.8. A Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 100 mg (N=210)		Clarithromycin 500 mg BID (N=200)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event[c]	85	(40%)	101	(51%)
BODY SYSTEM WHO Term				
AUTONOMIC NERVOUS SYSTEM	5	(2%)	6	(3%)
Mouth Dry	1	(<1%)	5	(3%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	36	(17%)	23	(12%)
Dizziness	12	(6%)	6	(3%)
Headache	20	(10%)	9	(5%)
GASTROINTESTINAL SYSTEM	26	(12%)	47	(24%)
Constipation	1	(<1%)	6	(3%)
Diarrhea	6	(3%)	14	(7%)
Nausea	12	(6%)	19	(10%)
Stools Loose	1	(<1%)	5	(3%)
Vomiting	3	(1%)	6	(3%)
PSYCHIATRIC	9	(4%)	17	(9%)
Insomnia	3	(1%)	13	(7%)
RESPIRATORY SYSTEM	20	(10%)	17	(9%)
Rhinitis	8	(4%)	5	(3%)
Sinusitis	6	(3%)	2	(1%)
SPECIAL SENSES	10	(5%)	32	(16%)
Taste Perversion	4	(2%)	31	(16%)

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.

Table 4b.9. A Summary of the Most Commonly Reported Treatment-Related Adverse Events[a,b] by Body System (All Treated Subjects)

	Trovafloxacin 100 mg (N=210)		Clarithromycin 500 mg BID (N=200)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event[c]	42	(20%)	76	(38%)
BODY SYSTEM WHO Term				
AUTONOMIC NERVOUS SYSTEM	4	(2%)	4	(2%)
Mouth Dry	1	(<1%)	3	(2%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	18	(9%)	12	(6%)
Dizziness	6	(3%)	5	(3%)
Headache	7	(3%)	2	(1%)
Vertigo	3	(1%)	4	(2%)
GASTROINTESTINAL SYSTEM	15	(7%)	40	(20%)
Constipation	0	(0%)	5	(3%)
Diarrhea	5	(2%)	11	(6%)
Nausea	11	(5%)	18	(9%)
Stools Loose	1	(<1%)	5	(3%)
Vomiting	0	(0%)	5	(3%)
GENERAL	2	(<1%)	5	(3%)
Moniliasis	1	(<1%)	4	(2%)
PSYCHIATRIC SYSTEM	7	(3%)	7	(4%)
Insomnia	2	(<1%)	5	(3%)
SPECIAL SENSES	4	(2%)	31	(16%)
Taste Perversion	4	(2%)	31	(16%)

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.

The most commonly reported treatment-related adverse events in the trovafloxacin group were nausea, headache, and dizziness and the most commonly reported treatment-related adverse events in the clarithromycin group were taste perversion, nausea, and diarrhea.

Fourteen (14) subjects experienced serious adverse events (3 subjects in the trovafloxacin group and 11 subjects in the clarithromycin group). With the exception of one subject in the clarithromycin group, whose serious adverse event (nausea/vomiting) was considered by the investigator to be related to study drug, all serious adverse events were attributed to other illnesses (acute pneumothorax, respiratory failure, atrial fibrillation, angina pectoris, acute exacerbation of COPD, cerebral vascular accident, or fever of unknown origin) or to the disease under study (bronchitis and/or bronchospasm). The serious adverse event(s) resolved for 13 subjects and resulted in death (due to cardiac arrest) for one subject in the clarithromycin group.

No subject in the trovafloxacin group had a clinically significant liver or renal function laboratory abnormality.

Sponsor's Summary and Conclusions: Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to clarithromycin 500 mg twice daily for 7 days for clinical success rates at the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. Pathogen eradication rates for *H. influenzae* at both the end of treatment and the end of study were higher in the trovafloxacin group compared to the clarithromycin group (end of treatment: 92% versus 75%, respectively; end of study: 92% versus 63%, respectively). The overall incidence of all and treatment-related adverse events was lower among subjects in the trovafloxacin group as compared to subjects in the clarithromycin group (40% and 20% versus 51% and 38%, respectively). The percentage of subjects with adverse events leading to discontinuation was comparable between the two treatment groups (2% and 4%, respectively). Subjects in the trovafloxacin group had lower frequencies of gastrointestinal system (12% versus 24%) and special senses (5% versus 16%) adverse events and a higher frequency of central and peripheral nervous system (17% versus 12%) adverse events compared to subjects in the clarithromycin group. The frequency and type of clinically significant laboratory abnormalities were comparable between the two treatment groups.

Reviewer's Summary and Conclusions: *Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to clarithromycin 500 mg twice daily for 7 days in terms of clinical success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.*

There was a higher incidence of both adverse events, regardless of relationship to study drug, and treatment-related adverse events in the clarithromycin arm ($p=0.04$ and $p<0.0001$, respectively). The most commonly reported adverse events in the trovafloxacin group were headache (10%), dizziness (6%), and nausea (6%) and the most commonly reported adverse events in the clarithromycin group were taste perversion (16%), nausea (10%), diarrhea (7%), and insomnia (7%).

IV.C. Protocol 154-141

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL COMPARING 7 DAYS OF ORAL THERAPY WITH TROVAFLOXACIN (100 MG DAILY) AND CIPROFLOXACIN (500 MG BID) FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS.

Study Dates: 21 December 1994 to 21 September 1995

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

Study Design: Study 154-141 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily) versus ciprofloxacin

(500 mg twice daily) administered orally for 7 days for the treatment of acute bacterial exacerbation of chronic bronchitis.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥40 years of age at the baseline visit, with clinically documented acute bacterial exacerbation of chronic bronchitis were eligible to participate in this study.

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

Clinical response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the 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 signs of infection such as disappearance or diminution in purulent sputum production, changes in dyspnea and cough 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 chronic bronchitis to the baseline level that existed prior to the occurrence of acute bacterial exacerbation), improvement (resolution of sputum purulence but incomplete resolution of the other signs and symptoms of chronic bronchitis and no requirement for additional antibiotic), or failure (lack of resolution of any of the signs and symptoms of chronic bronchitis or a need for additional antibiotic for inadequate response).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Visit 3; Day 8) and at the end of study (Visit 4; Day 28), or at the time of discontinuation from the 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 and;
- Pathogen eradication rates at EOT.

Secondary efficacy endpoints were:

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

Reviewer's Note: As with studies 154-101 and 154-109, the reviewing medical officer, Dr. Alivisatos, considered clinical response at EOS to be the primary efficacy endpoint. Please see her review for a definition of MO outcome and MO evaluability criteria. MO results will be presented below alongside sponsor results.

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

Sponsor Efficacy Results:

Analysis Groups

Table 4c.1 outlines the number of patients enrolled, treated, and used in each of the sponsor analysis groups.

Reviewer's Note: Somewhat fewer trovafloxacin patients were included in the bacteriologically ITT and evaluable analysis groups, due mostly to a higher number of negative baseline cultures in the trovafloxacin group. Neither difference was statistically significant (p = 0.29 and 0.13, respectively, using the test of equal proportions based on the normal approximation to the binomial distribution).

Table 4c.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (100 mg daily)		Ciprofloxacin (500 mg BID)	
Entered Study[a]	131		125	
All Treated	131	(100%)	125	(100%)
Completed Treatment	121	(92%)	114	(91%)
Completed Study	123	(94%)	120	(96%)
Evaluated for Efficacy				
Clinical Intent-to-Treat	125	(95%)	121	(97%)
Clinically Evaluable[b]	116	(89%)	115	(92%)
Bacteriologically Intent-to-Treat	70	(53%)	75	(60%)
Bacteriologically Evaluable[b]	60	(46%)	69	(55%)
Assessed for Safety				
Adverse Events	131	(100%)	125	(100%)
Laboratory Tests	124	(95%)	118	(94%)

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

Of the 256 randomized subjects, six trovafloxacin subjects and four ciprofloxacin subjects had an inappropriate baseline diagnosis due to insufficient symptoms or inappropriate sputum histology and were excluded from all clinical and bacteriological intent-to-treat and evaluable analyses.

Of the 246 clinical ITT subjects, 15 were not clinically evaluable (9 subjects in the trovafloxacin group and 6 subjects in the ciprofloxacin group); thus, 231 (116, trovafloxacin and 115, ciprofloxacin) were clinically evaluable. The most common reason for exclusion from clinical efficacy analyses was insufficient therapy due to early discontinuation from treatment or study (7 trovafloxacin and 5 ciprofloxacin subjects). Other reasons were no post-baseline clinical assessment, no post-baseline assessment in evaluable analysis windows, prior antibiotic therapy, and concomitant antibiotic therapy for intercurrent illness.

Of the 246 clinical ITT subjects, 101 were not included in the bacteriological intent-to-treat analysis due to negative baseline cultures (55, trovafloxacin and 46, ciprofloxacin); thus, 145 (70, trovafloxacin and 75, ciprofloxacin) subjects were included in the bacteriological intent-to-treat analysis.

Of the 231 clinically evaluable subjects, 102 subjects were not included in the bacteriologically evaluable analyses (trovafloxacin 56 subjects and ciprofloxacin 46 subjects); thus, 129 (60, trovafloxacin and 69, ciprofloxacin) were bacteriologically evaluable. The most common reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (trovafloxacin, 52 subjects and ciprofloxacin, 44 subjects). Other reasons were baseline culture outside specified visit window and no post-baseline cultures.

Discontinuations

Of the 256 treated subjects, 21 subjects were prematurely discontinued from treatment as summarized in Table 4c.2.

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

	Trovafloxacin 100 mg (N=131)		Ciprofloxacin 500 mg BID (N=125)		Total (N=256)	
	Number and Percentage (%) of Subjects					
Total Discontinued	10	(8%)	11	(9%)	21	(8%)
Discontinuations Related to Study Drug:	2	(2%)	6	(5%)	8	(3%)
Adverse Event	1	(<1%)	5	(4%)	6	(2%)
Insufficient Response	1	(<1%)	1	(<1%)	2	(<1)
Discontinuations Unrelated to Study Drug:	8	(6%)	5	(4%)	13	(5%)
Adverse Event	2	(2%)	2	(2%)	4	(2%)
Lost to Follow-up	5	(4%)	1	(<1%)	6	(2%)
Other	0		1	(<1%)	1	(<1%)
Withdrawn Consent	1	(<1%)	1	(<1%)	2	(<1%)

Demographics

One hundred fifty-three (153) of the 256 treated subjects were male (76, trovafloxacin; 77, ciprofloxacin) and 103 were female (55, trovafloxacin; 48, ciprofloxacin). The males and females in the trovafloxacin and ciprofloxacin 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 ciprofloxacin groups (33% and 43% ex-smoker, 16% and 15% never smoked, and 51% and 42% 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 acute bacterial exacerbation of chronic bronchitis. The median duration since onset of acute bacterial exacerbation of chronic bronchitis was 6 days for subjects in both the trovafloxacin and ciprofloxacin

treatment groups (range of 1 to 163 days for trovafloxacin patients, 1 to 81 days for ciprofloxacin patients). Similar results were observed for clinically evaluable subjects.

Clinical Response

A summary of clinical response for clinically evaluable subjects at EOT and EOS is presented by treatment group in Table 4c.3. Clinical response was considered therapeutically equivalent between trovafloxacin and clarithromycin at both EOT and EOS.

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

	Trovafloxacin 100 mg (N=116)		Ciprofloxacin 500 mg BID (N=115)		95% CI
	Number and Percentage (%) of Subjects				
End of Treatment:					
Number of Subjects Assessed	116	(100%)	115	(100%)	
Success (Cure + Improvement)	111	(96%)	106	(92%)	(-2.6, 9.7)
Distribution of Clinical Response:					
Cure	47	(41%)	47	(41%)	
Improvement	64	(55%)	59	(51%)	
Failure	5	(4%)	9	(8%)	
End of Study:					
Number of Subjects Assessed	110	(100%)	102	(100%)	
Success (Cure + Improvement)	95	(86%)	81	(79%)	(-3.2, 17.1)
Distribution of Clinical Response:					
Cure	87	(79%)	62	(61%)	
Improvement	8	(7%)	19	(19%)	
Failure	5	(5%)	9	(9%)	
Relapse	10	(9%)	12	(12%)	

Table 4c.4 summarizes sponsor clinical success rates for clinically evaluable subjects at both the end of treatment and end of study for the most frequently isolated baseline pathogens.

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

	Trovafloxacin 100 mg (N=63)	Ciprofloxacin 500 mg BID (N=71)	Trovafloxacin 100 mg (N=59)	Ciprofloxacin 500 mg BID (N=65)
	Number and Percentage (%) of Subjects			
Pathogen	End of Treatment		End of Study	
H. influenzae	15/17 (88%)	18/20 (90%)	12/16 (75%)	14/19 (74%)
M. catarrhalis	13/13	12/13	11/13	9/12
H. parainfluenzae	7/7	11/12	6/6	8/10
S. aureus	12/13	9/10	9/11	8/9

a ≥10 isolates of a given pathogen in any treatment group. Percents are displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Results

Table 4c.5 presents a summary of sponsor-defined pathogen eradication rates for bacteriologically evaluable subjects at both the end of treatment and end of study for the most frequently isolated baseline pathogens.

Table 4c.5. Summary of Sponsor-Defined Pathogen Eradication Rates at EOT and EOS For the Most Frequently Isolated Baseline Pathogens[a] (Bacteriologically Evaluable Subjects)

	Trovafloxacin 100 mg (N=60)	Ciprofloxacin 500 mg BID (N=69)	95% CI	Trovafloxacin 100 mg (N=55)	Ciprofloxacin 500 mg BID (N=62)	95% CI
	Number of Pathogens					
Pathogen	End of Treatment			End of Study		
H. influenzae	15/16 (94%)	18/19 (95%)	-16.5, 14.6	13/15 (87%)	13/16 (81%)	-20.3, 31.1
M. catarrhalis	12/12	12/12	ND	10/12	9/12	ND
H. parainfluenzae	7/7	11/12	ND	6/6	9/10	ND
S. aureus	11/12	8/9	ND	10/11	7/8	ND

ND = Not Determined
a ≥10 isolates of a given pathogen in any treatment group. Percents are 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 4c.6 presents clinical response for the MO clinically evaluable patient group at both EOT and EOS. Clinical response at EOS was considered primary. As with the sponsor's analysis, trovafloxacin was considered therapeutically equivalent to ciprofloxacin at both EOT and EOS.*

Table 4c.6. Clinical Response at EOT and EOS (MO Clinically Evaluable Subjects)

	Trovafloxacin 100 mg	Ciprofloxacin 500 mg BID	95% CI
	Number and Percentage (%) of Subjects		
End of Treatment:			
Number of Subjects Assessed	109 (100%)	101 (100%)	
Success (Cure + Improvement)	104 (95%)	92 (91%)	(-3.4, 12.1)
End of Study:			
Number of Subjects Assessed	109 (100%)	101 (100%)	
Success (Cure + Improvement)	93 (85%)	79 (78%)	(-4.3, 18.5)

Safety Results: The number and percentage of subjects with adverse events (all causalities and treatment-related), discontinuations due to adverse events, and clinically significant laboratory values is presented in Table 4c.7. Tables 4c.8 and 4c.9 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 4c.7. A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values

	Trovafloxacin 100 mg daily	Ciprofloxacin 500 mg BID
	Number and Percentage (%) of Subjects	
Adverse Events: All Causalities	51/131 (39%)	50/125 (40%)
Treatment-Related Adverse Events	25/131 (19%)	27/125 (22%)
Discontinuations Due to an Adverse Event[a]	3/131 (2%)	7/125 (6%)
Clinically Significant Laboratory Values	20/124 (16%)	17/118 (14%)

a With the exception of two subjects in the trovafloxacin group and two subjects in the ciprofloxacin group, all of whom were discontinued due to adverse events that were attributed to other illnesses or to the disease under study, all subjects who were discontinued from treatment had adverse events that were considered by the investigator to be study drug-related.

Table 4c.8. A Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 100 mg (N=131)		Ciprofloxacin 500 mg BID (N=125)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event[c]	51	(39%)	50	(40%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	10	(8%)	14	(11%)
Dizziness	5	(4%)	7	(6%)
Headache	5	(4%)	4	(3%)
GASTROINTESTINAL SYSTEM	25	(19%)	27	(22%)
Abdominal Pain	4	(3%)	2	(2%)
Constipation	4	(3%)	1	(<1%)
Diarrhea	4	(3%)	6	(5%)
Dyspepsia	1	(<1%)	4	(3%)
Nausea	11	(8%)	13	(10%)
PSYCHIATRIC	8	(6%)	11	(9%)
Insomnia	5	(4%)	5	(4%)

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.

Table 4c.9. A Summary of the Most Commonly Reported Treatment-Related Adverse Events[a,b] by Body System (All Treated Subjects)

	Trovafloxacin 100 mg (N=131)		Ciprofloxacin 500 mg BID (N=125)	
	Number and Percentage (%) of Subjects			
Number of Subjects With at Least One Adverse Event[c]	25	(19%)	27	(22%)
BODY SYSTEM WHO Term				
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	3	(2%)	6	(5%)
Dizziness	3	(2%)	5	(4%)
Tremor	0	(0%)	3	(2%)
GASTROINTESTINAL SYSTEM	17	(13%)	19	(15%)
Abdominal Pain	2	(2%)	2	(2%)
Constipation	2	(2%)	1	(<1%)
Diarrhea	1	(<1%)	3	(2%)
Dyspepsia	0	(0%)	3	(2%)
Flatulence	2	(2%)	1	(<1%)
Nausea	9	(7%)	9	(7%)
Stools Loose	2	(2%)	2	(2%)
Vomiting	2	(2%)	2	(2%)
PSYCHIATRIC SYSTEM	5	(4%)	4	(3%)
Insomnia	2	(2%)	2	(2%)
Somnolence	2	(2%)	0	(0%)
REPRODUCTIVE SYSTEM	1	(<1%)	1	(<1%)
Vaginitis[d]	1	(2%)	1	(2%)
SPECIAL SENSES	2	(2%)	1	(<1%)
Taste Perversion	2	(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.
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 in the number of males or females appropriately.

Nausea was the most commonly reported treatment-related adverse event in both groups (each group, 7%).

Four subjects in the trovafloxacin group and seven subjects in the ciprofloxacin group experienced serious adverse events. Of these, one subject in the trovafloxacin group died 20 days post-treatment. This death was considered to be unrelated to study drug and was attributed to the subject's underlying illness (hypertension).

No clinically significant laboratory abnormalities were noted in any trovafloxacin subject for liver function tests.

Sponsor's Summary and Conclusions: Trovafloxacin 100 mg once daily for 7 days was statistically equivalent to that of ciprofloxacin 500 mg twice daily for 7 days for clinical

success rates in subjects with acute bacterial exacerbation of chronic bronchitis. Sponsor-defined pathogen eradication rates were similar between the two treatment groups. The overall incidence of adverse events for subjects in the trovafloxacin group was comparable to that of subjects in the ciprofloxacin group (39% and 40%, respectively), as was the frequency of treatment-related adverse events (19% and 22%, respectively) and adverse events leading to discontinuation (2% and 6%, respectively). The most commonly reported adverse event in both treatment groups was nausea. The frequency and type of adverse laboratory events were comparable between the two treatment groups.

Reviewer's Summary and Conclusions: *Trovafloxacin 100 mg once daily for 7 days was considered therapeutically equivalent to ciprofloxacin 500 mg twice daily for 7 days in terms of clinical success rates at both the end of treatment and end of study in subjects with acute bacterial exacerbation of chronic bronchitis. This was true for both the sponsor and the MO analyses.*

The most commonly reported adverse events in the trovafloxacin group were nausea (8%), dizziness (4%), headache (4%), and insomnia (4%) and the most commonly reported adverse events in the ciprofloxacin group were nausea (10%), dizziness (6%), diarrhea (5%), and insomnia (4%).

IV.D. Protocol 154-108

Reviewer's Note: This study is considered supportive by both the sponsor and the review team as it examined two 5 day regimens of trovafloxacin for the treatment of acute bacterial exacerbation of chronic bronchitis. The sponsor wishes to market a 7 day regimen of trovafloxacin for the treatment of acute bacterial exacerbation of chronic bronchitis. Results are summarized briefly below.

A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING TROVAFLOXACIN WITH AMOXYCILLIN FOR THE TREATMENT OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Study Dates: December 8, 1994 - December 19, 1995

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

Study Design: Study 154-108 was a randomized, double-blind, double-dummy, comparative, multicenter trial of trovafloxacin (100 mg once daily or 200 mg once daily) versus amoxycillin (500 mg three times daily) administered orally for 5 days for the treatment of acute bacterial exacerbation of chronic bronchitis.

	Evaluation Groups: Trovafloxacin (100 mg daily)		Trovafloxacin (200 mg daily)		Amoxycillin (500 mg TID)	
Entered Study[a]	145		135		132	
All Treated	145	(100%)	134	(100%)	132	(100%)
Completed Treatment	136	(94%)	129	(96%)	128	(97%)
Completed Study	133	(92%)	129	(96%)	126	(95%)
Evaluated for Efficacy						
Clinical Intent-to-Treat	135	(93%)	126	(93%)	116	(88%)
Clinically Evaluable[b]	128	(88%)	118	(87%)	114	(86%)
Bacteriologically Intent-to-Treat	91	(63%)	85	(63%)	80	(61%)
Bacteriologically Evaluable[b]	84	(58%)	79	(59%)	79	(60%)
Assessed for Safety						
Adverse Events	145	(100%)	134	(100%)	132	(100%)
Laboratory Tests	136	(94%)	126	(94%)	126	(95%)

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

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women ≥40 years of age at the baseline visit, with clinically documented acute bacterial exacerbation of chronic bronchitis were eligible to participate in this study.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of clinical and laboratory signs of infection) and bacteriologic response (based on eradication of causative organisms isolated from sputum specimens). 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: Sponsor-defined clinical success rates (cure + improvement) were similar among all three treatment groups in both the clinically evaluable and intent-to-treat analyses at the end of treatment and at the end of study.

A Summary of the Sponsor's Assessment of Clinical Response

(Clinically Evaluable Subjects)

	End of Treatment			End of Study		
	Trovafloxacin 100 mg (N=128)	Trovafloxacin 200 mg (N=118)	Amoxycillin 500 mg TID (N=114)	Trovafloxacin 100 mg (N=123)	Trovafloxacin 200 mg (N=113)	Amoxycillin 500 mg TID (N=109)
	Number and Percentage (%) of Subjects					
Number of Subjects Assessed	128 (100%)	118 (100%)	114 (100%)	123 (100%)	113 (100%)	109 (100%)
Success (Cure + Improvement)	116 (91%)	104 (88%)	101 (89%)	105 (85%)	87 (77%)	86 (79%)
Cure	45 (35%)	30 (25%)	33 (29%)	90 (73%)	69 (61%)	71 (65%)
Improvement	71 (55%)	74 (63%)	68 (60%)	15 (12%)	18 (16%)	15 (14%)
Failure	12 (9%)	14 (12%)	13 (11%)	12 (10%)	14 (12%)	13 (12%)
Relapse	NA	NA	NA	6 (5%)	12 (11%)	10 (9%)

(Clinically Intent-to-Treat Subjects)

	End of Treatment			End of Study		
	Trovafloxacin 100 mg (N=135)	Trovafloxacin 200 mg (N=126)	Amoxycillin 500 mg TID (N=116)	Trovafloxacin 100 mg (N=135)	Trovafloxacin 200 mg (N=126)	Amoxycillin 500 mg TID (N=116)
	Number and Percentage (%) of Subjects					
Number of Subjects Assessed	135 (100%)	126 (100%)	116 (100%)	135 (100%)	126 (100%)	116 (100%)
Success (Cure + Improvement)	121 (90%)	109 (87%)	103 (89%)	115 (85%)	97 (77%)	93 (80%)
Cure	48 (36%)	32 (25%)	33 (28%)	97 (72%)	76 (60%)	75 (65%)
Improvement	73 (54%)	77 (61%)	70 (60%)	18 (13%)	21 (17%)	18 (16%)
Failure	14 (10%)	17 (13%)	13 (11%)	14 (10%)	17 (13%)	13 (11%)
Relapse	NA	NA	NA	6 (4%)	12 (10%)	10 (9%)

Clinical Success Rates For the Most Frequently Isolated Baseline Pathogens[a]

(Clinically Evaluable Subjects)

	Trovafloxacin 100 mg (N=86)	Trovafloxacin 200 mg (N=80)	Amoxycillin 500 mg TID (N=79)	Trovafloxacin 100 mg (N=82)	Trovafloxacin 200 mg (N=78)	Amoxycillin 500 mg TID (N=77)
	Number of Subjects					
Pathogen	End of Treatment			End of Study		
H. influenzae	38/44 (86%)	41/44 (93%)	31/39 (79%)	31/40 (78%)	36/42 (86%)	25/39 (64%)
M. catarrhalis	15/17 (88%)	14/17 (82%)	18/20 (90%)	15/17 (88%)	11/17 (65%)	17/20 (85%)
S. pneumoniae	21/23 (91%)	22/25 (88%)	19/21 (90%)	21/23 (91%)	22/25 (88%)	16/20 (80%)

a ≥10 isolates of a given pathogen in any treatment group.
A subject could have had more than one pathogen isolated at baseline.
Several subjects were not evaluated clinically at the end of treatment.

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 the following table.

A Summary of the Number and Percentage of Subjects With Adverse Events, Discontinuations Due to Adverse Events, and Clinically Significant Laboratory Values						
	Trovafloxacin 100 mg daily (N=145)		Trovafloxacin 200 mg daily (N=134)		Amoxycillin 500 mg TID (N=132)	
Number and Percentages (%)of Subjects						
Adverse Events: All Causalities	14/145	(10%)	31/134	(23%)	20/132	(15%)
Treatment-Related Adverse Events	9/145	(6%)	16/134	(12%)	12/132	(9%)
Discontinuations From Treatment Due to an Adverse Event	5/145	(3%)	5/134	(4%)	3/132	(2%)
Discontinuations Due to a Treatment-Related Adverse Event	3/145	(2%)	4/134	(3%)	1/132	(1%)
Clinically Significant Laboratory Values	20/136	(15%)	18/126	(14%)	21/126	(17%)

V. ACUTE SINUSITIS

The efficacy and safety of oral trovafloxacin for the treatment of sinusitis was assessed in two comparative trials, one double-blind (154-115) and one open-label (154-138), and one noncomparative trial with sinus aspirates (154-114). The comparator agents were clarithromycin (154-115) and amoxicillin/clavulanate (154-138). These trials are reviewed below.

Reviewer's Note: The sponsor assessed whether efficacy differed in various subgroups in the sinusitis trials as part of the Integrated Summary of Efficacy. Results were similar across geographic location (USA/Canada vs. non-USA/Canada), gender, race, and age.

V.A. Protocol 154-114

AN OPEN NONCOMPARATIVE, MULTI-CENTER TRIAL DESIGNED TO ASSESS THE EFFICACY AND SAFETY OF 10 DAYS ORAL THERAPY WITH TROVAFLOXACIN (200 MG ONCE DAILY) FOR THE TREATMENT OF ACUTE SINUSITIS.

Study Dates: 15 November, 1994 - 3 August, 1995

Study Objectives: The objective of this study was to evaluate the safety and efficacy of trovafloxacin administered as a 200 mg oral dose for 10 days for the treatment of subjects with acute sinusitis.

Study Design: Study 154-114 was an unblinded, non-comparative, multicenter trial.

Diagnoses and Criteria for Inclusion of Subjects: Outpatient men or women, ≥16 years of age at the baseline assessment, with clinically documented acute sinusitis and a positive sinus x-ray.

Efficacy and Safety Evaluations: Efficacy evaluations included clinical response (assessment based on resolution or improvement of radiological and clinical signs and symptoms of infection) and bacteriologic response (based on eradication or presumptive eradication of causative organisms isolated from trans-antral aspirations at baseline).

Clinical response was to be determined by the sponsor and evaluated at Visit 2 (Day 4), the end of therapy (Visit 3, Day 11), and at the end of study (Visit 4, Day 24) or at the time of discontinuation from study. The clinical response was to be classified as cure (resolution of signs and symptoms of acute sinusitis to the level that existed before baseline and improvement in x-ray findings), improvement (improvement but incomplete resolution of signs and symptoms of acute sinusitis to the level that existed before baseline and no requirement for additional antibiotic), or failure (lack of resolution or worsening of any signs and symptoms of acute sinusitis or the need for an additional antibiotic for inadequate response).

Bacteriological response was to be determined by the sponsor and evaluated at the end of treatment (Day 11) and at the end of study (Day 24), or at the time of discontinuation from the study. Bacteriological response for each pathogen was to be classified by the sponsor as eradication, presumed eradication, persistence, presumed persistence, or relapse.

Primary efficacy endpoints were:

- Sponsor-defined clinical response at EOT and;
- 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 5a.1 outlines the number of patients enrolled, treated, and used in each of the analysis groups.

Table 5a.1. Evaluation Groups

Evaluation Groups:	Trovafloxacin (200 mg/day)	
Entered Study[a]	255	(100%)
All Treated	254	(>99%)
Completed Treatment	243	(96%)
Completed Study	242	(95%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	251	(98%)
Clinically Evaluable[b]	235	(92%)
Bacteriological Intent-to-Treat	131	(51%)
Bacteriological Evaluable[b]	125	(49%)
Assessed for Safety		
Adverse Events	254	(100%)
Laboratory Tests	247	(97%)

a Subjects who were enrolled; Percentages for efficacy based on enrolled subjects as the denominator and percentages for safety based on all treated subjects.

b Based on End of Treatment assessment.

Of the 255 enrolled subjects, four subjects had an inappropriate baseline diagnosis and were excluded from all clinical and bacteriological ITT and evaluable analyses.

Of the 251 clinical ITT subjects, 16 were not clinically evaluable; thus, 235 subjects were clinically evaluable. Reasons for exclusion from clinical efficacy analyses were no post-baseline clinical assessments (4 subjects), no post-baseline assessment in evaluable analysis windows (5 subjects), insufficient therapy due to early discontinuation from treatment or

study (4 subjects), prior antibiotic therapy (5 subjects), and concomitant antibiotic therapy for intercurrent illness (3 subjects).

Of the 251 clinical ITT subjects, 120 were not included in the bacteriological ITT analysis due to negative baseline cultures; thus, 131 subjects were included in the bacteriological ITT analysis.

Of the 235 clinically evaluable subjects, 110 subjects were not included in the bacteriologically evaluable analyses; thus, 125 subjects were bacteriologically evaluable. The only reason for exclusion from the bacteriologically evaluable analyses was no baseline pathogen (110 subjects).

Discontinuations

Of the 254 treated subjects, 11 subjects were prematurely discontinued from treatment as summarized in Table 5a.2.

Table 5a.2 Summary of Premature Discontinuations From Treatment (All Treated Subjects)

	Trovafloxacin 200 mg (N=254)	
	Number and Percentage (%) of Subjects	
Total Discontinued	11	(4%)
Discontinuations Related to Study Drug:	6	(2%)
Adverse Event	4	(2%)
Insufficient Response	2	(<1%)
Discontinuations Unrelated to Study Drug:	5	(2%)
Adverse Event	1	(<1%)
Did Not Meet Randomization Criteria	1	(<1%)
Lost to Follow-up	1	(<1%)
Withdrew Consent	2	(<1%)

Demographics

One hundred and twenty-three (123) male and 131 female subjects received treatment. Male and female subjects were generally comparable with respect to age, race, and weight. The distribution of male and female subjects according to smoking classification was (22% and 17% ex-smoker, 48% and 64% never smoked, and 30% and 19% 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 acute sinusitis. The median (range) duration since onset of acute sinusitis was 8 days. Similar results were observed for clinically evaluable subjects.

Clinical Response

Sponsor-defined clinical response rates for clinically evaluable subjects at EOT and EOS are presented in Table 5a.3. Table 5a.4 presents clinical response rates by baseline pathogen for clinically evaluable subjects at EOT and EOS.

Table 5a.3 Summary of Sponsor-Defined Clinical Response Rates at EOT and EOS (Clinically Evaluable Subjects)

	Trovafloxacin 200 mg (N=235)		95% CI
	Number and Percentage (%) of Subjects		
End of Treatment:			
Number of Subjects Assessed	235	(100%)	
Success (Cure + Improvement)	213	(91%)	(86.9, 94.4)
Distribution of Clinical Response:			
Cure	110	(47%)	
Improvement	103	(44%)	
Failure	22	(9%)	
End of Study:			
Number of Subjects Assessed	227	(100%)	
Success (Cure + Improvement)	199	(88%)	(83.4, 91.9)
Distribution of Clinical Response:			
Cure	174	(77%)	
Improvement	25	(11%)	
Failure	22	(10%)	
Relapse	6	(3%)	

Table 5a.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=235)		Trovafloxacin 200 mg (N=227)	
	Number of Subjects			
Pathogen	End of Treatment		End of Study	
S. pneumoniae	24/25	(96%)	24/25	(96%)
H. influenzae	38/45	(84%)	36/45	(80%)
S. aureus	18/18	(100%)	16/16	(100%)
M. catarrhalis	21/23	(91%)	19/21	(90%)

a ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed only when denominator is ≥15. A subject could have had more than one pathogen isolated at baseline.

Bacteriologic Response

Table 5a.5 summarizes pathogen eradication rates for bacteriologically evaluable patients at EOT and EOS.

Table 5a.5. Summary of Sponsor-Defined Pathogen Eradication Rates[a] (Bacteriologically Evaluable Subjects)

	Trovafloxacin 200 mg (N=125)	Trovafloxacin 200 mg (N=121)
	Number of Pathogens	
Pathogen[b]	End of Treatment	End of Study
S. pneumoniae	24/25 (96%)	24/25 (96%)
H: influenzae	44/45 (98%)	43/45 (96%)
S. aureus	18/18 (100%)	16/16 (100%)
M. catarrhalis	22/23 (96%)	19/21 (90%)

a Includes subjects with presumptive eradication (subjects clinically improved or cured who did not undergo post-treatment transantral aspiration of the sinus).

b ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed when denominator is ≥15. A subject could have more than one pathogen isolated at baseline.

Disqualified Investigator

Reviewer's Note: One of the investigators involved in this study, Dr. Fiddes, has plead guilty to several violations of FDA regulations. To examine the robustness of results in this study, the data were examined after excluding patients enrolled at Dr. Fiddes' center.

A total of 32 patients were enrolled by Dr. Fiddes. Of the 28 patients considered clinically evaluable at EOT, 8 were cures, 19 were improved, and 1 was a failure. At EOS, 25 patients were considered clinically evaluable: 18 patients were cured, 6 improved, 1 a failure, and none had relapsed. Twenty-three patients were considered bacteriologically evaluable at EOT: 2 of 2 patients with S. pneumoniae were presumed eradicated, 6 of 7 patients with H. influenzae were presumed eradicated (the 7th was presumed persistent), 1 of 1 patient with S. aureus was presumed eradicated, 12 of 12 patients with M. catarrhalis were presumed eradicated, and 1 of 1 patient with S. pyogenes was presumed eradicated (no patient had more than one baseline pathogen isolated). At EOS, 21 patients were considered bacteriologically evaluable: 2 of 2 patients with S. pneumoniae were presumed eradicated, 6 of 7 patients with H. influenzae were presumed eradicated (the 7th was presumed persistent), 1 of 1 patient with S. aureus was presumed eradicated, 10 of 10 patients with M. catarrhalis were presumed eradicated, and 1 of 1 patient with S. pyogenes was presumed eradicated (again, no patient had more than one baseline pathogen isolated).

Results excluding patients from Dr. Fiddes' center are presented in Tables 5a.6 and 5a.7, respectively, for clinical and bacteriologic outcome. On the whole, results are fairly robust. The most noticeable difference is in the number of patients with M. catarrhalis -- approximately half of the patients with M. catarrhalis were enrolled at Dr. Fiddes' center. When these patients are excluded, there are only 11 patients enrolled with M. catarrhalis (slightly below the number of 15 recommended in the Division of Anti-Infective Drug

Products 1992 "Points to Consider" document); the eradication rates are somewhat lower although they still appear acceptable.

Table 5a.6 FDA Analysis of Sponsor-Defined Clinical Response Rates at EOT and EOS, *Excluding Patients From Dr. Fiddes' Center* (Clinically Evaluable Subjects)

	Trovafloxacin 200 mg (N=207)		95% CI
	Number and Percentage (%) of Subjects		
End of Treatment:			
Number of Subjects Assessed	207	(100%)	
- Success (Cure + Improvement)	186	(90%)	(85.7, 94.0)
Distribution of Clinical Response:			
Cure	102	(49%)	
Improvement	84	(41%)	
Failure	21	(10%)	
End of Study:			
Number of Subjects Assessed	202	(100%)	
Success (Cure + Improvement)	175	(87%)	(82.0, 91.3)
Distribution of Clinical Response:			
Cure	156	(77%)	
Improvement	19	(9%)	
Failure	21	(10%)	
Relapse	6	(3%)	

Table 5a.7. FDA Analysis of Sponsor-Defined Pathogen Eradication Rates[a], *Excluding Patients From Dr. Fiddes' Center* (Bacteriologically Evaluable Subjects)

	Trovafloxacin 200 mg (N=102)	Trovafloxacin 200 mg (N=100)
	Number of Pathogens	
Pathogen[b]	End of Treatment	End of Study
S. pneumoniae	22/23 (96%)	22/23 (96%)
H. influenzae	38/38 (100%)	37/38 (97%)
S. aureus	17/17 (100%)	15/15 (100%)
M. catarrhalis	10/11 (91%)	9/11 (82%)

a Includes subjects with presumptive eradication (subjects clinically improved or cured who did not undergo post-treatment transantral aspiration of the sinus).

B ≥15 isolates of a given pathogen at any evaluation period. Percents are displayed when denominator is ≥15.

A subject could have 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 5a.8. Tables 5a.9 and 5a.10 summarize the most commonly reported adverse events and treatment-related adverse events, respectively, by body system.

Table 5a.8. 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
	Number and Percentage (%) of Subjects
Adverse Events: All Causalities	137/254 (54%)
Treatment-Related Adverse Events	87/254 (34%)
Discontinuations Due to an Adverse Event[a]	5/254 (2%)
Clinically Significant Laboratory Abnormalities	34/247 (14%)

a With the exception of one subject who was discontinued due to unrelated adverse events, all subjects were discontinued from treatment due to adverse events that were considered by the investigator to be study drug-related.

Table 5a.9 Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causalities (All Treated Subjects)

	Trovafloxacin 200 mg (N=254)	
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event[c]	137	(54%)
BODY SYSTEM WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	83	(33%)
Dizziness	51	(20%)
Headache	34	(13%)
Vertigo	7	(3%)
GASTROINTESTINAL SYSTEM	40	(16%)
Nausea	30	(12%)
Vomiting	10	(4%)
Diarrhea	7	(3%)
RESPIRATORY SYSTEM	26	(10%)
Epistaxis	9	(4%)

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.

Table 5a.10 Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - Treatment-Related (All Treated Subjects)

	Trovafloxacin 200 mg (N=254)	
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event[c]	87	(34%)
BODY SYSTEM WHO Term		
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	59	(23%)
Dizziness	45	(18%)
Headache	11	(4%)
Vertigo	6	(2%)
GASTROINTESTINAL SYSTEM	35	(14%)
Nausea	27	(11%)
Vomiting	9	(4%)
Diarrhea	6	(2%)

a ≥2 % 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.

Two subjects experienced serious adverse events unrelated to study drug. There were no subject deaths during the study.

Sponsor's Summary and Conclusion: Trovafloxacin 200 mg once daily for 10 days was safe and effective in the treatment of acute sinusitis. The percentage of subjects discontinued from treatment due to adverse events was 2%. The overall percentage of subjects reporting adverse events was 54%; treatment-related adverse events were reported in 34% of subjects. The most commonly reported adverse events were dizziness and headache. No subjects were discontinued due to laboratory abnormalities.

Reviewer's Summary and Conclusion: *Trovafloxacin 200 mg once daily for 10 days appears to have been effective in the treatment of acute sinusitis in this trial. Caution should be taken in interpreting results, however, due to the fact that this was an uncontrolled trial. Eighteen percent of trovafloxacin patients reported dizziness that was considered treatment related. Eleven percent of trovafloxacin patients reported nausea that was considered treatment related.*

One of the investigators involved in this trial, Dr. Fiddes, has plead guilty to violations of FDA regulations. Results are fairly robust when patients from Dr. Fiddes' center are excluded. The number of evaluable patients with M. catarrhalis drops to 11 (slightly below the number of 15 recommended in the Division of Anti-Infective Drug Products 1992 "Points to Consider" document), however eradication rates still appear acceptable (10/11 = 91% patients are eradicated at EOT; 9/11 = 82% patients are eradicated at EOS).