CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-662/A029

STATISTICAL REVIEW(S)

October 10, 2000

STATISTICAL REVIEW AND EVALUATION

sNDA: 50-662 (S-029)
DRUG: Biaxin® Filmtab® (clarithromycin) Immediate Release Tablet
SPONSOR: Abbott Laboratories
INDICATIONS: Community acquired pneumonia

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Reviewer'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 one phase III controlled study as evidence to support that clarithromycin IR 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 the microorganism *Haemophilis influenzae* to the previously approved indication of CAP for this drug. Statistical review focuses on this comparative clinical trial which formed the basis of this application. The general design of the study is as follows:

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 clarithromycin IR tablets (1x250 mg BID) with those of a 7-day course of therapy with trovafloxacin tablets (1x200 mg QD) in the treatment of ambulatory subjects with CAP, whereas trovafloxacin acted an appropriate active control in this study. It was initiated on December 11, 1998 and completed on June 29, 1999.

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II. METHODS

In Study M98-927, approximately 150 subjects were planned to be 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.

Clinical and bacteriological assessments were performed within 48 hours before initiating study drug (Evaluation 1). 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 IR 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 IR versus trovafloxacin.*

Of note, in the protocol, the comparisons of interest were specified between two test treatments (clarithromycin IR and clarithromycin ER) and a control (trovafloxacin), and during the trial, more than one pair of groups was compared among clarithromycin IR, clarithromycin ER and trovafloxacin despite clarithromycin ER was withdrawn later in 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.

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. RESULTS

Of the 181 subjects who enrolled in the study, 95 were randomized to the clarithromycin IR treatment group, and 86 were randomized to the trovafloxacin treatment group. No enrolled subject was excluded from the ITT analyses. Thirty subjects (10 clarithromycin IR 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. Ninety-seven subjects (41 clarithromycin IR and 56 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 1. Significantly more subjects in the trovafloxacin treatment group excluded from the clinically evaluable analyses (p-value: 0.021) and the clinically and bacteriologically evaluable analyses (p-value: 0.003) than those in the clarithromycin IR treatment 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: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Subjects Included	
	Clarithromycin IR	Trovafloxacin
All Randomized Subjects	95	86
ITT Subjects	95 (100%)	86 (100%)
Clinically Evaluable Subjects	85 (89.5%)	66 (76.7%)
Clinical and Micro. Evaluable Subjects	54 (56.8%)	30 (34.9%)

TABLE 2: BASELINE DEMOGRAPHICS IN ITT SUBJECTS

Parameters	Clarithromycin IR (N=95)	Trovafloxacin (N=86)	P-value
Gender			
Male	45 (59.3%)	41 (54.4%)	1.000
Female	50 (40.7%)	45 (45.6%)	
Age (yrs.)			
Range (Min, Max)	(28, 76)	(19, 80)	
Mean ± SD	49.1 ± 13.8	47.3 ± 16.1	*0.407
Distribution			
≤ 40	24 (25.3%)	32 (37.2%)	0.210
41 ~ 64	52 (54.7%)	38 (44.2%)	
≥ 65	19 (20.0%)	16 (18.6%)	
Race			
White	85 (89.5%)	76 (88.4%)	0.675
Black	5 (5.3%)	7 (8.1%)	
Other	5 (5.3%)	3 (3.5%)	
Weight (kg)			
Range (Min, Max)	(48.1, 154.2)	(42.9, 158.8)	
Mean ± SD	81.9 ± 18.7	85.3 ± 20.6	*0.246

* 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 results showed that the cure rates of clarithromycin IR were marginally comparable to those of trovafloxacin, which was based on the 95% confidence interval for the difference in cure rates. However, the 97.5% confidence interval did not illustrate the therapeutic equivalence of the two treatment groups.*

TABLE 3: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin IR (N=85)	Trovafloxacin (N=66)
Cure Failure	76 (89.4%) 9 (10.6%)	63 (95.5%) 3 (4.6%)
IR Versus Trova.: Difference in Cure Rate	-6.0%, 95% C.I.: -15.6%, 3.6% 97.5% C.I.: -16.8%, 4.7%	

***Reviewer's Note**: Subject clinical responses for target pathogens for clinically and bacteriologically evaluable subjects are presented in Table 4. Two treatments appeared similar outcomes with no statistically significant treatment differences. More specifically, 100% of the typical pathogen H. influenzae isolated pretreatment were cured after treatment among the subjects in the clarithromycin IR group. 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: CLINICAL CURE RATES FOR TARGET PATHOGENS OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT			
Pathogen	Clarithromycin IR	Trovafloxacin	Fisher's P-value
Overall Pathogen	72/76 (94.7%)	40/41 (97.6%)	0.656
H. parainfluenzae	18/19 (94.7%)	9/9 (100%)	1.000
H. influenzae	15/15 (100%)	8/9 (88.9%)	0.375
M. pneumoniae	13/14 (92.9%)	11/11 (100%)	1.000
C. pneumoniae	7/9 (77.8%)	4/4 (100%)	1.000
S. pneumoniae	7/7 (100%)	3/3 (100%)	NA
S. aureus	6/6 (100%)	3/3 (100%)	NA
M. catarrhalis	5/5 (100%)	2/2 (100%)	NA
L. pneumophila	1/1 (100%)	0/0 (NA)	NA

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TABLE 5: ERADICATION RATES FOR TARGET PATHOGENS OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT			
Pathogen	Clarithromycin IR	Trovafloxacin	Fisher's P-value
Overall Pathogen	71/76 (93.4%)	39/41 (95.1%)	1.000
H. influenzae	15/15 (100%)	8/9 (88.9%)	0.375
H. parainfluenzae	17/19 (89.5%)	9/9 (100%)	1.000
M. pneumoniae	13/14 (92.9%)	11/11 (100%)	1.000
C. pneumoniae	7/9 (77.8%)	4/4 (100%)	1.000
S. pneumoniae	7/7 (100%)	2/3 (100%)	NA
S. aureus	6/6 (100%)	3/3 (100%)	NA
M. catarrhalis	5/5 (100%)	2/2 (100%)	NA
L. pneumophila	1/1 (100%)	0/0 (NA)	NA

***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 all these analyses demonstrated that clinical cure rates or bacteriological cure rates of clarithromycin IR were comparable to those of trovafloxacin, where the 95% and 97.5% confidence intervals were consistent with each other.*

TABLE 6: CLINICAL RESPONSES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin IR (N=54)	Trovafloxacin (N=30)
Cure Failure	52 (96.3%) 2 (3.7%)	29 (96.7%) 1 (3.3%)
IR Versus Trova.: Difference in Cure Rate	-0.4%, 95% C.I.: -11.1%, 10.4% 97.5% C.I.: -12.3%, 11.6%	

TABLE 7: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin IR (N=95)	Trovafloxacin (N=86)
Cure Failure Indeterminate	77 (81.1%) 9 (9.5%) 9 (9.5%)	65 (75.6%) 3 (3.5%) 18 (20.9%)
IR Versus Trova.: Difference in Cure Rate	5.5%, 95% C.I.: -7.7%, 18.6% 97.5% C.I.: -9.4%, 20.3%	

TABLE 8: BACTERIOLOGICAL RESPONSES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Bacteriological Response	Clarithromycin IR (N=54)	Trovafloxacin (N=30)
Cure Failure	51 (96.3%) 3 (3.7%)	28 (96.7%) 2 (3.3%)
IR Versus Trova.: Difference in Cure Rate	1.1%, 95% C.I.: -12.3%, 14.5% 97.5% C.I.: -13.9%, 16.1%	

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. Both 95% and 97.5% confidence intervals for the differences did show the equivalence of the two treatments for success rates, but did not for resolution rates, whereas clarithromycin IR had lower radiographic resolution rates in clinically evaluable subjects and higher ones in clinically and bacteriologically evaluable subjects.*

TABLE 9: RADIOGRAPHIC RESOLUTION AND SUCCESS RATES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT

	Clarithromycin IR (N=82)	Trovafloxacin (N=66)
RADIOGRAPHIC RESOLUTION RATE		
Resolution	65 (79.3%)	54 (81.8%)
IR Versus Trova.: Difference in Resolution Rate	-2.5%, 95% C.I.: -16.7%, 11.6% 97.5% C.I.: -18.5%, 13.4%	
RADIOGRAPHIC SUCCESS RATE		
Success	76 (92.7%)	63 (95.5%)
IR Versus Trova.: Difference in Success Rate	-2.8%, 95% C.I.: -11.7%, 6.1% 97.5% C.I.: -12.8%, 7.2%	

Note: Indeterminate and missing responses were excluded from calculation of radiographic response rates.

TABLE 10: RADIOGRAPHIC RESOLUTION AND SUCCESS RATES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

	Clarithromycin IR (N=52)	Trovafloxacin (N=30)
RADIOGRAPHIC RESOLUTION RATE		
Resolution	44 (84.6%)	24 (80.0%)
IR Versus Trova.: Difference in Resolution Rate	4.6%, 95% C.I.: -15.4%, 24.6% 97.5% C.I.: -17.9%, 27.1%	
RADIOGRAPHIC SUCCESS RATE		
Success	50 (96.2%)	28 (93.3%)
IR Versus Trova.: Difference in Success Rate	2.8%, 95% C.I.: -10.2%, 15.8% 97.5% C.I.: -11.6%, 17.3%	

Note: Indeterminate and missing responses were excluded from calculation of radiographic response rates.

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. No deaths were reported during the study.*

TABLE 11: ADVERSE EVENT RATES			
Safety Outcomes	Clarithromycin IR (N=95)	Trovafloxacin (N=86)	Fisher's P-value
With Any AE	42 (44.2%)	48 (55.8%)	0.138
With Drug Related AE	19 (20.0%)	20 (23.3%)	0.718
Serious AEs	4 (4.2%)	1 (3.5%)	1.000
Discontinuation Due To AEs	3 (3.2%)	1 (1.2%)	0.623

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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 IR minus control) are reported as $_{n1,n2}(l, u)_{p1,p2}$, where n1 is the number of clarithromycin IR subjects, n2 is the number of control subjects, l and u are the lower and upper bounds of the 97.5% confidence interval, respectively, p1 is the response rate in clarithromycin IR subjects, and p2 is the response rate in control subjects.*

This indication was primarily supported by one controlled study to demonstrate the efficacy and safety of clarithromycin IR.

Statistical evaluation of efficacy was primarily based upon the two-sided 97.5% confidence interval of the difference in clinical cure rates at TOC between the clarithromycin IR group and the 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.

- *The 97.5% confidence interval of the difference in clinical cure rates of clarithromycin IR minus trovafloxacin for clinically evaluable subjects was $_{85, 66}(-16.8\%, 4.7\%)_{89.4\%, 95.5\%}$, which failed to show the equivalence in efficacy of the two treatments in the treatment of CAP. The 97.5% confidence interval from ITT subjects demonstrated that clarithromycin IR was equivalent to trovafloxacin $_{95, 86}(-9.4\%, 20.3\%)_{81.1\%, 75.6\%}$.*

- *The efficacy of clarithromycin IR and trovafloxacin in the eradication and cure of eight target pathogens was examined, which concluded the similarity in eradication rates and cure rates for the two treatments. Overall pathogen eradication rates and cure rates were comparable between the two treatment groups.*

- *It is noteworthy that the eradication rate and cure rate for H. influenzae in clarithromycin IR were all 100%, whereas in trovafloxacin 88.9%, and trovafloxacin was approved for the treatment of ambulatory subjects with CAP caused by H. influenzae.*

- *In clinically evaluable subjects, clarithromycin IR and trovafloxacin had comparable bacteriological cure rates, and radiographic success rates. Clarithromycin IR had lower radiographic resolution rates.*

- *In clinically and bacteriologically evaluable subjects, clarithromycin IR and trovafloxacin had comparable clinical cure rates, bacteriological cure rates, and radiographic success rates. Clarithromycin IR had higher radiographic resolution rates.*

- *Two treatment groups were not significantly different with respect to the safety variables.*

/S/ 10/11/2000

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Archival: NDA: 50-662
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This review contains 11 pages and 11 tables.
MicrosoftWord 7.0/NDAbiaxin2
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