

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-775/S001

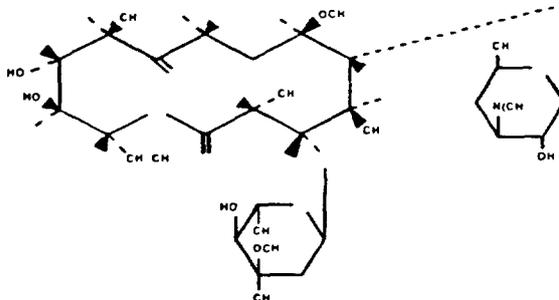
MEDICAL REVIEW

**MEDICAL OFFICER'S REVIEW OF NDA 50-775
CLINICAL SUPPLEMENT 001
BIAXIN[®] XL FILMTABS[®]**

Date Submitted:	September 29, 2000.
Date Received:	October 02, 2001.
Diskette Received:	October 02, 2001.
MOR Initiated:	June 06, 2001.
MOR Completed:	July 25, 2001.

APPLICANT: Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-3500

DRUG: **Generic:** Clarithromycin
 Trade: Biaxin[®] XL Filmtabs[®]
 Chemical Name: 6-O-Methylerythromycin
 Chemical Structure:



Molecular Formula: C₃₈H₆₉NO₁₃
Molecular Weight: 747.96

Pharmacology Category: Macrolide Anti-Infective
Dosage Form: Extended release filmtab
Strength: 500 mg

PROPOSED INDICATION:

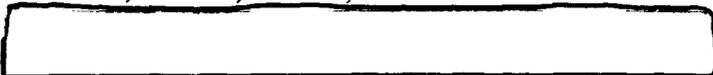
Pneumonia due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae* (TWAR), *Legionella pneumophila*, or *Mycoplasma pneumoniae*.

Related Material:

NDA – 50-662; 50-697; 50-698; 50-721

IND

DMF



SUBMISSION REVIEWED:

The submission consists of 55 volumes, and the clinical data are contained in volumes 4 to 55 inclusive.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

TABLE OF CONTENTS

EXECUTIVE SUMMARY.....	4
CLINICAL REVIEW	11
1. STUDY M99-077.....	15
2. STUDY M98-927.....	34
MEDICAL OFFICER'S COMBINED EFFICACY RESULTS.....	53
MEDICAL OFFICER'S EFFICACY CONCLUSIONS.....	53
SAFETY REVIEW.....	54
MEDICAL OFFICER'S RECOMMENDATIONS.....	67
REVIEW OF DRAFT LABELING.....	69

**APPEARS THIS WAY
ON ORIGINAL**

EXECUTIVE SUMMARY

I. Recommendations:

A. Recommendation on Approvability

Based upon the data reviewed and verified by the medical reviewer and the statistician, Biaxin® XL Filmtab® at the dose of 1000 mg every 24 hours for 7 days is recommended for approval in treatment of patients with community-acquired pneumonia caused by *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, *M. catarrhalis*, *C. pneumoniae*, or *M. pneumoniae*.

Biaxin® Filmtab®, Biaxin® Granules and Biaxin® XL Filmtab® have all been approved for several indications, and safety information on different formulations of clarithromycin is widely available. Based upon the safety data submitted for the two CAP studies, no new adverse events were identified. *The number of patients who reported abnormal taste as a side effect has increased from 6% to 7%.* There were no changes in the percentages of reported abnormal laboratory values.

A. Recommendations on Phase 4 Studies and/or Risk Management Steps

Biaxin® XL Filmtab® formulation was approved under NDA 50-775 on March 3, 2000. This application was filed to add a new indication – CAP to the package insert. No phase 4 studies are recommended at this time.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

Clarithromycin is a macrolide anti-infective. The chemical name is 6-O-Methylerythromycin. Biaxin® XL Filmtab® are an oral formulation given at the dosage of 1000-mg (two 500-mg tablets) once a day. It has been approved for two indications – Acute Maxillary Sinusitis and Acute Exacerbation of Chronic Bronchitis. This submission contains data from two phase 3 studies in patients with Community-Acquired Pneumonia.

The applicant submitted two clinical studies in support of the community-acquired pneumonia indication:

**APPEARS THIS WAY
ON ORIGINAL**

Protocol	Study Type	Dose/Frequency/Duration	Number of Patients	Geographic Location
Study M99-077	Multicenter, randomized, double-blind, active-controlled trial	Biaxin ER ^b 1000 mg qd for 7 days	156 randomized	United States, Canada
		Levofloxacin 500 mg qd for 7 days	143 randomized	
Study M98-927	Multicenter, randomized, double-blind, active-controlled trial ^a	Biaxin ER 1000 mg qd for 7 days	90 randomized	United States, Canada
		Trovofloxacin 200 mg qd for 7 days	86 randomized	

^a - Restrictions issued by FDA on June 9, 1999 regarding use of trovafloxacin resulted in the premature termination of the study; anticipated enrollment of 150 patients per arm was not attained.

^b - Several synonymous have been used for clarithromycin extended-release tablets through out this document – Biaxin ER; Biaxin® XL Filmtab®; Biaxin XL™ Filmtabs; clari ER; clarithromycin ER.

B. Efficacy

STUDY M99-077:

The clinical responses of clinically evaluable and ITT subjects at the test-of-cure visit was as follows:

STUDY M99-077: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
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%	

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%	

The confidence interval result verified that clarithromycin ER and levofloxacin were therapeutically equivalent with respect to cure rates at the test-of-cure visit for clinically evaluable and ITT patients.

STUDY M98-927:

The clinical responses of clinically evaluable and ITT subjects at the test-of-cure visit was as follows:

STUDY M98-927: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=85)	Trovafloxacin (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%	

STUDY M98-927: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=90)	Trovafloxacin (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%	

It should be noted that this study was prematurely terminated after FDA restricted the use of trovafloxacin, thus, this is only a supportive study. All the enrolled patients were included in the ITT population. An unusually large number of patients in the trovafloxacin group were excluded from the clinically evaluable population when compared to Biaxin XL group (20 versus 5). As noted in the tables above, 97.5% confidence intervals for the difference did not show equivalence of the two treatments. However, the point estimates for cure rates were roughly similar.

FDA'S COMBINED EFFICACY RATES:

The Combined Clinical Responses at Test-of-Cure Visit of all evaluable patients in studies M99-077 and M98-927 was as follows:

CLINICAL RESPONSES OF CLINICALLY EVALUABLE PATIENTS 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%)

The cure rates and the presumed eradication rates from studies M99-077 and M98-927 are as follows:

CURE AND ERADICATION RATES OF TARGET PATHOGENS IN CLINICALLY AND BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT IN TWO STUDIES			
Pathogen	Clarithromycin ER	Levofloxacin	Trovafloracin
<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>M. catarrhalis</i>	14/16 (87.5%)	11/14 (78.6%)	2/2 (100%)

C. Safety

Fifty-one investigative sites enrolled and treated 299 subjects with clarithromycin ER or levofloxacin in Study M99-077 and 31 investigative sites enrolled and treated 176 subjects with clarithromycin ER or trovafloxacin in Study M98-927. In the two Phase 3 CAP studies, 82 sites enrolled and treated a total of 475 subjects; 246 of these subjects took clarithromycin ER and 229 took levofloxacin or trovafloxacin.

In the studies that supported the clarithromycin ER NDA 50-775, 37 investigative sites enrolled and treated 283 subjects in Study M97-667 (Indication – Acute Maxillary Sinusitis) and 87 investigative sites enrolled and treated 620 subjects in Study M97-756 (Acute Exacerbation of Chronic Bronchitis). In the four clarithromycin ER pooled studies, 124 sites enrolled and treated a total of 1378 subjects; 705 of these subjects took clarithromycin ER and 673 took a comparator.

Demographic and Baseline Characteristics

Fifty-five percent of subjects in the CAP studies were male. The mean age of subjects in the CAP studies in the clarithromycin ER group was 48.5 years. A summary of presenting conditions, medical history, and social history is presented in the tables on the next two pages:

**APPEARS THIS WAY
 ON ORIGINAL**

Summary of Presenting Conditions, Medical History, and Social History (All Treated Subjects in Studies M99-077 and M98-927)				
	M99-077		M98-927	
	Clarithromycin ER	Levofloxacin	Clarithromycin ER	Trovaflxacin
Total Treated	156	143	90	86
Diseases/Conditions Present^a	(p-value not computed)		(p-value not computed)	
Surgical History	115 (74%)	105 (73%)	64 (71%)	68 (79%)
Respiratory	108 (69%)	91 (64%)	55 (61%)	57 (66%)
Eyes-Ears-Nose-Throat	91 (58%)	83 (58%)	50 (56%)	47 (55%)
Musculoskeletal	89 (57%)	84 (59%)	46 (51%)	57 (66%)
Gastrointestinal	65 (42%)	68 (48%)	45 (50%)	39 (45%)
Cardiovascular	68 (44%)	65 (45%)	41 (46%)	40 (47%)
Genitourinary	59 (38%)	56 (39%)	--	--
Endocrine-Metabolic	50 (32%)	59 (41%)	32 (36%)	28 (33%)
Drug Allergy/Sensitivity	59 (38%)	50 (35%)	30 (33%)	27 (31%)
Dermatological	48 (31%)	46 (32%)	--	--
Central Nervous System	53 (34%)	39 (27%)	--	--
Non-Drug Allergy	42 (27%)	39 (27%)	20 (22%)	21 (24%)
Psychiatric	39 (25%)	38 (27%)	--	--
Hematopoietic-Lymphatic	17 (11%)	18 (13%)	--	--
Peripheral Nervous System	6 (4%)	14 (10%)	--	--
Hepatic	9 (6%)	9 (6%)	8 (9%)	4 (5%)
Neurologic	--	--	41 (46%)	32 (37%)
Renal Disease	--	--	16 (18%)	13 (15%)
Occup/Env Hazard Exposure	--	--	7 (8%)	9 (10%)
Cancer	--	--	5 (6%)	5 (6%)
Immunodeficiency	--	--	2 (2%)	5 (6%)
Concurrent Illness^a	(p-value not computed)			
Musculoskeletal Disorder	62 (40%)	59 (41%)	--	--
Neuromuscular Disorder	26 (17%)	19 (13%)	--	--
Coronary Artery Disease	16 (10%)	12 (8%)	--	--
Diabetes Mellitus	9 (6%)	14 (10%)	--	--
Pulmonary Disease History^a	(p-value not computed)		(p-value not computed)	
CAP ^b	64 (41%)	40 (28%)	90 (100%)	86 (100%)
Acute Bronchitis	55 (35%)	45 (31%)	25 (28%)	26 (30%)
Chronic Bronchitis/COPD	33 (21%)	31 (22%)	--	--
Chronic Bronchitis	--	--	13 (14%)	8 (9%)
COPD	--	--	11 (12%)	6 (7%)
Bronchial Asthma	30 (19%)	17 (12%)	17 (19%)	13 (15%)
AECB	4 (3%)	7 (5%)	--	--
Overall Clinical Condition	(p=0.331)		(p=0.792)	
Good	37 (24%)	41 (29%)	31 (34%)	28 (33%)
Fair	119 (76%)	102 (71%)	59 (66%)	58 (67%)
Infection Status	(p=0.267)		(p=0.470)	
Mild	39 (25%)	44 (31%)	15 (17%)	18 (21%)
Moderate	117 (75%)	99 (69%)	75 (83%)	68 (79%)

a Reported by ≥5% of subjects in either treatment group of either study.

b M99-077 excluded the current CAP episode; M98-927 included the current CAP episode.

Summary of Presenting Conditions, Medical History, and Social History (continued) (All Treated Subjects in Studies M99-077 and M98-927)				
	M99-077		M98-927	
	Clarithromycin ER	Levofloxacin	Clarithromycin ER	Trovafloxacin
Total Treated	156	143	90	86
<u>Prior Medical Evaluation for this Infection</u>	(p=0.416)		(p=0.734)	
Yes	16 (10%)	19 (13%)	11 (12%)	12 (14%)
No	140 (90%)	124 (87%)	79 (88%)	74 (86%)
<u>Prior Medical Treatment for this Infection</u>	(p=0.647)		(p=0.820)	
Yes	56 (36%)	55 (38%)	32 (36%)	32 (37%)
No	100 (64%)	88 (62%)	58 (64%)	54 (63%)
<u>Number of CAP Infections in Past 12 Months</u>	(p=0.501)		(p=0.362)	
1	138 (88%)	130 (91%)	69 (77%)	68 (79%)
2	16 (10%)	10 (7%)	11 (12%)	14 (16%)
≥3	2 (1%)	3 (2%)	10 (11%)	4 (5%)
Mean (SD)	1.1 (0.5)	1.1 (0.4)	1.5 (1.0)	1.3 (0.8)
<u>Tobacco and Nicotine Use</u>	(p=0.047*)		(p=0.756)	
Non-User	58 (37%)	70 (49%)	35 (39%)	31 (36%)
Ex-User	44 (28%)	29 (20%)	24 (27%)	18 (21%)
User	54 (35%)	44 (31%)	31 (34%)	37 (43%)
<u>Alcohol History</u>	(p=0.769)		(p=0.654)	
Never Drinks	74 (47%)	69 (48%)	46 (51%)	47 (55%)
Drinker	71 (46%)	65 (45%)	40 (44%)	35 (41%)
Ex-Drinker	11 (7%)	8 (6%)	4 (4%)	4 (5%)
Unknown	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

* Indicates statistical significance at the 0.05 level

A statistically significant difference was observed between treatment groups in tobacco/nicotine use among both Clinically Evaluable Subjects (p=0.041;) and Intent-to-Treat Subjects (p=0.028;), with higher percentages of subjects in the clarithromycin ER group who were ex-users of tobacco/nicotine and higher percentages of subjects in the levofloxacin group who were non-users.

A summary of adverse events, excluding events judged not related or probably not related to study drugs, reported by ≥1% of subjects in the CAP studies (three or more subjects) or clarithromycin ER pooled studies (eight or more subjects) is presented by treatment group in the table on the following page, with incidence below 1.0% designated as <1%:

**APPEARS THIS WAY
 ON ORIGINAL**

Summary of Treatment-Emergent Adverse Event Incidence Rates (≥1%) by COSTART Term (Excluding Events Judged Not Related or Probably Not Related to Study Drugs in Phase 3 CAP Studies and Clarithromycin ER Pooled Studies)										
Adverse Event ^c	CAP Studies ^a (N=246) Severity ^d					CLA ER Pooled Studies ^b (N=705) Severity ^d				
	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
Taste perversion	17	7	0	24	10%	35	13	3	51	7%
Diarrhea	9	5	0	14	6%	29	11	1	41	6%
Nausea	5	2	0	7	3%	15	7	0	22	3%
Headache	4	1	0	5	2%	6	6	0	12	2%
Vomiting	0	4	0	4	2%	0	5	0	5	<1%
Rash	3	0	0	3	1%	3	1	1	5	<1%
Anorexia	1	2	0	3	1%	1	2	0	3	<1%

CAP = community-acquired pneumonia; CLA ER = clarithromycin extended release; Mod = moderate; Sev = severe

a Include M99-077 and M98-927.
 b Include M99-077, M98-927, M97-667, and M97-756.
 c Occurring in ≥1% of subjects in either the CAP studies or the pooled studies.
 d Table summarizes the most severe occurrence of each COSTART term from each subject.

Applicant's data- Volume 29, page 20

Deaths

One death was reported during the clarithromycin ER CAP studies. A 56-year-old female smoker (Investigator Shu, Subject 2044) with chronic COPD assigned to clarithromycin ER in Study M99-077, died on Study Day 3; autopsy cause of death was pneumonia due to viral influenza and *Haemophilus influenzae*. The investigator considered the death probably not related to study drug. There were no deaths in patients randomized to receive levofloxacin or trovafloxacin for community-acquired pneumonia. For further details, the reader is referred to the safety section of this review. (Ref: page 63)

**APPEARS THIS WAY
 ON ORIGINAL**

CLINICAL REVIEW

I. Introduction and Background

Biaxin[®] XL Filmtabs[®] has been approved for marketing in the United States of America under NDA 50-775. Biaxin[®] XL Filmtabs[®] are indicated for the treatment of adults with mild to moderate infection caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

The present clinical program was designed to collect data on the efficacy and safety of clarithromycin extended-release (ER) tablets for the treatment of community-acquired pneumonia (CAP). By agreement with the sponsor, only one robust clinical study for treatment of CAP was required. Study M98-927 was initially set up as the only pivotal study; however, this study was prematurely terminated because trovafloxacin use was restricted due to safety reasons by the FDA in 1999. As a result of the above action, the sponsor initiated study M99-077 as the pivotal study. Study M98-927 was submitted as a supportive study.

M99-077: Comparison of the Safety and Efficacy of Clarithromycin Extended-Release (1000 mg QD) to Levofloxacin (500 mg QD) for the Treatment of Community-Acquired Pneumonia.

M98-927: Comparison of the Safety and Efficacy of Clarithromycin IR (250 mg BID) or ER (1000 mg QD) to Trovafloxacin (200 mg QD) for the Treatment of Community-Acquired Pneumonia.

II. Chemistry & Manufacturing, Animal Pharmacology & Toxicology, Biopharmaceutics.

This section is not applicable to this NDA supplement review. The applicant has not been submitted any additional new information for review.

Microbiology.

The reader is referred to the microbiology review by Dr. Sousan Altaie, dated March 19, 2001.

Biostatistics.

The reader is referred to the biostatistical review by Dr. Joel Jiang, dated June 28, 2001.

III. Human Pharmacokinetics and Pharmacodynamics.

This section is not applicable to this NDA supplement review. The applicant has not been submitted any additional PK/PD information for review.

IV. Description of Clinical Data and Sources.

A. The safety and efficacy data submitted were gathered from clinical trials conducted by the applicant. As noted before, Biaxin[®] XL Filmtabs[®] has been approved for Acute Exacerbation of Chronic Bronchitis and Acute Maxillary Sinusitis caused by certain susceptible organisms. This approval was given in May, 2000 (Refer to the Medical Officer's Review, dated February 8, 2000). Post-marketing data have not been submitted with this application.

B. The following table provides summary information for the two studies in this submission, including number of investigators and number of subjects treated by treatment group:

Protocol	Study Type	Dose/Frequency/Duration	Number of Patients	Geographic Location/# of Investigators
Study M99-077	Multicenter, randomized, double-blind, active-controlled trial	Biaxin ER 1000 mg qd for 7 days	156 randomized	United States, Canada; 51 investigators
		Levofloxacin 500 mg qd for 7 days	143 randomized	
Study M98-927	Multicenter, randomized, double-blind, active-controlled trial*	Biaxin ER 1000 mg qd for 7 days	90 randomized	United States, Canada ; 31 investigators
		Trovofloxacin 200 mg qd for 7 days	86 randomized	

* - Restrictions issued by FDA on June 9, 1999 regarding use of trovafloxacin resulted in the premature termination of the study; anticipated enrollment of 150 patients per arm was not attained.

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review Method

A. How the review was conducted

The applicant has submitted two clinical trials in support of the indication for Community Acquired Pneumonia. Data from each trial will be reviewed for efficacy separately and then efficacy results will be combined to give an overall efficacy summary of the data. Safety data from both studies will be reviewed and reported as an integrated summary.

B. Overview of Materials consulted in Review

The applicant has submitted a paper copy of the supplemental NDA. In addition, an electronic version of the clinical section of the NDA has been submitted.

C. Overview of Methods used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations audited selected sites for both the studies. Their final report is pending at the writing of this review. The Medical Officer is not aware of any serious problems found in the DSI inspection of selected study sites and their principal investigators. In addition, the Medical Officer has reviewed a random sample of 20% of the enrolled patient population for each study. The Medical Officer agrees with the applicant's analysis.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The studies submitted in support of the indication sought were conducted with an approved formulation of clarithromycin. Both studies were conducted under an IND, thus were submitted to FDA for review. All investigators followed the guidances set up by the FDA to conduct trials in accordance with good clinical practices.

E. Evaluation of Financial Disclosure

The applicant has submitted a completed Form FDA 3454, which states the names of all the investigators. The applicant has certified that none of the listed investigators were the recipient of significant payments of any sorts as defined in 21 CFR 54.2(f).

V. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The applicant has submitted two studies in support of approval of the indication of CAP for Biaxin[®] XL Filmtabs[®]. There are adequate data to support efficacy and safety for approval of Biaxin[®] XL Filmtabs[®] for CAP caused by *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *C. pneumoniae* or *Streptococcus pneumoniae*.

Based on the data submitted by the applicant, it is the reviewer's opinion that *Staphylococcus aureus* should not be considered a target pathogen for CAP, thus CAP due to this organism has not been recommended for approval.

The review of the safety and efficacy data showed that the diagnostic criteria used to evaluate patients who supposedly had pneumonia due to *Legionella pneumophila* were inadequate, thus that particular claim cannot be recommended for approval. A teleconference was held between the applicant and the reviewer on June 12, 2001, and the concerns we had with the serologic diagnostic criteria used by the applicant to diagnose legionella pneumonitis were conveyed to the applicant. The applicant agreed with our conclusions. As per that conversation, the applicant will remove the claim for pneumonia caused by *Legionella pneumophila* from the proposed labeling and submit revised labeling.

No other major issues were raised in the review of the data. The reviewer concurred with the analyses performed by the applicant.

B. General Approach to Review of the Efficacy of the Drug

The applicant has submitted two studies in support of the CAP indication. Study M99-077 is the pivotal study, and Study M98-927 is the supportive study. Study M98-927 was initially set up as a pivotal study, but when restrictions were issued by FDA on June 9, 1999 regarding the use of trovofloxacin (comparator for this study), it resulted in the premature termination of the study; thus, the anticipated enrollment was not attained.

This document describes the efficacy and safety data from both the studies in detail. Each study is discussed separately, and then the results are combined. Final conclusions and recommendations are made based upon the requested draft labeling submitted by the applicant.

C. Detailed Review of Trials by Indication
Indication Reviewed – Community-Acquired Pneumonia

a). REVIEW OF STUDY M99-077.

Comparison of the Safety and Efficacy of Clarithromycin Extended-Release (1000 mg QD) to Levofloxacin (500 mg QD) for the Treatment of Community-Acquired Pneumonia

Investigative Sites

Abbott Laboratories [redacted] selected investigative sites. A total of 77 investigators in the US and Canada were recruited and received study drug supplies to conduct this study and 51 of these investigators enrolled subjects. A total of 299 subjects were enrolled. The study was conducted between November 2, 1999 and July 5, 2000.

The distribution of all treated subjects for each investigator is as follows:

Distribution of All Treated Subjects by Investigator					
Investigator	Clarithromycin ER	Levofloxacin	Investigator	Clarithromycin ER	Levofloxacin
USA			Miller	1	0
Acampora	1	1	Navarro	4	4
Adler	7	8	Otruba	8	8
Alwine	4	3	Patel	1	1
Bautista	1	0	Perlman	5	5
Bettis	5	5	Pien	0	2
Bray	3	3	Pinto	4	3
Bundy	2	3	Pogue	1	2
Carter	1	0	Raad	1	0
Chacko	2	2	Riffer	7	6
Chipman	9	9	Sokol	1	1
Cutler	0	1	Stewart	2	2
Dietrich	1	1	Suchyta	2	2
Elashker	2	1	Sullivan	6	6
Follett	2	2	Tarshis	8	6
Garrity	1	1	Villanueva	1	2
Gohill	1	1	Vrooman	2	2
Guzzetta	1	0	White	2	1
Harrison	6	6	CANADA		
Henry	4	4	Bayly	3	3
Hosko	1	1	Cameron	1	0
Jannetti	0	1	Coyle	2	0
Javaid	1	0	Dattani	11	10
Larsen	5	5	Gowda	1	0
McConnehey	6	5	Howlett	8	8
McDavid	0	1	Shu	6	5
McNeil	2	0	Total	156	143

Study Objectives

The primary objectives were to compare the safety and efficacy of a 7-day course of therapy with clarithromycin ER tablets (2 x 500 mg QD) to that of a 7-day course of therapy with levofloxacin tablets in capsules (2 x 250 mg QD) for the treatment of ambulatory subjects with CAP. Subjects who tested positive for *Legionella* spp. were to continue the assigned study drug therapy for an additional 7 days. Additionally, health care resource utilization was compared between the two treatment groups.

Investigational Plan

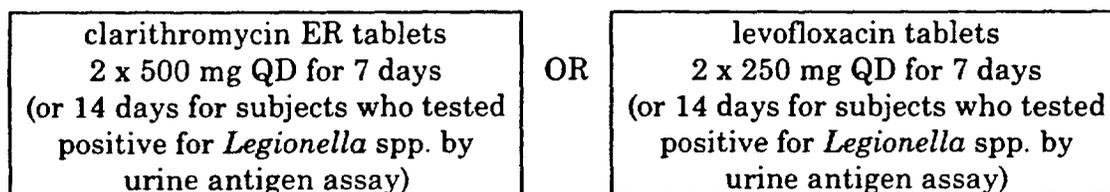
Overall Study Design and Plan - Description

This was a Phase 3, double-blinded, randomized, parallel-group, multicenter study in ambulatory subjects with CAP. Approximately 75 investigative sites were to be recruited in order to enroll approximately 300 subjects with a diagnosis of CAP. At each investigative site, subjects who presented with at least two protocol-required clinical signs and symptoms of CAP and who satisfied all the inclusion/exclusion criteria were randomized in a 1:1 ratio to receive either clarithromycin ER tablets (2 x 500 mg) once daily (QD) or levofloxacin tablets (2 x 250 mg) once daily (QD). The duration of therapy was to be 7 days for each regimen, unless the subject tested positive for *Legionella* spp. by urine antigen assay; these subjects were to continue the assigned study drug therapy for an additional 7 days for a total duration of 14 days of therapy.

The nature of the study was explained to subjects who presented with clinical signs and symptoms and radiographic evidence of CAP at Evaluation 1. After a signed informed consent form was obtained, a medical history, physical examination, vitals signs assessment, and laboratory evaluations were performed and recorded.

Female subjects of childbearing potential were required to have a negative urine HCG (human chorionic gonadotropin) pregnancy test prior to enrollment.

Eligible subjects were randomly assigned in a 1:1 ratio to receive either:



Eligible subjects could begin study-directed treatment (Evaluation 1) 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), at 7 days during

therapy if positive by *Legionella* spp. urinary antigen assays (Evaluation 3), within 72 hours after the last dose (Evaluation 4), and again at 14 to 21 days after the last dose of study drug (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. Culture and sensitivity testing was performed on specimens of expectorated, purulent sputum qualified by Gram stain. Posttreatment sputum culture was performed if the subject had a persistent cough productive of Gram-stained qualified sputum. Sputum specimens were also tested for *Legionella* spp. by culture; other methods (i.e., serologic and urine antigen assays) were also used to detect *Legionella* spp. Serum was obtained from each subject for detection of *M. pneumoniae* and *C. pneumoniae* by serology.

Health Care Resource Utilization questionnaires were completed at Evaluations 4 and 5 in the clinic for subjects continuing in the study or by telephone for subjects who prematurely terminated from the study. The investigator or designee recorded the responses to the questionnaires on the appropriate case report form pages.

Safety was determined through periodic laboratory tests, medical history, physical examination, and monitoring of adverse events. Study drug tolerance was evaluated by investigator observation and evaluation of adverse event severity.

Subjects participated in the trial for approximately 3 to 5 weeks, depending upon the schedule of evaluation visits. The duration of the study from enrollment of the first to last subject was approximately 7 months.

Assuming the clinical cure rates for the two treatment groups were approximate 85% and a clinical evaluability rate of 80%, approximately 300 subjects were to be enrolled to obtain 240 clinically evaluable subjects.

A complete study schematic is presented in the table on the following page:

**APPEARS THIS WAY
ON ORIGINAL**

Study Schematic					
Evaluation	1	2	3 ^a	4	5 ^b
Procedure	Pre-Therapy (Within 48 Hours Before Therapy)	On-Therapy (Within 48-72 Hours After Initiation)	On-Therapy (Day 7 ± 24 hours)	Post-Therapy (Within 72 hours After the Last Dose)	Test-of-Cure (At 14-21 Days After the Last Dose)
Study Day	-2 to 1 ^c	3-4	6-8 ^a	8-10 (15-17) ^a	21-28 (28-35) ^a
Informed Consent	X				
Medical/Social History	X				
Physical Examination	X				X ^k
Clinical Signs/Symptoms	X	X		X	X
Vital Signs	X	X	X	X	X
Gram Stain	X ^d	X ^m	X ^m	X ^m	X ^m
Lower Respiratory Tract Culture	X ^e	X ^e	X ^e	X ^e	X ^e
Blood and Urine Samples for Atypical Pathogens	X				X ^l
Clinical Laboratory Tests	X	X ^j		X ^f	X ^{g,h}
Pregnancy Test (if applicable)	X				
Monitor co-medications	X	X	X	X	X
Chest radiograph	X	X ⁱ	X ⁱ	X ⁱ	X
Monitor Adverse Events		X	X	X	X
Dispense Medication/Instructions	X		X		
Health Care Resource Utilization				X ^l	X ^l
Study Drug Compliance Check		X	X	X	X ^h
Clinical Response					X

a Shaded Visit 3: Subjects from whom *Legionella* spp. Was isolated were to receive an additional 7 days of study drug at this visit and had the procedures performed.

b Subjects who were prematurely withdrawn from the study were to complete Evaluation 5 procedures within 72 hours after the last dose of study drug and prior to institution of any new therapeutic modalities.

c Study Day 1 was the day the first dose was administered.

d If the subject was still producing purulent sputum.

e Qualified sputum only.

f Blood samples for atypical pathogens only - no urine samples.

g Clinically significant abnormal laboratory values detected at this visit were to be followed until they resolved, stabilized, or became explicable.

h Only if subject was prematurely withdrawn from the study.

i If clinically indicated.

j WBC and differentials only.

k Height not done at this visit.

l For all subjects, including those who prematurely terminated from the study.

m. If productive of sputum.

Medical Officer's Comments:

The inclusion and exclusion criteria, efficacy and safety assessments were all acceptable by the reviewer because the applicant followed the July 1998 FDA Guidances. The efficacy procedures outlined in the protocol are acceptable. The culture and susceptibility procedures are acceptable also. The following section gives details for the diagnostic criteria used to evaluate patients with pneumonia due to atypical pathogens. The applicant used the following criteria for diagnosis of atypical pathogens:

Atypical Pathogens

Blood samples were obtained from all subjects at Evaluations 1 and 5 for serologic assays of *M. pneumoniae*, *C. pneumoniae*, and *Legionella pneumophila*. Sputum samples were also collected for culture of *Legionella* spp. and urine was collected at Evaluation 1 only for *Legionella* urine antigen testing.

Diagnosis of infection due to *L. pneumophila*, *C. pneumoniae* or *M. pneumoniae* was made on the basis of the clinical and radiographic evidence of pneumonia, in addition to one or more of the following (serologic or antigen) test results.

***Legionella pneumophila* Test Results**

The interpretation of *Legionella* Urinary Antigen was:

Acute or recent infection: Positive (indicative of acute or recent *Legionella* infection).

The interpretation of *Legionella pneumophila*, serogroups 1-6 titers was:

Acute or recent infection: When a single titer was greater than 1:256 OR when there was a four-fold change in titer.

***Mycoplasma pneumoniae* Test Results**

The interpretation of *Mycoplasma pneumoniae* titers was:

Acute or recent infection: When the IgG titer was greater than or equal to 1:128 OR there is a four-fold change in IgG titer OR when the IgM titer was greater than or equal to 1:16.

**APPEARS THIS WAY
ON ORIGINAL**

***Chlamydia pneumoniae* Test Results**

The interpretation of *Chlamydia pneumoniae* titers was:

- Recent infection:** When the IgM titer was greater than or equal to 1:10
OR when the IgG titer was greater than or equal to
1:512 OR when the IgG titer showed a four-fold change
in titer (either rise or fall).
- Indeterminate
results** Nonspecific fluorescence was noted when reading the
MIF slide; a code of "Invalid/Interfering Substance"
was placed in the result area when background
fluorescence did not allow accurate interpretation.

Medical Officer's Comments:

The applicant has utilized an approved FDA Test Kit for serologic diagnosis of infections caused by Chlamydia pneumoniae. A standard diagnostic kit has been utilized for diagnosis of Mycoplasma pneumoniae, which is acceptable. Diagnosis of Legionella pneumophila is relatively straightforward if selective BCYE agar is utilized, and Urinary Antigen testing has become more acceptable in the diagnosis of acute illness compared to serologic testing. It should be noted that none of the patients in the clarithromycin group in this study had a positive culture, and only one patient had positive urinary antigen but that patient was unevaluable for other reasons. The detailed serologic results will be addressed and discussed with the clinical and bacteriologic outcome results later on in the review.

Study Subjects

Disposition of Subjects

Two hundred ninety-nine (299) subjects were randomized in the study and took study drug; 156 subjects took clarithromycin extended-release (ER) tablets and 143 subjects took levofloxacin tablets in capsules. Overall, 14% (42/299) of the treated subjects prematurely discontinued from the study; 17% (26/156) of subjects prematurely discontinued from study in the clarithromycin ER group and 11% (16/143) of subjects prematurely discontinued from study in the levofloxacin group. The most frequent reason for withdrawal from study in both groups was adverse event, cited by 4% (7/156) of subjects in the clarithromycin ER group and 2% (3/143) of subjects in the levofloxacin group. Additional reasons for premature discontinuation from study in the clarithromycin ER and levofloxacin groups included subject request (four subjects and two subjects, respectively), investigator request (four subjects and two subjects, respectively), clinical deterioration (two subjects in each treatment group), lost to follow-up (two subjects in each treatment group), and "other" reasons (seven subjects and four subjects, respectively); in

addition, one subject in the levofloxacin group was discontinued due to noncompliance.

Overall, 6% (17/299) of the subjects prematurely discontinued treatment; 8% (12/156) of subjects prematurely discontinued study drug in the clarithromycin ER group and 3% (5/143) of subjects prematurely discontinued study drug in the levofloxacin group. The most frequent reason for discontinuing study drug was adverse event, cited by 3% (5/156) of subjects in the clarithromycin ER group and <1% (1/143) of subjects in the levofloxacin group.

Additional reasons for prematurely discontinuing study drug by subjects in the clarithromycin ER and levofloxacin groups included subject request (four subjects and one subject, respectively); "other" reasons (two subjects in each treatment group); in addition, one subject in the clarithromycin ER group prematurely discontinued study drug due to clinical deterioration and one subject in the levofloxacin group prematurely discontinued study drug due to noncompliance.

The details of the subjects who prematurely discontinued study drug are presented by treatment group in the table on the following page:

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Subjects Whose Treatment Was Prematurely Discontinued					
Primary Reason for Discontinuation	Investigator	Subject #	Age (years)	Sex	Days on Therapy
Clarithromycin ER Group					
Adverse Event	Bray	2081	68	F	3
	Bray	2388	45	F	3
	Chacko	2074 ^a	44	M	2
	Riffer	2382	42	F	1
	Shu	2044	56	F	Unknown ^b
Subject Request	Larsen	2393	43	F	1
	Pinto	2211	73	M	2
	Sullivan	2337	51	M	6
	Tarshis	2487	63	M	4
Clinical Deterioration	Tarshis	2488	65	M	5
Other	Javaid	2212 ^c	76	M	2
	Larsen	2326 ^d	72	F	2
Levofloxacin Group					
Adverse Event	Harrison	2161	59	F	1
Subject Request	Sullivan	2204	34	F	2
Subject Noncompliance	Pien	2352	63	F	10 ^e
Other	Adler	2256 ^e	57	M	4
	Howlett	2288 ^f	69	M	3

a Adverse event of worsening of pneumonia symptoms and underlying COPD.
 b Three days of therapy were assumed as study drug container was not returned to investigator.
 c Pre-existing condition of dysphagia; violation of selection criterion requiring ability to swallow.
 d Protocol violation.
 e Went to emergency room and antibiotic was changed.
 f Exclusionary pretreatment laboratory values.
 g Duration exceeded 7 days due to missed doses rather than additional doses; subject misunderstood daily dosing instructions.

Applicant's data – Volume 4, page 122

Applicant's Efficacy Evaluation

Clinically Evaluable Subject Population

All of the following criteria were to have been satisfied for a subject to be considered clinically evaluable:

- The inclusion/exclusion criteria were satisfied.
- The subject had taken prescribed study drug for a minimum of 3 full days to qualify for efficacy evaluation as a clinical failure or at least 80% of prescribed study drug to qualify as a clinical cure.
- The subject did not receive any other systemic antimicrobial agent during the period 7 days (2 weeks if long-acting) prior to the start of study drug until Evaluation 5, unless the subject was considered a study treatment failure.

Clinically and Bacteriologically Evaluable Subject Population

In addition to the above criteria, subjects must have had a positive culture, serology, and/or urinary antigen assay for a target CAP pathogen prior to therapy.

Intent-to-Treat Subject Population

All subjects who took at least one dose of study drug and had a clinical diagnosis of CAP confirmed by a positive pretreatment chest radiograph were included in the Intent-to-Treat Subject population.

All-Treated Subjects Population

All subjects who took at least one dose of study drug were included in the All-Treated Subjects population.

Disposition of Subjects by Data Sets

One hundred fifty-six (156) subjects were randomized to and took clarithromycin ER and 143 were randomized to and took levofloxacin. One hundred nine (63 clarithromycin ER and 46 levofloxacin) subjects were excluded from the bacteriological analyses of efficacy. Of these, 64 (36 clarithromycin ER and 28 levofloxacin) subjects did not have a target pathogen isolated at pretreatment. Of the remaining 45 subjects who were excluded, 26 subjects did not meet the selection criteria; four subjects did not return for the Test-of-Cure Visit; four subjects did not have a chest x-ray performed at the Test-of-Cure Visit; three subjects used confounding medications; two subjects each were noncompliant with the treatment regimen, returned for the Test-of-Cure Visit outside the allowable window, and had an interfering therapeutic procedure performed; and one subject each had a confounding illness and an unacceptable pretreatment Gram stain.

Forty-seven (28 clarithromycin ER and 19 levofloxacin) subjects were excluded from the clinical efficacy analyses. Twenty-seven subjects were excluded because they did not meet selection criteria; six subjects were excluded because they did not return for the Test-of-Cure Visit; four subjects did not have a chest x-ray performed at the Test-of-Cure Visit; three subjects used confounding medication; two subjects each were noncompliant with the treatment regimen, had an interfering therapeutic procedure performed, and returned for the Test-of-Cure Visit outside the allowable window; and one subject had a confounding illness.

Twenty-three (14 clarithromycin ER and nine levofloxacin) subjects were excluded from the Intent-to-Treat efficacy analyses because they did not meet the selection criteria that required a chest x-ray consistent with pneumonia.

The number of subjects included in the efficacy analyses is presented by data set in the table below:

Disposition of Subjects by Data Set		
	<u>Clarithromycin ER</u>	<u>Levofloxacin</u>
Total Randomized & Took Study drug (All-Treated Subjects Population)	156	143
Intent-to-Treat Analyses	142	134
Excluded from the Intent-to-Treat Analyses	14	9
Selection criteria not met (chest x-ray not consistent w/ pneumonia)	14	9
Clinically Evaluable Analyses	128	124
Excluded from the Clinically Evaluable Analyses	28	19
Selection criteria not met (all reasons; specific reasons in parentheses; listed below)	16	11
Subject did not return for Test-of-Cure Visit	3	3
Chest x-ray not performed at Test-of-Cure Visit	3	1
Used confounding medication	1	2
Subject noncompliance with treatment regimen	2	0
Interfering therapeutic procedure performed	2	0
Mistiming of Test-of-Cure Visit	1	1
Confounding illness	0	1
Bacteriologically Evaluable Analyses	93	97
Excluded from the Bacteriologically Evaluable Analyses ^a	63	46
No target pathogen isolated pretreatment	36	28
Selection criteria not met	16	10
(Chest radiograph was not consistent with pneumonia) ^b	(14)	(9)
(Evidence of excluded pulmonary disease) ^b	(0)	(1)
(Subject unable to swallow tablets/capsules intact) ^b	(1)	(0)
(Subject had pulmonary sarcoidosis plus acute infection) ^b	(1)	(0)
Subject did not return for Test-of-Cure Visit	2	2
Chest x-ray not performed at Test-of-Cure Visit	3	1
Used confounding medication	1	2
Subject noncompliance with treatment regimen	2	0
Interfering therapeutic procedure performed	2	0
Mistiming of Test-of-Cure Visit	1	1
Confounding illness	0	1
Pretreatment Gram stain unacceptable	0	1
<p>a If a subject is both bacteriologically and clinically nonevaluable, then the bacteriological nonevaluable reason is presented.</p> <p>b Selection criteria violations are identified in the tables by protocol section numbers.</p>		

Applicant's data – Volume 4, page 127

**APPEARS THIS WAY
ON ORIGINAL**

Demographic and Other Baseline Characteristics

Demographics

There were no statistically significant differences between the treatment groups in sex, race, age, or weight. The majority of the subjects were male (55%) and Caucasian (92%). The mean age of all subjects was 50.0 years, and age ranged from 18 to 91 years. Table 11.2a presents the demographic information for All-Treated Subjects.

Demographic Information (All-Treated Subjects Population)			
Demographic Characteristic	Number of Subjects by Treatment Group		P-value ^a
	Clarithromycin ER	Levofloxacin	
Total Treated	156		143
<u>Sex</u>			0.200
Female	64 (41%)	70 (49%)	
Male	92 (59%)	73 (51%)	
<u>Race^b</u>			0.296
Caucasian	146 (94%)	129 (90%)	
Black	6 (4%)	7 (5%)	
Asian	4 (3%)	6 (4%)	
Other	0 (0%)	1 (1%)	
<u>Age (years)</u>			0.247
<40	46 (29%)	40 (28%)	
40-64	79 (51%)	63 (44%)	
≥65	31 (20%)	40 (28%)	
Mean (SD)	49.0 (16.2)	51.2 (16.5)	
Range	19 - 89	18 - 91	
<u>Weight (kg)</u>			0.838
<70	49 (31%)	42 (29%)	
≥70	106 (68%)	100 (70%)	
Missing	1 (1%)	1 (1%)	
Mean (SD)	82.3 (23.3)	81.8 (20.7)	
Range	40 - 186	36 - 141	

^a P-values are from Fisher's exact test comparing treatment groups (sex, race), or a one-way analysis of variance model comparing treatment groups (age, weight).
^b Race comparison was done with respect to two categories: Caucasian and all other races combined.

Applicant's data – Volume 4, page 128

Presenting Conditions, Medical History, and Diagnoses

The applicant has summarized the presenting conditions, medical history, and social history for All-Treated Subjects in the tables on the next two pages:

Summary of Presenting Conditions, Medical History, and Social History (All-Treated Subjects Population)					
	Number of Subjects by Treatment Group				P-value ^a
	Clarithromycin ER		Levofloxacin		
Total Treated	156		143		
<u>Diseases/Conditions Present^b</u>					Not Computed
Surgical History	115	(74%)	105	(73%)	
Respiratory	108	(69%)	91	(64%)	
Eyes-Ears-Nose-Throat	91	(58%)	83	(58%)	
Musculoskeletal	89	(57%)	84	(59%)	
Gastrointestinal	65	(42%)	68	(48%)	
Cardiovascular	68	(44%)	65	(45%)	
Genitourinary	59	(38%)	56	(39%)	
Endocrine-Metabolic	50	(32%)	59	(41%)	
Drug Allergy/Sensitivity	59	(38%)	50	(35%)	
Dermatological	48	(31%)	46	(32%)	
Central Nervous System	53	(34%)	39	(27%)	
Non-Drug Allergy	42	(27%)	39	(27%)	
Psychiatric	39	(25%)	38	(27%)	
Hematopoietic-Lymphatic	17	(11%)	18	(13%)	
Peripheral Nervous System	6	(4%)	14	(10%)	
Hepatic	9	(6%)	9	(6%)	
<u>Concurrent Illness^b</u>					Not computed
Musculoskeletal Disorder	62	(40%)	59	(41%)	
Neuromuscular Disorder	26	(17%)	19	(13%)	
Coronary Artery Disease	16	(10%)	12	(8%)	
Diabetes Mellitus	9	(6%)	14	(10%)	
<u>Pulmonary Disease History^b</u>					Not computed
Community-Acquired Pneumonia ^c	64	(41%)	40	(28%)	
Acute Bronchitis	55	(35%)	45	(31%)	
Chronic Bronchitis/COPD	33	(21%)	31	(22%)	
Bronchial Asthma	30	(19%)	17	(12%)	
Acute Exacerbation of Chronic Bronchitis	4	(3%)	7	(5%)	
<u>Overall Clinical Condition</u>					0.331
Good	37	(24%)	41	(29%)	
Fair	119	(76%)	102	(71%)	
<u>Infection Status</u>					0.267
Mild	39	(25%)	44	(31%)	
Moderate	117	(75%)	99	(69%)	
<u>Prior Medical Evaluation for this Infection</u>					0.416
Yes	16	(10%)	19	(13%)	
No	140	(90%)	124	(87%)	

a P-values are from Cochran-Mantel-Haenszel for overall clinical condition, infection status, prior medical evaluation, and prior medical treatment.
 b Present in ≥5% of subjects in either treatment group.
 c Excludes concurrent CAP episode.

Summary of Presenting Conditions, Medical History, and Social History (All-Treated Subjects Population) (continued)					
	Number of Subjects by Treatment Group				P-value*
	Clarithromycin ER		Levofloxacin		
<u>Prior Medical Treatment for this Infection</u>					0.647
Yes	56	(36%)	55	(38%)	
No	100	(64%)	88	(62%)	
<u>Number of CAP Infections in Past 12 Months</u>					0.501
1	138	(88%)	130	(91%)	
2	16	(10%)	10	(7%)	
≥3	2	(1%)	3	(2%)	
Mean (SD)	1.1 (0.5)		1.1 (0.4)		
<u>Tobacco and Nicotine Use</u>					0.047*
Non-User	58	(37%)	70	(49%)	
Ex-User	44	(28%)	29	(20%)	
User	54	(35%)	44	(31%)	
<u>Alcohol History</u>					0.769
Never Drinks	74	(47%)	69	(48%)	
Drinker	71	(46%)	65	(45%)	
Ex-Drinker	11	(7%)	8	(6%)	
Unknown	0	(0%)	1	(<1%)	
* Indicates statistical significance at the 0.05 level.					
a P-values are from ANOVA for Number of CAP Infections in Past 12 Months and from Fisher's exact test for tobacco use and alcohol use. Tobacco usage comparison was done with respect to two categories: non-user and the combined user and ex-user category. Alcohol consumption comparison was done with respect to two categories: non-drinker and the combined drinker and ex-drinker categories.					

Applicant's data – Volume 4, page 131

A statistically significant difference was observed between treatment groups in tobacco and nicotine use ($p=0.047$); a higher percentage of subjects in the clarithromycin ER group than in the levofloxacin group was an ex-user and a higher percentage of subjects in the levofloxacin group than in the clarithromycin ER group was a non-user. This difference was not expected to affect the outcome of the study.

Medical Officer's Comments:

A statistically significant difference was observed between treatment groups in tobacco/nicotine use among both Clinically Evaluable Subjects ($p=0.041$;) and Intent-to-Treat Subjects ($p=0.028$;) with higher percentages of subjects in the clarithromycin ER group who were ex-users of tobacco/nicotine and higher percentages of subjects in the levofloxacin group who were non-users. The investigators were instructed to collect information on duration of tobacco use in ex-smokers, but these data were not collected in the CRFs reviewed. The increased number of non-users in the levofloxacin group would mean that these patients may

respond to treatment more quickly, and their signs and symptoms of pneumonia may resolve faster.

Pretreatment Signs and Symptoms

All subjects were required to produce sputum at the pretreatment visit; the majority of subjects reported moderate sputum production (61%), mucopurulent appearance of sputum (62%), and <1 oz. per day (53%). All but two subjects had cough. Other frequently reported signs and symptoms at pretreatment for both groups combined included rales/rhonchi/crackling/ wheezing (95% of subjects), congestion (91%), dyspnea (86%), and chest discomfort (73%). Few subjects exhibited dullness on percussion (28%), egophony (22%), or fever (16%), and no subject presented with hypothermia (0%). A statistically significant difference was observed between the treatment groups in pretreatment sputum appearance ($p=0.050$); a higher percentage of subjects in the clarithromycin ER group than in the levofloxacin group had purulent sputum (43% versus 33%), while a higher percentage of subjects in the levofloxacin group than in the clarithromycin ER group had mucopurulent sputum (66% versus 57%).

Concurrent Medications

Use of medications pretreatment was similar between the treatment groups for the All-Treated Subjects population; 83% of subjects in the clarithromycin ER group and 82% of the subjects in the levofloxacin group were taking medications at the pretreatment evaluation. Overall, the most frequently used ($\geq 25\%$) therapeutic classifications of medication at pretreatment were nonsteroidal anti-inflammatory agents (34%); analgesics, antipyretics, and anti-inflammatory agents (29%), and sympathomimetic agents (26%).

During the study, 92% of the All-Treated Subjects population in the clarithromycin ER group and 90% of the subjects in the levofloxacin group used concurrent medications. The majority of concurrent medications were used for treatment of coughs, colds, fevers, and other symptoms associated with respiratory tract symptoms. Overall, 42% of all subjects used sympathomimetic agents; 40% used nonsteroidal anti-inflammatory agents; 38% used analgesics, antipyretics, and anti-inflammatory agents; 24% used expectorants; 24% used opiate agonists; 23% used antitussives; and 19% used H₁-receptor antagonists during the study. The most frequently used specific medications were: acetaminophen (34% of subjects), albuterol (25%), guaifenesin (24%), acetylsalicylic acid (19%), dextromethorphan (16%), ibuprofen and pseudoephedrine (15% each). The percentages of subjects in the clarithromycin ER and levofloxacin groups who used these drugs were generally similar.

Three subjects (one clarithromycin ER and two levofloxacin) were excluded from the clinically and bacteriologically evaluable analyses as well as the clinically evaluable analyses because they took medications that could affect the outcome of the study. Details of these three subjects are presented in the table below:

Subjects Excluded From the Clinically and Bacteriologically Evaluable and Clinically Evaluable Efficacy Analyses Due to Confounding Medications			
Investigator/ Subject Number	Confounding Medication	Study Days (days posttreatment)	Indication
Subjects Excluded From Clarithromycin ER Group			
Tarshis/2001#	BIAXIN Filmtab®	8 (1) - 17 (10)	<i>Legionella pneumonia</i>
Subjects Excluded From Levofloxacin Group			
Bayly/2303	Ciprofloxacin	18 (11) - 28 (21)	Urinary tract infection
Tarshis/2486#	Clindamycin	11 (4) - 20 (13)	Infected molar
# Subject prematurely discontinued from study.			

Applicant's data - Volume 4, page 136

Medical Officer's Comments:

The urinary antigen test for L. pneumophila (serogroups 1-6) was positive at the pretreatment visit for one subject (Tarshis Subject 2001); additional study drug was sent, per protocol, to continue his randomized therapy. However, the investigator placed this subject on BLAXIN Filmtab®, as study drug was not received by the next scheduled visit.

FDA's Efficacy Results

The efficacy outcomes as presented in the NDA by the applicant were verified by the statistician, Dr. Joel Jiang. Thus, the following tables were generated by Dr. Jiang and this Medical Reviewer concurs with the analyses. The only difference between the applicant's analysis and FDA is the inclusion of Legionella pneumophila as a causative agent for CAP. The reviewer will address that issue in the bacteriologic outcome section of the efficacy review.

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%)

STUDY M99-077: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
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%	

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%	

Medical Officer's Comments:

The point estimates for clarithromycin ER's efficacy in the evaluable and ITT analyses is acceptable. The confidence interval result verified that Biaxin XL and levofloxacin were therapeutically equivalent with respect to cure rates at the test-of-cure visit for clinically evaluable patients.

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
<i>Overall Pathogen</i>	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

Medical Officer's Comments:

The applicant made the diagnosis of CAP caused by Legionella pneumophila in seven (7) patients in the clarithromycin group based only on a single titer or a four-fold change in titer (serology alone). Out of those seven patients, five had mixed infection, and in the remaining two patients, the titers decreased during treatment.

According to this reviewer's assessment, none of these patients had a true infection with Legionella pneumophila.

The other 4 patients with positive serology for Legionella pneumophila in the clarithromycin group had mixed infection with one of the target pathogens (H. influenzae, S. pneumoniae or M. catarrhalis). In the reviewer's opinion, none of these patients had acute infection with Legionella pneumophila.

This Medical Reviewer's overall opinion is that none of the patients enrolled in this study had true infection caused by Legionella pneumophila. The reviewer did not ask the statistician to re-analyze the data minus the eleven patients, nine of whom had other target pathogens isolated with positive serologic test for Legionella pneumophila because it would not have changed the overall outcome.

STUDY M99-077: ERADICATION RATES FOR TARGET PATHOGENS OF BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT			
Pathogen	Clarithromycin ER	Levofloxacin	Fisher's P-value
<i>Overall Pathogen</i>	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

Medical Officer's Comments:

The Applicant has included Staphylococcus aureus as a target pathogen for community-acquired pneumonia. The reviewer's opinion is that pneumonia due to S. aureus is not community-acquired but either hospital-acquired (nosocomial), or in patients with an underlying immunocompromised condition. Patients with pneumonia due to S. aureus usually require intravenous therapy. Based on the data submitted by the applicant, the reviewer's opinion is that S. aureus should not be considered a target pathogen for community-acquired pneumonia.

**APPEARS THIS WAY
 ON ORIGINAL**

STUDY M99-077: CLINICAL RESPONSES OF 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%	

STUDY M99-077: BACTERIOLOGICAL RESPONSES OF 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%	

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%	

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%	

Applicant's Efficacy Conclusions

At the Test-of-Cure Visit, no statistically significant differences were observed between the treatment groups in clinical cure rates, subject bacteriological cure rates, overall pathogen eradication rates, radiographic resolution rates, and radiographic success rates. The 95% confidence intervals (CI) for the differences of these parameters demonstrated that the two treatment regimens were equivalent. Clinical signs and symptoms of CAP resolved or improved in subjects treated with either regimen.

At the Test-of-Cure Visit, no statistically significant treatment differences were observed among Clinically Evaluable Subjects and Intent-to-Treat Subjects in the percentage of subjects demonstrating resolution or resolution and improvement in any clinical sign or symptom.

Results of this study indicate that clarithromycin ER (2 x 500 mg QD for 7 days) was equivalent to levofloxacin (2 x 250 mg QD for 7 days) in treating adult subjects with community-acquired pneumonia caused by *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*.

Medical Officer's Efficacy Conclusions:

*Based on the data submitted and verified by the medical reviewer and the statistician, Biaxin[®] XL Filmtabs[®] at the dose of 1000 mg every 24 hours for 7 days is as effective as levofloxacin 500 mg every 24 hours for 7 days in treatment of patients with community-acquired pneumonia caused by *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, *M. catarrhalis*, *C. pneumoniae*, or *M. pneumoniae*.*

*As discussed previously, *S. aureus* should not be considered a target pathogen in community-acquired pneumonia, and the applicant has not submitted convincing evidence in support of CAP caused by *Legionella pneumophila*.*

**APPEARS THIS WAY
ON ORIGINAL**

b). REVIEW OF STUDY M98-927.

Comparison of the Safety and Efficacy of Clarithromycin IR (250 mg BID) or ER (1000 mg QD) to Trovafloxacin (200 mg QD) for the Treatment of Community-Acquired Pneumonia

Investigative Sites

Abbott Laboratories [REDACTED] selected investigative sites. Fifty-eight investigators were approved to receive study drug and 35 investigators enrolled subjects into the study; four of these investigators did not enroll subjects into the clarithromycin ER group. Thirty-one investigators enrolled a total of 176 subjects into the clarithromycin ER and trovafloxacin groups. The study was conducted from December 11, 1998 to June 29, 1999.

Restrictions issued by the FDA on June 9, 1999 regarding the use of trovafloxacin resulted in the premature termination of the study. The blind was to be broken for any subject who was receiving study drug, so that subjects on trovafloxacin could be immediately discontinued from treatment. Two subjects were unblinded, both of whom were receiving trovafloxacin and were prematurely terminated from the study; the blind was not broken for a third subject who was prematurely terminated from the study and was subsequently identified as being assigned to trovafloxacin. The methods for this study are presented for all three study groups while the results section pertains to the clarithromycin ER and trovafloxacin groups only. A separate report presented data from the clarithromycin IR and trovafloxacin groups (NDA 50-662 Supplement 029 – Refer to the Medical Officer's Review dated July 20, 2000).

The distribution of All-Treated Subjects in the clarithromycin ER and trovafloxacin groups for each investigator is presented in the table on the following page:

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Distribution of All-Treated Subjects by Investigator					
Investigator	Clarithromycin ER	Trovafloxacin	Investigator	Clarithromycin ER	Trovafloxacin
Acampora	2	2	Patel	20	20
Bundy	2	2	Perlman	4	4
Cronic	0	1	Pierone	1	1
Degarmo	2	3	Pinto	4	4
Duff	0	2	Scheinberg	1	0
Gaman	4	3	Schneider	2	2
Garrity	2	1	Schrenker	1	2
Hall	2	2	Sheikh	1	0
Harrison	8	7	Sokol	3	2
Honsinger	4	2	Spiotta	0	1
Hosko	2	2	Stein	1	0
Hutchins	2	1	Sullivan	9	9
Jones (OR)	2	3	Tarshis	4	4
Jones (UT)	1	0	Vrooman	2	2
Nadeemullah	1	1	Wilhelm	0	1
Navarro	3	2	Total	90	86

Study Objectives

The primary objectives were to compare the safety and efficacy of a 7-day course of therapy with either clarithromycin IR tablets (1 x 250 mg BID) or clarithromycin ER tablets (2 x 500 mg QD) to that of a 7-day course of therapy with trovafloxacin mesylate tablets (1 x 200 mg QD) for the treatment of ambulatory subjects with CAP.

Investigational Plan

Overall Study Design and Plan - Description

This was a Phase 3, randomized, double-blind, parallel-group multicenter study in ambulatory subjects with CAP. Approximately 60 investigators were to enroll approximately 450 subjects (150 subjects per treatment group). Subjects with clinical signs and symptoms of CAP who met all the inclusion/exclusion criteria were randomized in a 1:1:1 ratio at each investigational site to receive for 7 days either clarithromycin IR (1 x 250 mg BID) plus placebo for clarithromycin ER and placebo for trovafloxacin mesylate, clarithromycin ER (2 x 500 mg QD) plus placebo for clarithromycin IR and placebo for trovafloxacin mesylate, or trovafloxacin mesylate (1 x 200 mg QD) plus placebo for clarithromycin IR and placebo for clarithromycin ER.

Assuming a clinical evaluability rate of 80%, approximately 450 subjects were to be enrolled to obtain 360 Clinically Evaluable Subjects. The nature of the study was explained to subjects who presented with clinical signs and symptoms of CAP at Evaluation 1. After informed consent was obtained, a medical and social history was recorded. Physical examination, vital signs assessment, and laboratory

evaluations were performed. A chest x-ray was obtained to confirm the presence of an acute pulmonary infiltrate consistent with CAP. Female subjects of childbearing potential were required to have a negative urine HCG (human chorionic gonadotropin) pregnancy test prior to enrollment.

Clinical and bacteriological assessments were performed within 48 hours before initiating study drug (Evaluation 1). Clinical signs and symptoms of CAP were documented, and the subject's infection status and clinical condition were assessed. Blood and urine samples were obtained for serologic testing and urine antigen assays for atypical pathogens. A specimen of expectorated sputum was obtained for Gram stain and culture with susceptibility testing. An acceptable sputum (defined as <10 squamous epithelial cells and >25 leukocytes per low power field [100X]) was required for enrollment. However, eligible subjects could be enrolled into the study on the basis of a qualified Gram stain, chest x-ray confirming acute pulmonary infiltrate, and clinical evidence prior to the availability of culture, serology and urine antigen assay results.

Eligible subjects were randomly assigned in a 1:1:1 ratio to receive either:

clarithromycin IR tablets 1 x 250 mg BID for 7 days (plus placebo for clarithromycin ER and trovafloxacin)	O R	clarithromycin ER tablets 2 x 500 mg QD for 7 days (plus placebo for clarithromycin IR and trovafloxacin)	O R	trovafloxacin mesylate tablets (placed in capsules) 1 x 200 mg QD for 7 days (plus placebo for clarithromycin IR and clarithromycin ER)
---	--------	--	--------	---

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; Test-of-Cure Visit). Radiographic assessments were performed at Evaluations 2 and 3 only if clinically indicated. Clinical response and radiographic response were assigned at Evaluation 4. 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 3-4 weeks. The total duration of the study from first enrollment to last subject follow-up was approximately 7 months.

A complete study schematic is presented in the table on the following page:

Study Schematic				
Evaluation Visit	1	2	3	4 ^a
Timing (Range of Days)	Pre-Therapy (Within 48 Hrs. Before Therapy)	On-Therapy (Within 48-72 Hrs. After Initiation)	Post-Therapy (Within 72 Hrs. After the Last Dose)	Test-of-Cure (At 14-21 Days After the Last Dose)
Study Day	-2 to 1 ^b	3-4	8-10	21-28
Informed Consent	X			
Medical/Social History	X			
Physical Examination	X			X
Clinical Signs/Symptoms	X	X	X	X
Vital Signs	X	X	X	X
Gram Stain	X	X ^c	X ^c	X ^c
Lower Respiratory Tract Specimen	X	X ^c	X ^c	X ^c
Blood and Urine Samples for Atypical Pathogens	X			X
Clinical Laboratory Tests	X		X ^e	X ^{e,f}
Pregnancy Test (if applicable)	X			
Monitor co-medications	X	X	X	X
Chest X-ray	X	X ^d	X ^d	X
Monitor Adverse Events	X	X	X	X
Dispense Medication/Instructions	X			
Study Drug Compliance Check		X	X	X
Clinical Response				X
<p>a Subjects who were prematurely withdrawn from the study were to complete Evaluation 4 procedures within 72 hours after the last dose of study drug and prior to initiation of any new therapeutic modalities.</p> <p>b Study Day 1 was the day the first dose was administered.</p> <p>c If culturable material was available.</p> <p>d If clinically indicated.</p> <p>e Clinically significant abnormal laboratory values detected at this visit were to be followed until they resolved, stabilized, or became explicable due to other known causes.</p> <p>f Only if subject prematurely withdrew from the study.</p>				

Medical Officer's Comments:

The inclusion and exclusion criteria, efficacy and safety assessments were all acceptable by the reviewer because the applicant followed the July 1998 FDA Guidances. The efficacy procedures outlined in the protocol are acceptable. The culture and susceptibility procedures are acceptable also. The medical reviewer has made specific comments regarding diagnostic criteria used for atypical microorganisms for study M99-077 (Ref: pages 19 and 20). These criteria and comments apply to this study also.

Study Subjects

This report presents data for subjects (176) assigned to the clarithromycin ER and trovafloxacin groups. A comparison of the clarithromycin IR and trovafloxacin groups was presented in a separate report (NDA 50-662 Supplement 029 – Refer to Medical Officer's Review dated July 20, 2000).

Disposition of Subjects

One hundred seventy-six (176) subjects were randomized to clarithromycin extended-release (ER) and trovafloxacin in the study and took study drug; 90 subjects took clarithromycin ER tablets and 86 subjects took trovafloxacin tablets in capsules.

Overall, 11% (19/176) of the treated subjects prematurely discontinued from the study; 6% (5/90) of subjects discontinued from study in the clarithromycin ER group and 16% (14/86) of subjects discontinued from study in the trovafloxacin group.

Primary reasons for premature discontinuation from the study were adverse event (one clarithromycin ER subject and two trovafloxacin subjects), insufficient improvement (two clarithromycin ER subjects and one trovafloxacin subject), lost to follow-up (two trovafloxacin subjects), noncompliance (one trovafloxacin subject), and "other" reasons (two clarithromycin ER subjects [one subject withdrew due to minimal improvement in signs and symptoms of pneumonia and one had a relapse of pneumonia] and eight trovafloxacin subjects [three subjects discontinued when the sponsor terminated the study, two subjects withdrew consent, and one subject each used a confounding antibiotic, had military leave, and moved away]).

Overall, 4% (7/176) of the subjects prematurely discontinued treatment; 2% (2/90) of subjects discontinued study drug in the clarithromycin ER group and 6% (5/86) of subjects discontinued study drug in the trovafloxacin group. One subject in each treatment group prematurely discontinued treatment due to adverse events. One subject in the clarithromycin ER group withdrew due to insufficient improvement. Additionally, four subjects in the trovafloxacin group prematurely discontinued study drug due to "other" reasons.

The details of the subjects who prematurely discontinued study drug are presented by treatment group in the following table:

**APPEARS THIS WAY
ON ORIGINAL**

Subjects Whose Treatment Was Prematurely Discontinued					
<u>Primary Reason for Discontinuation</u>	<u>Investigator</u>	<u>Subject #</u>	<u>Age (years)</u>	<u>Sex</u>	<u>Days on Therapy</u>
Clarithromycin ER Group					
Adverse Event	Patel	1576	55	F	2
Insufficient Improvement	Sokol	1004	58	F	3
Trovafloxacin Group					
Adverse Event	Degarmo	1087	61	F	5
Other	Gaman	1411 ^a	24	F	3
	Pinto	1408 ^a	49	F	3
	Vrooman	1383 ^a	31	M	5
	Patel	1361 ^b	39	M	1

a Sponsor terminated the study.
 b Patient withdrew consent.

Applicant's data – Volume 17, page 67

The treatment assignment blind was broken for two subjects during the study. Two subjects (Investigator Pinto, Subject 1408 and Investigator Vrooman, Subject 1383) had their study assignment blind broken due to sponsor request in order to identify those subjects receiving trovafloxacin (after FDA restriction on use of trovafloxacin). Subjects 1408 and 1383 discontinued prematurely because they were receiving trovafloxacin. A third subject was prematurely discontinued from the study due to sponsor request without the study blind being broken (Investigator Gaman, Subject 1411); this subject was subsequently identified as being assigned to trovafloxacin.

Applicant's Efficacy Evaluation

Clinically Evaluable Subject Population

All of the following criteria were to have been satisfied for a subject to be considered clinically evaluable:

The subject had a positive chest x-ray for an acute pulmonary infiltrate that was consistent with CAP.

The subject had taken study drug for a minimum of three full days to qualify for efficacy evaluation as a clinical (bacteriological) failure; to qualify as a clinical (bacteriological) cure, the subject had taken at least 80% of prescribed study medication and had not prematurely discontinued before Evaluation 3.

The subject did not receive any other systemic antimicrobial agent during the period 14 days (30 days if long-acting) prior to the start of study drug through the subject's final clinical visit (Evaluation 4), unless the subject was considered a study treatment failure or the antimicrobial agent was not considered to have had an effect on the infection.

The subject did not receive any interfering therapeutic procedures or any other potential confounding intervention during the study, unless the subject was considered a treatment failure or the therapeutic procedure/intervention was not considered to have an effect on the infection.

The subject did not violate any selection criteria unless it was considered not to affect the efficacy evaluation.

The subject returned for Evaluation 4 (7-28 days posttreatment) or the subject was considered a treatment failure before Evaluation 4.

A clinical evaluation was conducted at Evaluation 4 (7-28 days posttreatment) or the subject was a treatment failure before Evaluation 4.

Clinically and Bacteriologically Evaluable Subject Population

In addition to the above conditions, subjects must have had an acceptable pretreatment gram stain (<10 squamous epithelial cells and >25 polymorphonucleated leukocytes per low power field) and at least one target pathogen (*H. influenzae*, *H. parainfluenzae*, *S. aureus*, *L. pneumophila*, *S. pneumoniae*, or *M. catarrhalis*) was isolated from the pretreatment culture or at least one target pathogen (*M. pneumoniae*, *C. pneumoniae*, or *L. pneumophila*) was identified via serology or antigen testing. Subjects with positive serologic test results for atypical pathogens were considered evaluable with variation if the pretreatment sputum was not qualified by Gram staining.

Intent-to-Treat Subject Population

All subjects who took at least one dose of study drug and had a clinical diagnosis of CAP confirmed by a positive pretreatment chest x-ray were included in the Intent-to-Treat subject population.

Disposition of Subjects by Data Sets

Ninety (90) subjects were randomized to and took clarithromycin ER and 86 were randomized to and took trovafloxacin. Twenty-five subjects (5 clarithromycin ER and 20 trovafloxacin) were excluded from the clinically evaluable analyses. Eight subjects were excluded because they did not return for the Test-of-Cure Visit, eight returned for the Test-of-Cure Visit outside the allowable window, four subjects used confounding medication, four subjects did not have a chest x-ray performed at the Test-of-Cure Visit, and one subject did not meet the selection criteria.

Seventy-one subjects (32 clarithromycin ER and 39 trovafloxacin) were excluded from the clinical and bacteriological evaluable analyses of efficacy. Of these, 53 (29 clarithromycin ER and 24 trovafloxacin) subjects did not have a target pathogen isolated at pretreatment. Of the remaining 18 subjects who were excluded,

7 subjects did not return for the Test-of-Cure Visit, two subjects had an unacceptable Gram stain at pretreatment, four subjects returned for the Test-of-Cure Visit outside the allowable window, two subjects used confounding medications, two subjects did not have a chest x-ray performed at the Test-of-Cure Visit, and one subject did not meet the selection criteria. Several of the subjects excluded from the bacteriologically evaluable analyses for no pretreatment pathogen were excluded from the clinically evaluable analyses for other reasons. No subject was excluded from the Intent-to-Treat efficacy analyses. The number of subjects included in the efficacy analyses is presented by data set in the following table:

Disposition of Subjects by Data Set		
	<u>Clarithromycin ER</u>	<u>Trovaflaxacin</u>
Total Randomized	90	86
Total Took Study Medication (All-Treated Subjects Population)	90	86
Intent-to-Treat Analyses	90	86
Clinically Evaluable Analyses	85	66
Excluded from the Clinically Evaluable Analyses	5	20
Subject did not return for Test-of-Cure Visit	0	8
Mistiming of Test-of-Cure Visit	2	6
Used confounding medication	1	3
Chest x-ray was not performed at the Test-of-Cure Visit	1	3
Selection criteria not met (no Evaluation 1 signs and symptoms)	1	0
Bacteriologically Evaluable Analyses	58	47
Excluded from the Bacteriologically Evaluable Analyses ^a	32	39
No target pathogen isolated pretreatment	29	24
Subject did not return for Test-of-Cure Visit	0	7
Mistiming of Test-of-Cure Visit	1	3
Pretreatment Gram stain unacceptable	0	2
Selection criteria not met (no Evaluation 1 signs and symptoms)	1	0
Used confounding medication	0	2
Chest x-ray was not performed at the Test-of-Cure Visit	1	1
a If a subject is both bacteriologically and clinically nonevaluable, then the bacteriological nonevaluable reason is presented.		

Applicant's data – Volume 17, page 71

Demographic and Other Baseline Characteristics

Demographics

There were no statistically significant differences between the treatment groups in sex, race, age, or weight in any subject population. The majority of the subjects were female (52%) and white (88%). The mean age of all subjects was 47.5 years, and age ranged from 19 to 81 years. The table on the following page presents the demographic information for All-Treated Subjects.

Demographic Information (All-Treated Subjects Population)			
Demographic Characteristic	Number of Subjects by Treatment Group		P-value ^a
	Clarithromycin ER	Trovafloxacin	
Total Treated	90		
Sex	86		>0.999
Female	47 (52%)	45 (52%)	
Male	43 (48%)	41 (48%)	
Race ^b			0.821
White	78 (87%)	76 (88%)	
Black	6 (7%)	7 (8%)	
Asian	1 (1%)	0 (0%)	
Other	5 (6%)	3 (3%)	
Age (years)			0.896
<40	34 (38%)	32 (37%)	
40-64	37 (41%)	38 (44%)	
≥65	19 (21%)	16 (19%)	
Mean (SD)	47.6 (16.3)	47.3 (16.1)	
Range	19 - 81	19 - 80	
Weight (kg)			0.655
<45	1 (1%)	1 (1%)	
45 - <70	27 (30%)	21 (24%)	
≥70	62 (69%)	63 (73%)	
No data	0 (0%)	1 (1%)	
Mean (SD)	83.9 (19.5)	85.3 (20.6)	
Range	44 - 159	43 - 159	

^a - P-values are from Fisher's exact test comparing treatment groups (sex, race), or a one-way analysis of variance model comparing treatment groups (age, weight).
^b Race comparison was done with respect to two categories: white and all other races combined.

Applicant's data – Volume 17, page 72

Presenting Conditions, Medical History, and Diagnoses

There were no statistically significant differences between treatment groups in presenting conditions, medical history, and social history in any subject population. The majority of subjects were in fair (66%) clinical condition, and had a moderate (81%) infection. The current infection was the first within the past 12 months in 78% of the subjects. The two tables on the next two pages summarize the presenting conditions, medical history, and social history for All-Treated Subjects:

**APPEARS THIS WAY
 ON ORIGINAL**

Summary of Presenting Conditions, Medical History, and Social History (All-Treated Subjects Population)			
Characteristic	Number of Subjects by Treatment Group		P-value ^a
	Clarithromycin ER	Trovafloracin	
Total Treated	90	86	
<u>Diseases/Conditions Present</u>			Not computed
Surgical History	64 (71%)	68 (79%)	
Respiratory Disease	55 (61%)	57 (66%)	
Musculoskeletal	46 (51%)	57 (66%)	
Head-Eyes-Ears-Nose-Throat	50 (56%)	47 (55%)	
Gastrointestinal	45 (50%)	39 (45%)	
Cardiovascular	41 (46%)	40 (47%)	
Neurologic	41 (46%)	32 (37%)	
Endocrine Disorder	32 (36%)	28 (33%)	
Drug Allergy	30 (33%)	27 (31%)	
Non-Drug Allergy	20 (22%)	21 (24%)	
Renal Disease	16 (18%)	13 (15%)	
Occup./Environmental Hazard Exposure	7 (8%)	9 (10%)	
Hepatic Disease	8 (9%)	4 (5%)	
Cancer	5 (6%)	5 (6%)	
Immunodeficiency	2 (2%)	5 (6%)	
Drug/Alcohol Abuse	3 (3%)	3 (3%)	
<u>Pulmonary Disease History</u>			Not computed
Community-Acquired Pneumonia	90 (100%)	86 (100%)	
Acute Bronchitis	25 (28%)	26 (30%)	
Bronchial Asthma	17 (19%)	13 (15%)	
Chronic Bronchitis	13 (14%)	8 (9%)	
COPD	11 (12%)	6 (7%)	
Lung Abscess	0 (0%)	1 (1%)	
<u>Overall Clinical Condition</u>			0.792
Good	31 (34%)	28 (33%)	
Fair	59 (66%)	58 (67%)	
<u>Infection Status</u>			0.470
Mild	15 (17%)	18 (21%)	
Moderate	75 (83%)	68 (79%)	
<u>Prior Medical Evaluation for Current Infection</u>			0.734
Yes	11 (12%)	12 (14%)	
No	79 (88%)	74 (86%)	
<u>Prior Medical Treatment for Current Infection</u>			0.820
Yes	32 (36%)	32 (37%)	
No	58 (64%)	54 (63%)	

a P-values are from Fisher's exact test for tobacco use and alcohol consumption, from Cochran-Mantel-Haenszel for overall clinical condition, infection status, prior medical evaluation and prior medical treatment, and from ANOVA for number of LRTI infections within past 12 months.

Summary of Presenting Conditions, Medical History, and Social History (All-Treated Subjects Population) (Continued)					
Characteristic	Number of Subjects by Treatment Group				P-value ^a
	Clarithromycin ER		Trovaflaxacin		
Number of LRTI Infections in Past 12 Months					0.362
1	69	(77%)	68	(79%)	
2	11	(12%)	14	(16%)	
≥3	10	(11%)	4	(5%)	
Mean (SD)	1.5	(1.0)	1.3	(0.8)	
Tobacco Use^b					0.756
Non-Tobacco User	35	(39%)	31	(36%)	
Ex-Tobacco User	24	(27%)	18	(21%)	
Tobacco User	31	(34%)	37	(43%)	
Alcohol Consumption^c					0.654
Non-Drinker	46	(51%)	47	(55%)	
Ex-Drinker	4	(4%)	4	(5%)	
Occasional Drinker	29	(32%)	24	(28%)	
Drinker	11	(12%)	11	(13%)	
<p>a P-values are from Fisher's exact test for tobacco use and alcohol consumption, from Cochran-Mantel-Haenszel for overall clinical condition, infection status, prior medical evaluation and prior medical treatment, and from ANOVA for number of LRTI infections within past 12 months.</p> <p>b Tobacco usage comparison was done with respect to two categories: non-user and the combined user and ex-user categories.</p> <p>c Alcohol consumption comparison was done with respect to two categories: non-drinker and the combined drinker, occasional drinker and ex-drinker categories.</p>					

Applicant's Data – Volume 17, page 75

Pretreatment Signs and Symptoms

A statistically significant difference was observed between treatment groups in pretreatment immature neutrophils (bands) among Intent-to-Treat Subjects and All-Treated Subjects (p=0.036); none of the clarithromycin ER subjects and 5% of the trovafloxacin subjects had >15% immature neutrophils at pretreatment. All subjects had cough and were producing sputum at pretreatment. Other frequently reported signs and symptoms at pretreatment for both groups combined included rales/crackling (86%), dyspnea (80%), and rhonchi/wheezing (77%).

Concurrent Medications

Use of medications at pretreatment was similar between the treatment groups for the All-Treated Subjects population; 74% of subjects in the clarithromycin ER group and 79% of the subjects in the trovafloxacin group were taking medications at pretreatment. Overall, the most frequently used therapeutic classifications of medication at pretreatment were analgesics, antipyretics, and anti-inflammatory agents (31%); nonsteroidal anti-inflammatory agents (24%); sympathomimetic agents (23%); expectorants (18%); and antidepressants (16%).

At pretreatment and prior to study drug administration, 36% of the subjects in the clarithromycin ER group and 37% of the subjects in the trovafloxacin group were using medications to treat CAP. Overall, the most frequently used acute CAP medications at pretreatment were analgesics, antipyretics, and anti-inflammatory agents (22%); expectorants (15%); antitussives (14%); and sympathomimetic agents (14%).

During the study, 93% of the subjects in the clarithromycin ER group and 97% of the subjects in the trovafloxacin group used concurrent medications. The majority of concurrent medications were used for treatment of coughs, fevers, and other symptoms associated with CAP. Overall, 44% of all subjects used expectorants; 43% used opiate agonists; 38% used sympathomimetic agents; 37% used analgesics, antipyretics, and anti-inflammatory agents; 32% used nonsteroidal anti-inflammatory agents; 21% used H₁-receptor antagonists; and 19% used antitussives. The most frequently used specific medications included guaifenesin (43% of subjects), acetaminophen (35%), hydrocodone (30%), albuterol (17%), acetylsalicylic acid (16%), pseudoephedrine (15%), ibuprofen (13%), and dextromethorphan (13%). The percentages of subjects in the clarithromycin ER and trovafloxacin groups who used the above drugs were similar.

Two subjects in the trovafloxacin group were excluded from the bacteriologically and clinically evaluable analyses, because they took medications that could affect the outcome of the study. Four subjects (one clarithromycin ER and three trovafloxacin) were excluded from the clinically evaluable analyses, because they took confounding medications prior to the Test-of-Cure Visit. All of the subjects who were clinically nonevaluable were also bacteriologically nonevaluable; however, in the clinically and bacteriologically evaluable data set, bacteriological reasons for nonevaluability (e.g., no target pathogen) were listed above clinical reasons (e.g., confounding medication). The two subjects who were clinically nonevaluable due to confounding medications had no target pathogen isolated pretreatment. Details of the four subjects excluded from the clinically evaluable efficacy analyses due to confounding medications are presented in the table on the following page:

**APPEARS THIS WAY
ON ORIGINAL**

Subjects Excluded From Clinically Evaluable Efficacy Analyses Due to Confounding Medications			
Investigator/ Subject Number	Confounding Medication	Study Day ^b	Indication
Subjects Excluded From Clarithromycin ER Group			
Gaman/1111*	Achromycin (500 mg/day)	-6 - -1 (5)	Acne
Subjects Excluded From Trovafloxacin Group			
Honsinger/1016*#	Augmentin®	15 (8) - 24 (17)	Otitis media
Jones/1175	Prednisone (>10 mg/day)	4 5 6	Asthma
Pierone/1151#	Levaquin®	11 (4) - ongoing	Maxillary sinusitis

Subject prematurely discontinued from study, bacteriologically and clinically nonevaluable.
 a Bacteriologically nonevaluable: no target pathogen isolated pretreatment.
 b Number in parentheses indicates days posttreatment.

Applicant's data - Volume 17, page 81

FDA's Efficacy Results

The efficacy outcomes as presented in the NDA by the applicant were verified by the statistician, Dr. Joel Jiang. Thus, the following tables were generated by Dr. Jiang and this Medical Reviewer concurs with the analyses. The only difference between the applicant's analysis and FDA is the inclusion of *Legionella pneumophila* as a causative agent for CAP. The reviewer will address that issue in the bacteriologic outcome section of the efficacy review.

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%)
Bact. Evaluable Subjects	58 (64.4%)	47 (54.7%)

STUDY M98-927: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=85)	Trovafloxacin (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%	

STUDY M98-927: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=90)	Trovaflaxacin (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%	

Medical Officer's Comments:

It should be noted that this study was prematurely terminated after FDA restricted the use of trovaflaxacin, thus, this is only a supportive study. All the enrolled patients were included in the ITT population. An unusually large number of patients in the trovaflaxacin group were excluded from the clinically evaluable population when compared to Biaxin XL group (20 versus 5). As noted in the tables above, 97.5% confidence intervals for the difference did not show equivalence of the two treatments.

STUDY M98-927: CLINICAL CURE RATES FOR TARGET PATHOGENS OF BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT			
Pathogen	Clarithromycin ER	Trovaflaxacin	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

**APPEARS THIS WAY
 ON ORIGINAL**

STUDY M98-927: ERADICATION RATES FOR TARGET PATHOGENS OF BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT			
Pathogen	Clarithromycin ER	Trovafloxacin	Fisher's P-value
<i>Overall Pathogen</i>	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

Medical Officer's Comments:

The applicant made the diagnosis of CAP caused by Legionella pneumophila in four patients in the clarithromycin group based only on a single titer or a four-fold change in titer (serology alone). Out of those four patients, two patients' titers decreased during treatment. According to this reviewer's assessment, none of these patients had a true infection with Legionella pneumophila.

The other 3 patients with positive serology for Legionella pneumophila in the clarithromycin group had mixed infection with one of the target pathogens (H. influenzae, S. pneumoniae or M. catarrhalis). In the reviewer's opinion, none of these patients has acute infection with Legionella pneumophila.

This Medical Reviewer's overall opinion is that none of the patients enrolled in this study had true infection caused by Legionella pneumophila. The reviewer did not ask the statistician to re-analyze the data minus the seven patients, three of whom had other target pathogens isolated, because it would not have changed the overall outcome.

The Applicant has included Staphylococcus aureus as a target pathogen for community-acquired pneumonia. The reviewer's opinion is that pneumonia due to S. aureus is not community-acquired but either hospital-acquired (nosocomial), or in patients with an underlying immunocompromised condition. Patients with pneumonia due to S. aureus usually require intravenous therapy. Based on the data submitted by the applicant, the reviewer's opinion is that S. aureus should not be considered a target pathogen for community-acquired pneumonia.

STUDY M98-927: CLINICAL RESPONSES OF BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical Response	Clarithromycin ER (N=58)	Trovafloracin (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%	

STUDY M98-927: BACTERIOLOGICAL RESPONSES OF BACTERIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Bacteriological Response	Clarithromycin ER (N=58)	Trovafloracin (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%	

Medical Officer's Comments:

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. In ITT population, the clinical responses of clarithromycin ER were comparable to those of trovafloracin. The results from 95% and 97.5% confidence intervals were all consistent with each other. The reason for discrepancy in results between the clinically evaluable patients and the ITT population was that significantly more subjects in the trovafloracin treatment group were excluded from the clinically evaluable analyses (p-value: 0.001) than those in the clarithromycin ER treatment group, and as mentioned previously in the review, this was due to the premature termination of the study.

STUDY M98-927: RADIOGRAPHIC RESOLUTION AND SUCCESS RATES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
	Clarithromycin ER (N=85)	Trovafloracin (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%	

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

Applicant's Efficacy Conclusions

At the Test-of-Cure Visit, no statistically significant differences were observed between the treatment groups in clinical cure rates, subject bacteriological cure rates, and overall pathogen eradication rates. Similarly, no statistically significant differences were observed in radiographic resolution or success rates. Clinical signs and symptoms of CAP resolved in subjects treated with either regimen. Results of this study indicate that clarithromycin ER (1000 mg QD for 7 days) and trovafloxacin (200 mg QD for 7 days) were equally effective in treating community-acquired pneumonia in adult subjects.

Medical Officer's Efficacy Conclusions:

In this study, 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 reason for discrepancy in results between the clinically evaluable patients and the ITT population was that significantly more subjects in the trovafloxacin treatment group were excluded from the clinically evaluable analyses (p-value: 0.001) than those in the clarithromycin ER treatment group, and as mentioned previously in the review, this was due to the premature termination of the study due to safety concerns regarding trovafloxacin.

Based on the data submitted and verified by the medical reviewer and the statistician in this prematurely terminated trial, Biaxin® XL Filmtabs® at the dose of 1000 mg every 24 hours for 7 days compared to trovafloxacin 200 mg every 24 hours for 7 days failed to show equivalence, but the clinical response in the bacteriologically evaluable patients at the test-of-cure visit was 89.7% for the clarithromycin ER group, which is acceptable. Due to the premature termination of

NDA 50-775/S001
Biaxin® XL Filmtabs®

*this trial, the data from this trial is used only as supportive evidence for the indication of community-acquired pneumonia.
As discussed previously, S. aureus is not considered a target pathogen in community-acquired pneumonia and the applicant has not submitted convincing evidence in support of CAP caused by Legionella pneumophila.*

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**