

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-775/S001

STATISTICAL REVIEW(S)

June 28, 2001

STATISTICAL REVIEW AND EVALUATION

sNDA: 50-775 (S-001)

DRUG: Biaxin® XL Filmtab® (clarithromycin) Extended-Release Tablet

SPONSOR: Abbott Laboratories

INDICATIONS: Community acquired pneumonia

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Review's Note: Throughout the review, the following terms are abbreviated and referred to as:

CAP = community acquired pneumonia, ER = extended-release, F-U = Follow-up, ITT = Intent-to-Treat, IR = immediate-release, TOC = Test of Cure. Reviewer comments are given in italics throughout the review.

I. INTRODUCTION

The Sponsor submitted two phase III controlled studies as evidence to support that clarithromycin ER was safe and efficacious for the treatment of ambulatory subjects with CAP when compared with current established therapies. The purpose of this supplement to a NDA was to add pneumonia due to *Haemophilis influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae* to the Biaxin XL label in the previously approved indication of CAP. Statistical review focuses on these comparative clinical trials which formed the basis of this application. The general design of the studies is as follows:

Study M99-077 was a randomized, double-blind, parallel, and multicenter (51 centers) trial which compared the safety and efficacy of a 7-day course of therapy with clarithromycin ER tablets (2x500 mg QD) with those of a 7-day course of therapy with levofloxacin tablets (2x250 mg QD) in the treatment of ambulatory subjects with CAP. Subjects who tested positive for *Legionella* spp. were to continue the assigned study during therapy for an additional 7 days. It was initiated on November 2, 1999 and completed on July 5, 2000.

Study M98-927 was a randomized, double-blind, parallel, and multicenter (60 centers) trial which compared the safety and efficacy of a 7-day course of therapy with either clarithromycin IR tablets (1x250 mg BID) or clarithromycin ER tablets (2x500mg QD) with those of a 7-day course of therapy with trovafloxacin tablets (1x200 mg QD) in the treatment of ambulatory subjects with CAP. It was initiated on December 11, 1998 and completed on June 29, 1999.

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II. STUDY M99-077

II.A. METHODS

In Study M99-077, approximately 150 subjects were enrolled per treatment group. Subjects with clinical signs and symptoms of CAP who met the inclusion/exclusion criteria were randomized in a 1:1 ratio at each investigational site to receive one of the treatments.

Eligible subjects could begin study-directed treatment (Evaluation 1; Pre-Therapy) before the results of sputum culture and serologic tests were known providing that they had a pretreatment purulent sputum sample qualified by gram stain (performed by the investigator), and satisfied the inclusion/exclusion criteria. Subjects were evaluated within 48 to 72 hours after initiation of therapy (Evaluation 2; On Therapy Visit), at 7 days during therapy if positive by *Legionella* spp. urinary antigen assays (Evaluation 3; On Therapy Visit), within 72 hours after the last dose (Evaluation 4; Post Therapy Visit), and again at 14 to 21 days after the last dose of study drug (Evaluation 5; TOC Visit). Clinical response and radiographic response were assigned at Evaluation 5. Efficacy was determined by microbiologic evaluation of purulent and Gram-stained qualified sputum by culture, serology, or urinary antigen test results, radiographic response, and by the investigator's evaluation of clinical signs and symptoms of infection. Safety was determined through periodic laboratory tests, medical history, physical examination, and monitoring of adverse events. The range of duration of each subject's participation in the study was approximately 4 to 5 weeks, depending upon the schedule of evaluation study.

The primary efficacy variable was the clinical cure rate, defined as the percentage of subjects who had a clinical response of "cure". The investigator compared the clinical findings and x-ray results at TOC to the findings prior to study treatment for each subject and assigned a clinical response. The clinical response was rated using the definitions as clinical cure, clinical failure, and indeterminate. All other efficacy measures were considered secondary, including the bacteriological response and the radiographic response. The primary treatment comparisons were clarithromycin ER versus levofloxacin regarding the clinical cure rate in the clinically evaluable population.

Reviewer's Note: The Medical Officer agreed with the evaluability criteria defined by the Sponsor, and outcome assessment classified by the Sponsor.

All subjects who received at least one dose of study medication were included in the safety analyses. All adverse events that occurred between receipt of the first dose of study medication and the final visit were recorded.

Reviewer's Note: The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of clarithromycin ER versus levofloxacin.

Equivalence between the test treatment (clarithromycin ER) and the control (levofloxacin) with respect to the primary efficacy parameter was assessed by computing the two-tailed 95% confidence interval of the difference in response rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged based on the delta value 0.10, which is considered a clinically acceptable equivalence margin with respect to this indication.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one drug-related adverse event, the rate of serious adverse events, and the rate of discontinuation due to adverse events. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, and evaluability status. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

II.B. RESULTS

Of the 299 subjects who enrolled in the study, 156 were randomized to the clarithromycin ER treatment group, and 143 were randomized to the levofloxacin treatment group. Twenty-two subjects (14 clarithromycin ER and 9 levofloxacin) were excluded from the ITT analyses because their results from chest x-ray were not consistent with CAP. Forty-seven subjects (28 clarithromycin ER and 19 levofloxacin) were excluded from the clinically evaluable analyses, most of whom did not return for TOC Visit or did not perform chest x-ray at TOC Visit. One hundred nine subjects (63 clarithromycin ER and 46 levofloxacin) were excluded from the clinically and bacteriologically evaluable analyses, most of whom did not have any target pathogen isolated at pretreatment.

Reviewer's Note: The number and percentage of subjects included in each analysis group are presented in Table 1. There were no notable treatment differences with respect to the percentage of patients included in each analysis group. Demographic data are described for the clinically evaluable subjects in Table 2, and no statistically significant differences were detected in the pretreatment characteristics between the two treatment groups.

TABLE 1: STUDY M99-077: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP		
Evaluation Group	Subjects Included	
	Clarithromycin ER	Levofloxacin
All Randomized Subjects	156	143
ITT Subjects	142 (100%)	134 (100%)
Clinically Evaluable Subjects	128 (90.1%)	124 (86.7%)
Clinical and Micro. Evaluable Subjects	93 (65.5%)	97 (72.4%)

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Parameters	Clarithromycin ER (N=142)	Levofloxacin (N=134)	P-value
Gender			
Male	85 (59.9%)	65 (48.5%)	0.070
Female	57 (40.1%)	69 (51.5%)	
Age (yrs.)			
Range (Min, Max)	(19, 89)	(18, 91)	*0.307
Mean ± SD	49.0 ± 15.9	51.0 ± 16.5	
Distribution			
≤ 40	41 (28.9%)	37 (27.6%)	0.219
41 – 64	75 (52.8%)	61 (45.5%)	
≥ 65	26 (18.3%)	36 (26.9%)	
Race			
White	133 (93.7%)	120 (89.6%)	0.362
Black	6 (4.2%)	7 (5.2%)	
Other	3 (2.1%)	7 (5.2%)	
Weight (kg)			
Range (Min, Max)	(40, 186)	(36, 141)	*0.514
Mean ± SD	83.1 ± 23.9	81.3 ± 21.0	

* By t test. All others in the table, by Chi-squared test.

Reviewer's Note: The clinical responses are shown for clinically evaluable population in Table 3. The confidence interval result showed that clarithromycin ER and levofloxacin were therapeutically equivalent with respect to the cure rates at TOC.

Clinical Response	Clarithromycin ER (N=128)	Levofloxacin (N=124)
Cure	113 (88.3%)	107 (86.3%)
Failure	15 (11.7%)	17 (13.7%)
ER Versus Levo.: Difference in Cure Rate	2.0%, 95% C.I.: -7.0%, 11.0%	

Reviewer's Note: Subject clinical responses for eight target pathogens for clinically and bacteriologically evaluable subjects are presented in Table 4. Two treatments appeared similar outcomes with no statistically significant treatment differences. The similar results were observed from eradication rates of target pathogens for clinically and bacteriologically evaluable subjects, which are showed in Table 5.

TABLE 4: STUDY M99-077: CLINICAL CURE RATES FOR TARGET PATHOGENS OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Pathogen	Clarithromycin ER	Levofloxacin	Fisher's P-value
Overall Pathogen	134/154 (87.0%)	134/155 (86.5%)	1.000
<i>H. influenzae</i>	26/32 (81.3%)	27/28 (96.4%)	0.109
<i>M. catarrhalis</i>	9/11 (81.8%)	11/14 (78.6%)	1.000
<i>S. pneumoniae</i>	6/7 (85.7%)	20/22 (90.9%)	1.000
<i>H. parainfluenzae</i>	18/20 (90.0%)	15/18 (83.3%)	0.653
<i>S. aureus</i>	5/6 (83.3%)	3/3 (100%)	1.000
<i>C. pneumoniae</i>	26/28 (92.9%)	28/35 (80.0%)	0.277
<i>M. pneumoniae</i>	35/39 (89.7%)	22/26 (84.6%)	0.703
<i>L. pneumophila</i>	9/11 (81.8%)	8/9 (88.9)	1.000

TABLE 5: STUDY M99-077: ERADICATION RATES FOR TARGET PATHOGENS OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Pathogen	Clarithromycin ER	Levofloxacin	Fisher's P-value
Overall Pathogen	134/154 (87.0%)	136/155 (87.7%)	0.866
<i>H. influenzae</i>	25/32 (78.1%)	27/28 (96.4%)	0.057
<i>M. catarrhalis</i>	9/11 (81.8%)	12/14 (85.7%)	1.000
<i>S. pneumoniae</i>	6/7 (85.7%)	20/22 (90.9%)	1.000
<i>H. parainfluenzae</i>	18/20 (90.0%)	16/18 (88.9%)	1.000
<i>S. aureus</i>	6/6 (100%)	3/3 (100%)	NA
<i>C. pneumoniae</i>	26/28 (92.9%)	28/35 (80.0%)	0.277
<i>M. pneumoniae</i>	35/39 (89.7%)	22/26 (84.6%)	0.703
<i>L. pneumophila</i>	9/11 (81.8%)	8/9 (88.9)	1.000

Reviewer's Note: The clinical responses are shown for clinically and bacteriologically evaluable, and ITT populations in Tables 6 and 7, respectively. The bacteriological responses are shown for clinically and bacteriologically evaluable population in Table 8. The results from these analyses demonstrated that clinical cure rates of clarithromycin ER were comparable to those of levofloxacin in ITT subjects. However, for clinically and bacteriologically evaluable subjects, clarithromycin ER and levofloxacin were not shown therapeutically equivalent with respect to clinical cure rates or bacteriological cure rates.

TABLE 6: STUDY M99-077: CLINICAL RESPONSES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Clinical Response	Clarithromycin ER (N=93)	Levofloxacin (N=97)
Cure	81 (87.1%)	85 (87.6%)
Failure	12 (12.9%)	12 (12.4%)
ER Versus Levo.: Difference in Cure Rate	-0.5%, 95% C.I.: -11.0%, 10.0%	

TABLE 7: STUDY M99-077: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=142)	Levofloxacin (N=134)
Cure	115 (81.0%)	108 (80.6%)
Failure	15 (10.6%)	17 (12.7%)
Indeterminate	12 (8.5%)	9 (6.7%)
ER Versus Levo.: Difference in Cure Rate	0.4%, 95% C.I.: -9.6%, 10.4%	

TABLE 8: STUDY M99-077: BACTERIOLOGICAL RESPONSES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Bacteriological Response	Clarithromycin ER (N=93)	Levofloxacin (N=97)
Cure	80 (86.0%)	85 (87.6%)
Failure	13 (14.0%)	12 (12.4%)
ER Versus Levo.: Difference in Cure Rate	-1.6%, 95% C.I.: -12.3%, 9.1%	

Reviewer's Note: Radiographic resolution rates and success rates for clinically evaluable subjects, and clinically and bacteriologically evaluable subjects were presented in Tables 9 and 10, respectively. The results showed two treatments therapeutically equivalent in radiographic success rate, but did not display the equivalence in radiographic resolution rate.

TABLE 9: STUDY M99-077: RADIOGRAPHIC RESOLUTION AND SUCCESS RATES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
	Clarithromycin ER (N=128)	Levofloxacin (N=124)
RADIOGRAPHIC RESOLUTION RATE		
Resolution	75 (58.6%)	70 (56.5%)
ER Versus Levo.: Difference in Resolution Rate	2.1%, 95% C.I.: -10.9%, 15.1%	
RADIOGRAPHIC SUCCESS RATE		
Success	117 (91.4%)	104 (83.9%)
ER Versus Levo.: Difference in Success Rate	7.5%, 95% C.I.: -1.4%, 16.4%	

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TABLE 10: STUDY M99-077: RADIOGRAPHIC RESOLUTION AND SUCCESS RATES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
	Clarithromycin ER (N=93)	Levofloxacin (N=97)
RADIOGRAPHIC RESOLUTION RATE		
Resolution	53 (57.0%)	56 (57.7%)
ER Versus Levo.: Difference in Resolution Rate	-0.7%, 95% C.I.: -15.9%, 14.4%	
RADIOGRAPHIC SUCCESS RATE		
Success	84 (90.3%)	83 (85.6%)
ER Versus Levo.: Difference in Success Rate	4.8%, 95% C.I.: -5.5%, 15.0%	

Reviewer's Note: The summaries of safety outcomes are presented in Table 11. With regard to these safety variables, no statistically significant differences were observed between the treatment groups. One death in the clarithromycin ER treatment group was reported during the study, which was not considered related to study drug.

TABLE 11: STUDY M99-077: ADVERSE EVENT RATES			
Safety Outcomes	Clarithromycin ER (N=156)	Levofloxacin (N=143)	Fisher's P-value
With Any AE	78 (50.0%)	65 (45.5%)	0.487
With Drug Related AE	41 (26.3%)	29 (20.3%)	0.274
Serious AEs	11 (7.1%)	4 (2.8%)	0.114
Discontinuation Due To AEs	5 (3.2%)	1 (0.7%)	0.217

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III. STUDY M98-927

III.A. METHODS

In Study M98-927, approximately 150 subjects were enrolled per treatment group. Subjects with clinical signs and symptoms of CAP who met the inclusion/exclusion criteria were randomized in a 1:1:1 ratio at each investigational site to receive one of the treatments.

Clinical and bacteriological assessments were performed within 48 hours before initiating study drug (Evaluation 1; Pre-Therapy). Subjects returned to the clinic for clinical, bacteriological, and radiographic assessments within 48 to 72 hours after initiation of therapy (Evaluation 2; On Therapy Visit), within 72 hours after the last dose (Evaluation 3; Post Therapy Visit), and 14 to 21 days after the last dose (Evaluation 4; TOC Visit). Clinical response and radiographic response were assigned at Evaluation 4. Efficacy was assessed by resolution of clinical signs and symptoms of CAP and bacteriological eradication of pathogen. Safety was evaluated through monitoring of adverse events, laboratory tests, medical history, concomitant medications, physical examination, and vital signs. The total duration of each subject's participation in the study was approximately 4 weeks.

The primary efficacy variable was the clinical cure rate, defined as the percentage of subjects who had a clinical response of "cure". The investigator compared the clinical findings and x-ray results at TOC to the findings prior to study treatment for each subject and assigned a clinical response. The clinical response was rated using the definitions as clinical cure, clinical failure, and indeterminate. All other efficacy measures were considered secondary, including the bacteriological response and the radiographic response. The primary treatment comparisons were clarithromycin ER versus trovafloxacin regarding the clinical cure rate in the clinically evaluable population.

Reviewer's Note: *The Medical Officer agreed with the evaluability criteria defined by the Sponsor, and outcome assessment classified by the Sponsor.*

All subjects who received at least one dose of study medication were included in the safety analyses. All adverse events that occurred between receipt of the first dose of study medication and the final visit were recorded.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of clarithromycin ER versus trovafloxacin.*

Of note, in the protocol of this study, the comparisons of interest were specified between two test treatments (clarithromycin ER and clarithromycin IR) and the control (trovafloxacin), and during the trial, more than one pair of groups was compared among clarithromycin ER, clarithromycin IR and trovafloxacin despite clarithromycin IR was not incorporated into the NDA submission. Thus, an adjustment for multiple comparisons such as Bonferroni's adjustment was necessary to control the overall type I error rate. By applying Bonferroni's approach, equivalence of treatment difference with respect to efficacy variables was assessed by computing the two-tailed 97.5% confidence interval (giving the nominal significance level at 0.025 to maintain the overall significance level at 0.05) of the difference in response rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged based on the delta value 0.10, which is considered a clinically acceptable equivalence margin with respect to this indication.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one drug-related adverse event, the rate of serious adverse events, and the rate

of discontinuation due to adverse events. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics including demographics, baseline disease characteristics, and evaluability status. Quantitative variables were assessed using the t-test. Qualitative variables were assessed using Fisher's exact test.

III.B. RESULTS

Of the 176 subjects who enrolled in the study, 90 were randomized to the clarithromycin ER treatment group, and 86 were randomized to the trovafloxacin treatment group. No enrolled subject was excluded from the ITT analyses. Twenty-five subjects (5 clarithromycin ER and 20 trovafloxacin) were excluded from the clinically evaluable analyses, most of whom did not return for TOC Visit or returned for TOC Visit outside the allowable window. Seventy-one subjects (32 clarithromycin ER and 39 trovafloxacin) were excluded from the clinically and bacteriologically evaluable analyses, most of whom did not have a target pathogen isolated at pretreatment.

Reviewer's Note: The number and percentage of subjects included in each analysis group are presented in Table 12. Significantly more subjects in the trovafloxacin treatment group excluded from the clinically evaluable analyses (p-value: 0.001) than those in the clarithromycin ER treatment group. Demographic data are described for the clinically evaluable subjects in Table 13, and no statistically significant differences were detected in the pretreatment characteristics between the two treatment groups.

TABLE 12: STUDY M98-927: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP		
Evaluation Group	Subjects Included	
	Clarithromycin ER	Trovafloxacin
All Randomized Subjects	90	86
ITT Subjects	90 (100%)	86 (100%)
Clinically Evaluable Subjects	85 (94.4%)	66 (76.7%)
Clinical and Micro. Evaluable Subjects	58 (64.4%)	47 (54.7%)

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TABLE 13: STUDY M98-927: BASELINE DEMOGRAPHICS IN ITT SUBJECTS			
Parameters	Clarithromycin ER (N=90)	Trovafloracin (N=86)	P-value
Gender			
Male	43 (59.3%)	41 (54.4%)	1.000
Female	47 (40.7%)	45 (45.6%)	
Age (yrs.)			
Range (Min, Max)	(19, 81)	(19, 80)	*0.896
Mean ± SD	47.6 ± 16.3	47.3 ± 16.1	
Distribution			
≤ 40	34 (37.8%)	32 (37.2%)	0.887
41 ~ 64	37 (41.1%)	38 (44.2%)	
≥ 65	19 (21.1%)	16 (18.6%)	
Race			
White	78 (89.7%)	76 (88.4%)	0.619
Black	6 (6.7%)	7 (8.1%)	
Other	6 (6.7%)	3 (3.5%)	
Weight (kg)			
Range (Min, Max)	(44, 159)	(42.9, 158.8)	*0.655
Mean ± SD	83.9 ± 19.5	85.3 ± 20.6	

* By t test. All others in the table, by Chi-squared test.

Reviewer's Note: The clinical responses are shown for clinically evaluable population in Table 14. Neither 97.5% nor 95% confidence intervals for the differences did show the equivalence of the two treatments for the cure rates, whereas clarithromycin ER had lower cure rates.

TABLE 14: STUDY M98-927: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=85)	Trovafloracin (N=66)
Cure	74 (87.1%)	63 (95.5%)
Failure	11 (12.9%)	3 (4.5%)
ER Versus Trova.:	-8.4%, 95% C.I.: -18.5%, 1.7%	
Difference in Cure Rate	97.5% C.I.: -19.7%, 2.9%	

Reviewer's Note: Subject clinical responses for eight target pathogens for clinically and bacteriologically evaluable subjects are presented in Table 15. Two treatments appeared similar outcomes with no statistically significant treatment differences. The similar results were observed from eradication rates of target pathogens for clinically and bacteriologically evaluable subjects, which are showed in Table 16.

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TABLE 15: STUDY M98-927: CLINICAL CURE RATES FOR TARGET PATHOGENS OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Pathogen	Clarithromycin ER	Trovafloxacin	Fisher's P-value
Overall Pathogen	85/95 (89.5%)	65/67 (97.0%)	0.125
<i>H. influenzae</i>	11/13 (84.6%)	8/9 (88.9%)	1.000
<i>H. parainfluenzae</i>	13/16 (81.3%)	9/9 (100%)	0.280
<i>S. pneumoniae</i>	12/13 (92.3%)	3/3 (100%)	1.000
<i>M. pneumoniae</i>	13/15 (86.7%)	16/16 (100%)	0.226
<i>C. pneumoniae</i>	20/22 (90.1%)	17/18 (94.4%)	1.000
<i>L. pneumophila</i>	7/7 (100%)	7/7 (100%)	NA
<i>M. catarrhalis</i>	5/5 (100%)	2/2 (100%)	NA
<i>S. aureus</i>	4/4 (100%)	3/3 (100%)	NA

TABLE 16: STUDY M98-927: ERADICATION RATES FOR TARGET PATHOGENS OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Pathogen	Clarithromycin ER	Trovafloxacin	Fisher's P-value
Overall Pathogen	85/95 (89.5%)	64/67 (95.5%)	0.241
<i>H. influenzae</i>	11/13 (84.6%)	8/9 (88.9%)	1.000
<i>H. parainfluenzae</i>	13/16 (81.3%)	9/9 (100%)	0.280
<i>S. pneumoniae</i>	12/13 (92.3%)	2/3 (66.7%)	0.350
<i>M. pneumoniae</i>	13/15 (86.7%)	16/16 (100%)	0.226
<i>C. pneumoniae</i>	20/22 (90.1%)	17/18 (94.4%)	1.000
<i>L. pneumophila</i>	7/7 (100%)	7/7 (100%)	NA
<i>M. catarrhalis</i>	5/5 (100%)	2/2 (100%)	NA
<i>S. aureus</i>	4/4 (100%)	3/3 (100%)	NA

Reviewer's Note: The clinical responses are shown for clinically and bacteriologically evaluable, and ITT populations in Tables 17 and 18, respectively. The bacteriological responses are shown for clinically and bacteriologically evaluable population in Table 19. The results for clinically and bacteriologically evaluable subjects did not demonstrate therapeutic equivalence between the two treatments with respect to clinical cure rates and bacteriological cure rates, respectively, whereas the subjects in the clarithromycin ER group had lower rates. In ITT population, the clinical responses of clarithromycin ER were comparable to those of trovafloxacin. The results from 95% and 97.5% confidence intervals were all consistent with each other.

TABLE 17: STUDY M98-927: CLINICAL RESPONSES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Clinical Response	Clarithromycin ER (N=58)	Trovafloxacin (N=47)
Cure	52 (89.7%)	45 (95.7%)
Failure	2 (10.3%)	2 (4.3%)
ER Versus Trova.:	-6.1%, 95% C.I.: -17.7%, 5.6%	
Difference in Cure Rate	97.5% C.I.: -19.1%, 7.0%	

TABLE 18: STUDY M98-927: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=90)	Trovafoxacin (N=86)
Cure	77 (85.6%)	65 (75.6%)
Failure	11 (12.2%)	3 (3.5%)
Indeterminate	2 (2.2%)	18 (20.9%)
ER Versus Trova.:	10.0%, 95% C.I.: -2.8%, 22.7%	
Difference in Cure Rate	97.5% C.I.: -4.5%, 24.4%	

TABLE 19: STUDY M98-927: BACTERIOLOGICAL RESPONSES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Bacteriological Response	Clarithromycin ER (N=58)	Trovafoxacin (N=47)
Cure	52 (89.7%)	44 (93.6%)
Failure	6 (10.3%)	3 (6.4%)
ER Versus Trova.:	-4.0%, 95% C.I.: -16.4%, 8.5%	
Difference in Cure Rate	97.5% C.I.: -17.9%, 10.0%	

Reviewer's Note: Radiographic resolution rates and success rates for clinically evaluable subjects, and clinically and bacteriologically evaluable subjects were presented in Tables 20 and 21, respectively. Both 95% and 97.5% confidence intervals for the differences did show or marginally showed the equivalence of the two treatments for success rates in clinically evaluable subjects, but did not for resolution rates for both populations, nor for success rates in clinically and microbiological evaluable population, whereas clarithromycin ER had lower radiographic resolution rates than trovafoxacin.

TABLE 20: STUDY M98-927: RADIOGRAPHIC RESOLUTION AND SUCCESS RATES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
	Clarithromycin ER (N=85)	Trovafoxacin (N=66)
RADIOGRAPHIC RESOLUTION RATE		
Resolution	64 (75.3%)	54 (81.8%)
ER Versus Trova.:	-6.5%, 95% C.I.: -20.9%, 7.9%	
Difference in Resolution Rate	97.5% C.I.: -22.8%, 9.8%	
RADIOGRAPHIC SUCCESS RATE		
Success	80 (94.1%)	63 (95.5%)
ER Versus Trova.:	-1.3%, 95% C.I.: -9.8%, 7.1%	
Difference in Success Rate	97.5% C.I.: -10.8%, 8.1%	

TABLE 21: STUDY M98-927: RADIOGRAPHIC RESOLUTION AND SUCCESS RATES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
	Clarithromycin ER (N=58)	Trovafloracin (N=47)
RADIOGRAPHIC RESOLUTION RATE		
Resolution	42 (72.4%)	38 (80.9%)
ER Versus Trova.: Difference in Resolution Rate	-8.4%, 95% C.I.: -26.5%, 9.6% 97.5% C.I.: -28.8 %, 11.9%	
RADIOGRAPHIC SUCCESS RATE		
Success	55 (94.8%)	45 (95.7%)
ER Versus Trova.: Difference in Success Rate	-0.9%, 95% C.I.: -11.0%, 9.1% 97.5% C.I.: -12.1%, 10.3%	

Reviewer's Note: The summaries of safety outcomes are presented in Table 22. Significantly more subjects experienced adverse events in the trovafloracin group than in the clarithromycin ER group. No deaths were reported during the study.

TABLE 22: STUDY M98-927: ADVERSE EVENT RATES			
Safety Outcomes	Clarithromycin ER (N=90)	Trovafloracin (N=86)	Fisher's P-value
With Any AE	34 (37.8%)	48 (55.8%)	0.023
With Drug Related AE	19 (21.1%)	20 (23.3%)	0.856
Serious AEs	2 (2.2%)	1 (1.1%)	1.000
Discontinuation Due To AEs	1 (1.1%)	1 (1.2%)	1.000

**APPEARS THIS WAY
ON ORIGINAL**

IV. SUMMARY AND CONCLUSIONS **(Which May be Conveyed to the Sponsor)**

Reviewer's Note: In this section, confidence intervals for differences in cure rates (clarithromycin ER minus control) are reported as $n_1, n_2(l, u)_{p_1, p_2}$, where n_1 is the number of clarithromycin ER subjects, n_2 is the number of control subjects, l and u are the lower and upper bounds of the 95% or 97.5% confidence interval, respectively, p_1 is the response rate in clarithromycin ER subjects, and p_2 is the response rate in control subjects.

This indication was primarily supported by two controlled studies to demonstrate the efficacy and safety of clarithromycin ER.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% (Study M99-077) or 97.5% (Study M98-927) confidence interval of the difference in clinical cure rates at TOC between the clarithromycin ER group and the levofloxacin or trovafloxacin group for clinically evaluable subjects.

Statistical Evaluation of safety was based upon the comparison of adverse event rates between the treatment groups in all treated subjects by two-side Fisher's exact test.

Reviewer's Summary for the Results of the Two Studies:

- In both studies, the pretreatment characteristics were comparable between treatments across all analysis groups.
- In Study M99-077, the 95% confidence interval of the difference in clinical cure rates of clarithromycin ER minus levofloxacin for clinically evaluable subjects was $_{128, 124}(-7.0\%, 11.0\%)_{88.3\%, 86.3\%}$, which demonstrated equivalence in efficacy of two treatments in the treatment of CAP. The 95% confidence interval from ITT subjects also demonstrated that clarithromycin ER was equivalent to levofloxacin $_{142, 134}(-9.6\%, 10.4\%)_{81.0\%, 80.6\%}$.
- In Study M98-927, the 97.5% confidence interval of the difference in clinical cure rates of clarithromycin ER minus trovafloxacin for clinically evaluable subjects was $_{85, 66}(-19.7\%, 2.9\%)_{87.1\%, 95.5\%}$, which failed to show equivalence in efficacy of two treatments in the treatment of CAP. The 97.5% confidence interval from ITT subjects demonstrated that clarithromycin ER was equivalent to trovafloxacin $_{90, 86}(-4.5\%, 24.4\%)_{85.6\%, 75.6\%}$.
- The integrated summary of primary efficacy endpoints is shown in Tables 23 and 24.

TABLE 23: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT

Clinical Response	Clarithromycin ER (N=213)	Levofloxacin (N=124)	Trovafloxacin (N=66)
Cure	187 (87.8%)	107 (86.3%)	63 (95.5%)
Failure	26 (12.2%)	17 (13.7%)	3 (4.5%)

TABLE 24: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT

Clinical Response	Clarithromycin ER (N=232)	Levofloxacin (N=134)	Trovafloxacin (N=86)
Cure	192 (82.8%)	108 (80.6%)	65 (75.6%)
Failure	26 (11.2%)	17 (12.7%)	3 (3.5%)
Indeterminate	14 (6.0%)	9 (6.7%)	18 (20.9%)

- In both studies, the efficacy of clarithromycin ER and levofloxacin or trovafloxacin in the eradication and cure of eight target pathogens was examined, which concluded the similarity in eradication rates and cure rates between the treatments. Overall pathogen eradication rates and cure rates were comparable between the treatment groups. The cure rates and eradication rates of eight target pathogens are displayed in Tables 25 and 26, which are pooled from two studies.

TABLE 25: CURE RATES OF TARGET PATHOGENS IN CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT IN TWO STUDIES

Pathogen	Clarithromycin ER	Levofloxacin	Trovafloxacin
<i>M. pneumoniae</i>	48/54 (88.9%)	22/26 (84.6%)	16/16 (100%)
<i>C. pneumoniae</i>	46/50 (92.0%)	28/35 (80.0%)	17/18 (94.4%)
<i>H. influenzae</i>	37/45 (82.2%)	27/28 (96.4%)	8/9 (88.9%)
<i>H. parainfluenzae</i>	31/36 (86.1%)	15/18 (83.3%)	9/9 (100%)
<i>S. pneumoniae</i>	18/20 (90.0%)	20/22 (90.9%)	3/3 (100%)
<i>L. pneumophila</i>	16/18 (88.9%)	8/9 (88.9)	7/7 (100%)
<i>M. catarrhalis</i>	14/16 (87.5%)	11/14 (78.6%)	2/2 (100%)
<i>S. aureus</i>	9/10 (90.0%)	3/3 (100%)	3/3 (100%)
Overall Pathogen	219/249 (88.0%)	134/155 (86.5%)	65/67 (97.0%)

TABLE 26: ERADICATION RATES OF TARGET PATHOGENS IN CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT IN TWO STUDIES

Pathogen	Clarithromycin ER	Levofloxacin	Trovafloxacin
<i>M. pneumoniae</i>	48/54 (88.9%)	22/26 (84.6%)	16/16 (100%)
<i>C. pneumoniae</i>	46/50 (92.0%)	28/35 (80.0%)	17/18 (94.4%)
<i>H. influenzae</i>	36/45 (80.0%)	27/28 (96.4%)	8/9 (88.9%)
<i>H. parainfluenzae</i>	31/36 (86.1%)	16/18 (88.9%)	9/9 (100%)
<i>S. pneumoniae</i>	18/20 (90.0%)	20/22 (90.9%)	2/3 (66.7%)
<i>L. pneumophila</i>	16/18 (88.9%)	8/9 (88.9)	7/7 (100%)
<i>M. catarrhalis</i>	14/16 (87.5%)	12/14 (85.7%)	2/2 (100%)
<i>S. aureus</i>	10/10 (100%)	3/3 (100%)	3/3 (100%)
Overall Pathogen	219/249 (88.0%)	134/155 (86.5%)	65/67 (97.0%)

- In Study M99-077, two treatment groups were not significantly different with respect to the safety variables.
- In Study M98-927, significantly more subjects experienced adverse events in the trovafloxacin group than in the clarithromycin ER group.