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APPLICATION NUMBER:

50-775

STATISTICAL REVIEW(S)

NDA 50-775
Biaxin® XL Filmtab (clarithromycin extented-release tablets)

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STATISTICAL REVIEW AND EVALUATION

SPONSOR: Abbott Laboratories
INDICATIONS: Treatments of acute exacerbation of chronic bronchitis and acute maxillary sinusitis

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Review's Note: Throughout the review, the following terms are abbreviated and referred to as: AECB = Acute Exacerbation of Chronic Bronchitis, CRF = Case Report Form, ER = extended release, IR = immediate release. Reviewer comments are given in italics throughout the review.

I. ACUTE EXACERBATION OF CHRONIC BRONCHITIS

I.A. INTRODUCTION

The Applicant submitted one phase III controlled study as evidence to support that clarithromycin ER tablets (2x500 mg QD) was safe and efficacious for the treatments of acute exacerbation of chronic bronchitis when compared with clarithromycin IR tablets (1x500 mg BID). 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 M97-756 was a double blind, randomized, parallel-group, and multicenter trial which compared the efficacy and safety of a 7-day course of therapy with clarithromycin ER tablets (2x500 mg QD) with those of a 7-day course of therapy with clarithromycin IR tablets (1x500 mg BID) in the treatment of ambulatory subjects with acute exacerbation of chronic bronchitis. It was initiated on March 10, 1998 and completed on February 22, 1999.

I.B. STUDY M97-756

I.B.1. METHODS

Male and female subjects at least 12 years of age with a presumptive diagnosis of AECB were eligible for enrollment in this study provided that they met the inclusion/exclusion criteria. Eligible subjects were randomly assigned in a 1:1 ratio to 7 days treatment course with either clarithromycin ER tablets (2x500mg QD) plus placebo for clarithromycin ER or clarithromycin IR tablets (1x500mg BID) plus placebo for clarithromycin IR. After informed consent was obtained, a medical history was recorded, and physical examination, vital signs assessment, and laboratory evaluations were performed. Three evaluations were set in the study procedure. Clinical and bacteriological assessments were performed within 48 hours before starting study drug (Evaluation 1). Subjects returned to the clinic on Study Day 8-10 or within 48 hours after premature discontinuation of study drug (Evaluation 2) and once during Study Days 19 to 21 (Evaluation 3) for clinical and bacteriological assessments. Clinical response was assigned at Evaluation 3 (Test-of-Cure). Safety was evaluated through periodic laboratory tests, post-treatment physical examination, and monitoring of adverse events. The total duration of each subject's participation in the study was approximately 3 to 4 weeks. Enrolled subjects were evaluated and assigned to an appropriate data set for analysis. The clinically and bacteriologically evaluable, clinically evaluable, and intent-to-treat data sets were used for the efficacy analysis. All treated data set was used for the safety analysis.

Efficacy in this study was assessed by clinical resolution of signs and symptoms of AECB, and bacteriological eradication of pathogens. Bacteriological response was evaluated in subjects who were bacteriologically and clinically evaluable subjects, and intent-to-treat subjects with at least one target pathogen at pretreatment. Clinical response was evaluated in bacteriologically and clinically evaluable subjects, clinically evaluable subjects, and intent-to-treat subjects.

The primary efficacy variables were the clinical cure rate in the clinically evaluable subjects, the clinical cure rate in the clinically and bacteriologically evaluable subjects, the subject bacteriological cure rate in the clinically and bacteriologically evaluable subjects, and the overall pathogen eradication rate in the

clinically and bacteriologically evaluable subjects. The primary time point was the test-of-cure visit. All other efficacy measures were considered secondary, including the change in clinical signs and symptoms.

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

Please refer to the Medical Officer's review for detailed descriptions of the Sponsor's efficacy outcome definitions and Medical Officer's comments.

The safety of the study medication was monitored throughout the study by physical examinations, including vital signs, concomitant medications, the assessment of adverse events and laboratory evaluations. Subjects who took at least one dose of study medication (all treated subjects) were used for the safety analysis.

The comparisons of interest in these studies were conducted between clarithromycin ER and clarithromycin IR.

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

Equivalence between the treatments 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 0.15, which is considered a clinically acceptable equivalence margin with respect to this indication. Equivalence in efficacy was established based on the equivalence of all primary clinical and bacteriological responses, hence no multiplicity adjustments were applied.

Subset analyses by gender, age, and race were performed for the primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment 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. Quantitative variables were assessed using the t-test, and qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. The test for homogeneity of treatment effect was deemed significant at the 0.15 level.

I.B.2. RESULTS

A total of 620 subjects were randomized and took study drug; 317 subjects in the clarithromycin ER group and 303 subjects in the clarithromycin IR group. Of the intent-to-treat subjects, there were 300 received clarithromycin ER and 285 received clarithromycin IR. The subjects excluded from the intent-to-treat analyses were those who did not meet the selection criteria or were assessed by a disqualified investigator. Of the clinically evaluable subjects, there were 261 receiving clarithromycin ER and 259 receiving clarithromycin IR. Most of subjects excluded from the clinically evaluable analyses were those who did not meet selection criteria, did not return for test-of-treat visit, or used confounding medication.

Of the clinically and bacteriologically evaluable subjects, there were 100 received clarithromycin ER and 82 received clarithromycin IR. Most of subjects excluded from the clinically and bacteriologically evaluable analyses were those who did not have target pathogen isolated during pretreatment.

***Reviewer's Note**: The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 1. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group. Demographic information is described for all treated subjects in Table 2, and no statistical significant differences were detected between two treatment groups.*

TABLE 1: STUDY M97-756: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Analysis Group	Subjects Included	
	Clarithromycin ER	Clarithromycin IR
Randomized and Treated	317 (99.1%)	303 (98.7%)
Intent-to-Treat	300 (93.8%)	285 (92.8%)
Clinically Evaluable	261 (81.6%)	259 (84.4%)
Clinically and Bacteriologically Evaluable	100 (31.3%)	82 (26.7%)

TABLE 2: STUDY M97-756: SUMMARY OF DEMOGRAPHIC INFORMATION FOR ALL TREATED SUBJECTS

Number of Subjects	Clarithromycin ER (N=317)	Clarithromycin IR (N=303)	P-value
Gender			
Male	136 (42.9%)	134 (44.2%)	0.747
Femal	181 (57.1%)	169 (55.8%)	
Age	54.3 ± 15.9	54.6 ± 17.2	* 0.829
~ 40 yrs.	66 (20.8%)	65 (21.5%)	0.421
40 yrs. ~ 65 yrs.	161 (50.8%)	139 (45.9%)	
65 yrs. ~	90 (28.4%)	99 (32.7%)	
Race			
White	277 (87.4%)	262 (86.5%)	0.812
Other	40 (12.6%)	41 (13.5%)	

* P-value is obtained by t-test, otherwise, by Fisher's exact test

***Reviewer's Note:** At test-of-cure visit, bacteriological cure rates and overall pathogen eradication rates are shown for clinically and bacteriologically evaluable subjects in Tables 3 and 4, respectively. The 95% confidence interval results from analyses showed that clarithromycin ER was therapeutically equivalent to clarithromycin IR with respect to both rates.*

Subset analyses by gender, age, and race for the bacteriological cure rates are shown for clinically and bacteriologically evaluable subjects in Table 5. Significant heterogeneity of treatment effects was detected between the gender subgroups, and the treatment effects more favored clarithromycin ER in female subjects. Significant heterogeneity of treatment effects was also detected among the age subgroups, and the treatment effect favored clarithromycin ER in subjects with age between 40 and 65 years of old.

TABLE 3: STUDY M97-756: SUBJECT BACTERIOLOGICAL RESPONSES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TEST-OF-CURE VISIT		
Subject Bacteriological Response	Clarithromycin ER (N=99*)	Clarithromycin IR (N=82)
Cured Failure	85 (85.9%) 14 (14.1%)	70 (85.4%) 12 (14.6%)
Indeterminate	1	0
ER vs IR: Cure Rate	0.5%, 95% C.I.: -10.9%, 11.9%	
* Subject with indeterminate bacteriologic response was not included in calculating rate. If those subjects was included and classified as failure, the confidence interval was (-11.8%, 11.1%)		

TABLE 4: STUDY M97-756: PATHOGEN ERADICATION RATES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TEST-OF-CURE VISIT		
	Clarithromycin ER	Clarithromycin IR
Overall Pathogen		
	100/116 (86.2%)	86/98 (87.8%)
ER vs IR: Eradication Rate	-1.5%, 95% C.I.: -11.5%, 8.4%	
Target Pathogen		
H. influenzae	22/28 (78.6%)	17/22 (77.3%)
M. catarrhalis	22/25 (88.0%)	25/26 (96.2%)
S. pneumoniae	22/25 (88.0%)	9/11 (81.8%)
H. parainfluenzae	24/26 (92.3%)	25/28 (89.3%)
S. aureus	10/12 (83.3%)	10/11 (90.9%)

TABLE 5: STUDY M97-756: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF BACTERIOLOGICAL CURE RATES OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TEST-OF-CURE VISIT				
Subset	Clarithromycin ER	Clarithromycin IR	95% C.I.	Breslow-Day's P-Value
Male Female	37/46 (80.4%) 48/53 (90.6%)	33/35 (94.3%) 37/47 (78.7%)	(-30.2%, 2.5%) (-4.3%, 28.0%)	0.015
- 40 yrs. 40 yrs - 65 yrs. 65 yrs. -	14/19 (73.7%) 46/50 (92.0%) 25/30 (83.3%)	16/17 (94.1%) 25/32 (78.1%) 29/33 (87.9%)	(-48.7%, 7.9%) (-4.9%, 32.6%) (-25.1%, 16.0%)	0.046
White Other	76/88 (86.4%) 9/11 (81.8%)	61/72 (84.7%) 9/10 (90.0%)	(-10.6%, 13.9%) (-47.1%, 30.8%)	0.546

Reviewer's Note: *Clinical cure rates at test-of-cure of clinically and bacteriologically evaluable subjects and clinically evaluable subjects are presented in Table 6. In both analysis groups, clarithromycin ER and clarithromycin IR were therapeutically equivalent.*

Subset analyses by gender, age, and race for the clinical cure rates are shown for clinically and bacteriologically evaluable subjects and clinically evaluable subjects in Table 7, respectively. For clinically and bacteriologically evaluable subjects, significant heterogeneity of treatment effects was detected between the gender subgroups, and the treatment effects more favored clarithromycin ER in female subjects. Significant heterogeneity of treatment effects was also detected among the age subgroups, and

the treatment effect favored clarithromycin ER in subjects with age between 40 and 65 years of old. For clinically evaluable subjects, results were consistent across all three demographic aspects.

TABLE 6: STUDY M97-756: CLINICAL RESPONSES AT TEST-OF-CURE VISIT		
Clinically and Bacteriologically Evaluable Subjects		
Clinical Response	Clarithromycin ER (N=100)	Clarithromycin IR (N=82)
Cured Failure Indeterminate	83 (83.0%) 17 (17.0%) 0 (0%)	67 (81.7%) 15 (18.3%) 0 (0%)
ER vs IR: Cure Rate	1.3%, 95% C.I.: -11.0%, 13.5%	
Clinically Evaluable Subjects		
Clinical Response	Clarithromycin ER (N=261)	Clarithromycin IR (N=259)
Cured Failure Indeterminate	209 (80.1%) 52 (19.9%) 0 (0%)	214 (82.6%) 45 (17.4%) 0 (0%)
ER vs IR: Cure Rate	-2.5%, 95% C.I.: -9.6%, 4.5%	

TABLE 7: STUDY M97-756: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF CLINICAL CURE RATES AT TEST-OF-CURE VISIT				
Clinically and Bacteriologically Evaluable Subjects				
Subset	Clarithromycin ER	Clarithromycin IR	95% C.I.	Breslow-Day's P-Value
Male Female	35/47 (74.5%) 48/53 (90.6%)	30/35 (85.7%) 37/47 (78.7%)	(-30.8%, 8.3%) (-4.3%, 28.0%)	0.041
~ 40 yrs. 40 yrs ~ 65 yrs 65 yrs. ~	14/19 (73.7%) 45/51 (88.2%) 24/30 (80.0%)	16/17 (94.1%) 24/32 (75.0%) 27/33 (81.8%)	(-48.7%, 7.9%) (-6.7%, 33.2%) (-24.4%, 20.8%)	0.077
White Other	75/89 (84.3%) 8/11 (72.7%)	59/72 (81.9%) 8/10 (80.0%)	(-10.6%, 15.2%) (-53.0%, 38.4%)	0.610
Clinically Evaluable Subjects				
Subset	Clarithromycin ER	Clarithromycin IR	95% C.I.	Breslow-Day's P-Value
Male Female	84/110 (76.4%) 125/151 (82.8%)	88/116 (75.9%) 126/143 (88.1%)	(-11.5%, 12.5%) (-14.0%, 3.4%)	0.315
~ 40 yrs. 40 yrs ~ 65 yrs 65 yrs. ~	43/54 (79.6%) 109/132 (82.6%) 57/75 (76.0%)	49/56 (87.5%) 99/122 (81.1%) 66/81 (81.5%)	(-23.5%, 7.7%) (-8.8%, 11.7%) (-19.6%, 8.6%)	0.484
White Other	182/230 (79.1%) 27/31 (87.1%)	184/224 (82.1%) 30/35 (85.7%)	(-10.7%, 4.7%) (-18.2%, 21.0%)	0.682

Reviewer's Note: *Subject clinical cure rates for target pathogens of clinically and bacteriologically evaluable subjects at test-of-cure visit are presented in Table 8.*

TABLE 8: STUDY M97-756: SUBJECT CLINICAL CURE RATES FOR TARGET PATHOGENS OF CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TEST-OF-CURE VISIT		
	Clarithromycin ER	Clarithromycin IR
Target Pathogen		
H. influenzae	21/28 (75.0%)	17/22 (77.3%)
M. catarrhalis	22/26 (84.6%)	22/27 (81.5%)
S. pneumoniae	21/25 (84.0%)	8/11 (72.7%)
H. parainfluenzae	24/26 (92.3%)	25/28 (89.3%)
S. aureus	10/12 (83.3%)	10/11 (90.9%)

Reviewer's Note: *At test-of-cure visit, subject bacteriological responses, pathogen bacteriological responses, and clinical responses are shown for intent-to-treat subjects in Tables 9, 10, and 11, respectively. The results between clarithromycin ER and clarithromycin IR among intent-to-treat subjects were generally similar to those among the clinically and bacteriologically evaluable subjects or clinically evaluable subjects.*

TABLE 9: STUDY M97-756: SUBJECT BACTERIOLOGICAL RESPONSES OF INTENT-TO-TREAT SUBJECTS AT TEST-OF-CURE VISIT		
Subject Bacteriological Response	Clarithromycin ER (N=112*)	Clarithromycin IR (N=88*)
Cure	85 (75.9%)	70 (79.5%)
Failure	14 (12.5%)	12 (13.6%)
Indeterminate	13 (11.6%)	6 (6.8%)
ER vs IR: Cure Rate	-3.7%, 95% C.I.: -16.2%, 8.9%	
* Subjects must have at least one target pathogen at pretreatment in order to be included in the analyses. Indeterminate was rated as failure while calculating the rate.		

TABLE 10: STUDY M97-756: PATHOGEN ERADICATION RATES OF INTENT-TO-TREAT SUBJECTS AT TEST-OF-CURE VISIT		
	Clarithromycin ER	Clarithromycin IR
Overall Pathogen		
	100/130 (76.9%)	86/107 (80.4%)
ER vs IR: Eradication Rate	-3.5%, 95% C.I.: -14.7%, 7.8%	
Target Pathogen		
H. influenzae	22/32 (68.8%)	17/25 (68.0%)
M. catarrhalis	22/27 (81.5%)	25/30 (83.3%)
S. pneumoniae	22/29 (75.9%)	9/13 (69.2%)
H. parainfluenzae	24/30 (80.0%)	25/28 (89.3%)
S. aureus	10/12 (83.3%)	10/11 (90.9%)

TABLE 11: STUDY M97-756: CLINICAL RESPONSES OF INTENT-TO-TREAT SUBJECTS AT TEST-OF-CURE VISIT		
Clinical Response	Clarithromycin ER (N=300)	Clarithromycin IR (N=285)
Cure	211 (70.3%)	215 (75.4%)
Failure	52 (17.3%)	45 (15.8%)
Indeterminate	37 (12.3%)	25 (8.8%)
ER vs IR: Cure Rate	-5.1%, 95% C.I.: -12.6%, 2.4%	

Reviewer's Note: *For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of serious adverse events, and the rate of discontinuation due to adverse events are presented in Table 12. There were no significant differences with respect to these parameters except the rate of at least one adverse event, for which significantly more subjects experienced adverse events in the Clarithromycin ER group. One subject was dead during the treatment in the Clarithromycin ER group.*

TABLE 12: STUDY M97-756: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Clarithromycin ER (N=317)	Clarithromycin IR (N=303)	Fisher's P-value
With Any AE	124 (39.1%)	94 (31.0%)	0.036
With Treatment Related AE	70 (22.1%)	52 (17.2%)	0.131
Serious AEs	8 (2.5%)	4 (1.3%)	0.384
Discontinuation Due To AEs	6 (1.9%)	11 (3.6%)	0.223

II. ACUTE MAXILLARY SINUSITIS

II.A. INTRODUCTION

The Applicant submitted one phase III controlled study as evidence to support that clarithromycin ER tablets (2x500 mg QD) was safe and efficacious for the treatments of acute maxillary sinusitis when compared with clarithromycin IR tablets (1x500 mg BID). Statistical review focuses on this comparative clinical trial which formed the basis of this application. The general design of the studies is as follows:

Study M97-667 was a double blind, randomized, parallel-group, and multicenter trial which compared the efficacy and safety of a 14-day course of therapy with clarithromycin ER tablets (2x500 mg QD) with those of a 14-day course of therapy with clarithromycin IR tablets (1x500 mg BID) in the treatment of outpatient subjects with acute maxillary sinusitis. It was initiated on March 13, 1998 and completed on October 1, 1999.

II.B. STUDY M97-667

II.B.1. METHODS

Male and female subjects at least 12 years of age with a presumptive diagnosis of acute maxillary sinusitis were eligible for enrollment in this study provided that they met the inclusion/exclusion criteria. Eligible subjects were randomly assigned in a 1:1 ratio to 14 days treatment course with either clarithromycin ER tablets (2x500mg QD) plus placebo for clarithromycin ER or clarithromycin IR tablets (1x500mg BID) plus placebo for clarithromycin IR. In addition, all subjects were supplied with 0.05% oxymetazoline nasal spray to be used in conjunction with clarithromycin during the first 3 days of study drug therapy. After informed consent was obtained, a sinus x-ray was performed to confirm the diagnosis. If x-ray results were positive, the subject was enrolled in the study, a medical history was recorded, and physical examination, vital signs assessment, and laboratory evaluations were performed. Five visits were planed in the study procedure. Clinical and radiological assessments were performed prior to initiating study drug (Visit 1). Subjects were telephoned for interview once during Study Days 3 to 5 to determine whether signs and symptoms of maxillary sinusitis had improved or if a during-treatment visit (Visit 2) was necessary. Subjects returned to the clinic within 48 hours post-treatment (Visit 3) and once during Study Days 24 to 31 (Visit4). Clinical response was assigned at Visit 4 (Test-of-Cure). If clinical cure could not be assigned or if Visit 4 procedures were missing, the subject was to return 4 weeks after the last dose of study drug (Visit5). Safety was evaluated through periodic laboratory tests, post-treatment physical examination, and monitoring of adverse events. The total duration of each subject's participation in the study was approximately 4 to 6 weeks, depending on whether or not Visit 5 was required. Enrolled subjects were evaluated and assigned to an appropriate data set for analysis. The clinically evaluable data set was used for the primary efficacy analysis, with intent-to-treat subjects supporting the efficacy results. All treated data set was used for the safety analysis.

Efficacy in this study was assessed by clinical resolution of signs and symptoms of acute sinusitis, sinus x-ray. Clinical response was evaluated in clinically evaluable subjects and intent-to-treat subjects.

The primary efficacy variables were the clinical cure rate at test-of-cure in clinically evaluable subjects. All

other efficacy measures were considered secondary, including radiographic resolution rate and radiographic success rate.

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

Please refer to the Medical Officer's review for detailed descriptions of the Sponsor's efficacy outcome definitions and Medical Officer's comments.

The safety of the study medication was monitored throughout the study by concomitant medications, vital signs, and assessment of adverse events. Subjects who took at least one dose of study medication (all treated subjects) were used for the safety analysis.

The comparisons of interest in these studies were conducted between clarithromycin ER and clarithromycin IR.

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

Equivalence between the treatments 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 0.15, which is considered a clinically acceptable equivalence margin with respect to this indication.

Subset analyses by gender, age, and race were performed for the primary efficacy variables. Homogeneity of treatment effect across subgroups was assessed via Breslow-Day's test.

This reviewer conducted safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment 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. Quantitative variables were assessed using the t-test, and qualitative variables were assessed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. The test for homogeneity of treatment effect was deemed significant at the 0.15 level.

II.B.2. RESULTS

A total of 283 subjects were randomized and took study drug; 142 subjects in the clarithromycin ER group and 141 subjects in the clarithromycin IR group. Of the intent-to-treat subjects, there were 138 received clarithromycin ER and 136 received clarithromycin IR. Most of subjects excluded from the intent-to-treat analyses were those who did not meet the selection criteria. Of the clinically evaluable subjects, there were 122 receiving clarithromycin ER and 123 receiving clarithromycin IR. Most of subjects excluded from the clinically evaluable analyses were those whose clinical evaluation did not performed at test-of-cure visit, or who did not meet selection criteria.

***Reviewer's Note**: The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 13. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group. Demographic information is described for all treated subjects in Table 14, and no statistical significant differences were detected between two treatment groups.*

TABLE 13: STUDY M97-667: NUMBER OF SUBJECTS INCLUDED IN EACH ANALYSIS GROUP

Analysis Group	Subjects Included	
	Clarithromycin ER	Clarithromycin IR
All Randomized and Treated	142 (100%)	141 (100%)
Intent-to-Treat	138 (97.2%)	136 (96.5%)
Clinically Evaluable	122 (85.9%)	123 (87.2%)

TABLE 14: STUDY M97-667: SUMMARY OF DEMOGRAPHIC INFORMATION FOR THE ALL TREATED SUBJECTS

Number of Subjects	Clarithromycin ER (N=142)	Clarithromycin IR (N=141)	P-value
Gender			
Male	49 (34.5%)	53 (37.6%)	0.622
Femal	93 (65.5%)	88 (62.4%)	
Age	41.9 ± 13.6	41.0 ± 13.0	* 0.572
~ 40 yrs.	68 (47.9%)	67 (47.5%)	0.884
40 yrs ~ 65 yrs.	66 (46.5%)	68 (48.2%)	
65 yrs. ~	8 (5.6%)	6 (4.3%)	
Race			
White	119 (83.8%)	127 (90.1%)	0.158
Other	23 (16.2%)	14 (9.9%)	

* P-value is obtained by t-test, otherwise, by Fisher's exact test

***Reviewer's Note:** The cure rates at test-of-cure of clinically evaluable subjects are presented in Table 15. The 95% confidence interval results from analyses showed that clarithromycin ER was therapeutically equivalent to clarithromycin IR.*

Subset analyses by gender, age, and race for the clinical cure rates are shown for clinically evaluable subjects in Table 16. Results were consistent across all three demographic aspects.

TABLE 15: STUDY M97-667: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TEST-OF-CURE VISIT

Clinical Response	Clarithromycin ER (N=121*)	Clarithromycin IR (N=121*)
Cure	102 (84.3%)	94 (77.7%)
Failure	19 (15.7%)	27 (22.3%)
Indeterminate	1	2
ER vs IR: Cure Rate	6.6%, 95% C.I.: -4.1%, 17.3%	

* Subjects with indeterminate clinical response were not included in calculating rate. If those subjects was included and classified as failure, the confidence interval was (-3.6%, 18.0%)

TABLE 16: STUDY M97-667: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF CLINICAL CURE RATES OF CLINICALLY EVALUABLE SUBJECTS AT TEST-OF-CURE VISIT				
Subset	Clarithromycin ER	Clarithromycin IR	95% C.I.	Breslow-Day's P-Value
Male Female	32/41 (78.0%) 70/80 (87.5%)	56/71 (78.9%) 38/50 (76.0%)	(-18.6%, 16.9%) (-4.0%, 27.0%)	0.208
~ 40 yrs. 40 yrs ~ 65 yrs 65 yrs. ~	51/59 (86.4%) 47/57 (82.5%) 4/5 (80.0%)	43/55 (78.2%) 48/60 (80.0%) 3/6 (50.0%)	(-7.5%, 24.0%) (-13.4%, 18.3%) (-41.5%, 101.5%)	0.636
White Other	85/102 (83.3%) 17/19 (75.0%)	84/110 (76.4%) 10/11 (90.9%)	(-4.7%, 18.7%) (-30.5%, 27.6%)	0.650

Reviewer's Note: *The cure rates at test-of-cure of intent-to-treat subjects are presented in Table 17. The 95% confidence interval results from analyses showed that clarithromycin ER was therapeutically equivalent to clarithromycin IR.*

The radiographic responses at test-of-cure are shown for clinically evaluable and intent-to-treat subjects in Table 18, respectively. The results illustrated that clarithromycin ER was therapeutically equivalent to clarithromycin IR.

TABLE 17: STUDY M97-667: CLINICAL RESPONSES OF INTENT-TO-TREAT SUBJECTS AT TEST-OF-CURE VISIT		
Clinical Response	Clarithromycin ER (N=138)	Clarithromycin IR (N=136)
Cure Failure Indeterminate	105 (76.1%) 19 (13.8%) 14 (10.1%)	96 (70.6%) 27 (19.9%) 13 (9.6%)
ER vs IR: Cure Rate	5.5%, 95% C.I.: -5.7%, 16.7%	

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TABLE 18: STUDY M97-667: RADIOGRAPHIC RESPONSES AT TEST-OF-CURE VISIT		
Clinically Evaluable Subjects		
Clinical Response	Clarithromycin ER (N=111*)	Clarithromycin IR (N=107*)
Success (Resolution+Improvement) No Change Worsening	99 (89.2%) 7 (6.3%) 5 (4.5%)	97 (90.7%) 8 (7.5%) 2 (1.9%)%)
Missing	11	16
ER vs IR: Success Rate	-1.5%, 95% C.I.: -10.4%, 7.4%	
* Missing responses were excluded from calculation of radiographic response rates		
Intent-to-Treat Subjects		
Clinical Response	Clarithromycin ER (N=138)	Clarithromycin IR (N=136)
Success (Resolution+Improvement) No Change Worsening Missing	105 (76.1%) 7 (5.1%) 6 (4.3%) 20 (14.5%)	102 (75.0%) 8 (5.9%) 2 (1.5%) 24 (17.6%)
ER vs IR: Success Rate	1.1%, 95% C.I.: -9.8%, 12.0%	

Reviewer's Note: *For all treated subjects, the rate of at least one adverse event, the rate of at least one treatment related adverse event, and the rate of discontinuation due to adverse events are presented in Table 19. There were no significant differences with respect to these parameters. No serious adverse events were reported during the study.*

TABLE 19: STUDY M97-667: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Clarithromycin ER (N=142)	Clarithromycin IR (N=141)	Fisher's P-value
With Any AE	71 (50.0%)	71 (50.4%)	1.000
With Treatment Related AE	45 (31.7%)	40 (28.4%)	0.604
Serious AEs	2 (1.4%)	8 (5.7%)	0.060
Discontinuation Due To AEs	6 (4.2%)	11 (7.8%)	0.223

APPEARS THIS WAY ON ORIGINAL

III. 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 clarithromycin IR) are reported as* $_{n1,n2}(l, u)_{p1,p2}$*, where n1 is the number of clarithromycin ER patients, n2 is the number of clarithromycin IR patients, l and u are the lower and upper bounds of the 95% confidence interval, respectively, p1 is the response rate in clarithromycin ER subjects, and p2 is the response rate in clarithromycin IR subjects.*

TREATMENTS OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS

This indication was supported by one controlled study (M97-756) to demonstrate the efficacy and safety of clarithromycin ER.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in primarily efficacy variables between the clarithromycin ER group and the clarithromycin IR group at test-of-cure visit, including the clinical cure rate of clinically evaluable subjects, the clinical cure rate of clinically and bacteriologically evaluable subjects, the subject bacteriological cure rate of clinically and bacteriologically evaluable subjects, and the overall pathogen eradication rate of clinically and bacteriologically 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-sided Fisher's exact test.

1. The 95% confidence intervals for the difference in bacteriological cure rates at test-of-cure of clarithromycin ER minus clarithromycin IR for clinically and bacteriologically evaluable subjects were $_{99,\ 82}$ (-10.9%, 11.9%) $_{85.9\%,\ 85.4\%}$. The 95% confidence intervals for the difference in overall pathogen eradication rates at test-of-cure of clarithromycin ER minus clarithromycin IR for clinically and bacteriologically evaluable subjects were $_{116,\ 98}$ (-11.5%, 8.4%) $_{86.2\%,\ 87.8\%}$. The 95% confidence intervals for the difference in clinical cure rates at test-of-cure of clarithromycin ER minus clarithromycin IR for clinically and bacteriologically evaluable subjects and clinically evaluable subjects were $_{100,\ 82}$ (-11.0%, 13.5%) $_{83.0\%,\ 81.7\%}$ and $_{261,\ 259}$ (-9.6%, 4.5%) $_{80.1\%,\ 82.6\%}$, respectively. The results from these primary efficacy variables demonstrated that clarithromycin ER was therapeutically equivalent in efficacy to clarithromycin IR in the treatment of acute exacerbation of chronic bronchitis of adult subjects.

2. The rate of at least one adverse event was significantly higher in the clarithromycin ER group (39.1%) than the clarithromycin IR group (31.0%) (p-value=0.036). Two treatment groups were not significantly different in the rates of at least one treatment related adverse event, the rates of serious adverse events, and the rates of discontinuation due to adverse events.

<u>REVIEWER CONCLUSIONS</u>: For the adequate and well-controlled study M97-756, the efficacy analyses demonstrated that clarithromycin ER was therapeutically equivalent in efficacy to clarithromycin IR in the treatment of acute exacerbation of chronic bronchitis. Results from the safety analysis indicated that clarithromycin ER had significantly higher rates of at least one adverse event than its comparator formulation.

<u>RECOMMENDED REGULATORY ACTION</u>: Based on the above analyses, from an efficacy standpoint, a 7-day course of therapy with clarithromycin ER tablets (2x500 mg QD) is recommended for approval in the treatment of acute exacerbation of chronic bronchitis. However, the Medical Officer will have to determine

whether this treatment regimen has an acceptable safety profile.

TREATMENT OF ACUTE MAXILLARY SINUSITIS

This indication was supported by one controlled study (M97-667) to demonstrate the efficacy and safety of clarithromycin ER.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical cure rates at test-of cure between the clarithromycin ER group and the clarithromycin IR 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-sided Fisher's exact test.

1. The 95% confidence interval of the difference in clinical cure rates at test-of-cure of the clinically evaluable subjects was $_{121, 121}$ (-4.1%, 17.3%) $_{84.3\%, 77.7\%}$ which demonstrated that clarithromycin ER was therapeutically equivalent in efficacy to clarithromycin IR in the treatment of acute maxillary sinusitis.

2. Two treatment groups were not significantly different in safety with respect to the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of serious adverse events, and the rates of discontinuation due to adverse events.

REVIEWER CONCLUSIONS: *For the adequate and well-controlled study M97-667, the efficacy analyses demonstrated that clarithromycin ER was therapeutically equivalent in efficacy to clarithromycin IR in the treatment of acute maxillary sinusitis. Results from the safety analysis also suggested that both formulations yield comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, a 14-day course of therapy with clarithromycin ER tablets (2x500 mg QD) is recommended for approval in the treatment of acute maxillary sinusitis.*

/S/
Joel Jiang, Ph.D.
Statistician, DBIII

/S/ 2/8/00
Concur: Daphne Lin, Ph.D.
Team Leader, DBIII

/S/

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2/11/00

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This review contains 16 pages and 19 tables/figures.
MicrosoftWord 7.0/NDAbiaxin
2/2/00