CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-662/A029

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW OF NDA 50-662/S-029 BIAXIN FILMTABS

Date Submitted:	December 17, 1999.
Date Received:	December 20, 1999.
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MOR Initiated:	March 28, 2000.
MOR Draft Completed:	April 24, 2000.
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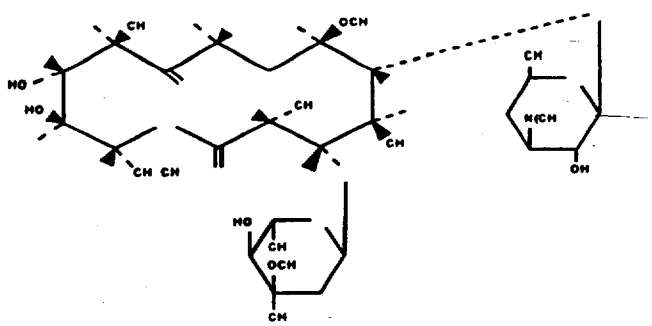
APPLICANT: Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park Ill 60064-3500.

DRUG:

Generic: Clarithromycin
Trade: Biaxin Filmtabs™
Chemical Name: 6-O-Methylerythromycin
Chemical Structure:



Molecular Formula: $C_{38}H_{69}NO_{13}$
Molecular Weight: 747.96.

Pharmacology Category: Macrolide Antiinfective
Dosage Form: Immediate Release Filmtab
Strength: 250-mg/500 mg

PURPOSE OF SUBMISSION:

Addition of the microorganism *Haemophilus influenzae* to the previously approved indication of Community-Acquired Pneumonia.

[redacted]

Related Material:

NDAs – 50-697; 50-698; 50-721
INDs [redacted]
DMFs [redacted]

SUBMISSION REVIEWED:

The submission consists of 8 volumes, and the clinical data are contained in volumes 1 to 8 inclusive.

Chemistry, Manufacturing and Controls:

Refer to the chemistry review by Dr. Andrew Yu.

Microbiology:

Refer to the microbiology review by Dr. Sousan Altaie.

Statistical:

Refer to the statistical review by Dr. Joel Jiang.

MEDICAL OFFICER'S REVIEW:

Lower respiratory tract infections (LRTIs) are the major cause of death due to infectious diseases in the United States, with pneumonia ranking as the sixth leading cause of death overall. The most common etiologic agent in community-acquired pneumonia (CAP) is *Streptococcus pneumoniae*, which accounts for approximately two-thirds of all cases of bacteremic pneumonia. Other pathogens implicated less frequently include *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Streptococcus pyogenes, Neisseria meningitidis, Moraxella catarrhalis, Klebsiella pneumoniae* and other gram-negative rods, *Legionella* species, influenza virus, and other microbes.
Clarithromycin (Abbott-56268; TE-031) is a novel macrolide antibiotic discovered by [redacted] and developed worldwide by Abbott Laboratories. The clarithromycin immediate-release tablets (250 mg and 500 mg) have been commercially available in Europe since 1989, in the U.S. since 1991, and in Canada since 1992. Clarithromycin is well-suited for therapy of LRTIs due to its broad spectrum of activity against respiratory pathogens and low incidence of adverse events in clinical studies; current approved indications for use in adults include pneumonia due to *M. pneumoniae, S. pneumoniae,* or *Chlamydia pneumoniae (TWAR).*

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

Study Identification:	M98-927
Study Phase:	3
Name of Drug:	Clarithromycin Immediate-Release (Abbott-56268)
Indication:	Community-Acquired Pneumonia
Structure:	Randomized
Blinding:	Double-Blind
Duration of Therapy:	7 days
Investigators:	35 investigators (multicenter) enrolled subjects in the United States
Method of Subject Assignment:	Subjects were randomly assigned in a 1:1:1 ratio at each investigational site to receive either clarithromycin extended-release tablets, 2 x 500 mg once a day (QD) for 7 days, or clarithromycin immediate-release tablets, 250 mg twice a day (BID) for 7 days, or trovafloxacin mesylate tablets in capsules, 1 x

200 mg QD for 7 days. **Subjects assigned to clarithromycin immediate-release and trovafloxacin were compared in this report.**

Study Initiation: December 11, 1998

Date of Early Termination: June 10, 1999

Study Completion (last subject completed): June 29, 1999

Synopsis

Name of Company: Abbott Laboratories		
Name of Finished Product: Clarithromycin Immediate-Release (IR) (A-56268)		
Name of the Active Ingredient: 6-0-methylerythromycin A		
Title of Study: 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.		
Investigator(s): 35 investigator sites enrolled subjects.	**Study Center:** Multicenter United States	
Publication (reference): N/A		
Study Period (years): Date of First Enrollment: December 11, 1998 Date of Early Termination: June 10, 1999 Date of Last Subject Completed: June 29, 1999	**Phase of Development:** 3	
Objectives: The primary objectives of this study were to compare the safety and efficacy of a 7-day course of therapy with either clarithromycin immediate-release (IR) tablets (1 x 250 mg BID) or clarithromycin extended-release (ER) tablets (2 x 500 mg QD) with those of a 7-day course of therapy with trovafloxacin mesylate tablets (1 x 200 mg QD) for the treatment of ambulatory subjects with community-acquired pneumonia (CAP).		
Methodology: This was a Phase 3, double blind, randomized, parallel-group, multicenter study in ambulatory subjects with CAP. Subjects were randomly assigned in a 1:1:1 ratio at each investigational site to receive either: clarithromycin extended-release (ER) tablets, 2 x 500 mg QD for 7 days, or clarithromycin immediate-release (IR) tablets, 1 x 250 mg BID for 7 days, or trovafloxacin mesylate tablets in capsules, 1 x 200 mg QD for 7 days. **Subjects assigned to clarithromycin IR (95 subjects) and trovafloxacin mesylate (86 subjects) were compared in this report.** Subjects assigned to clarithromycin ER (90 subjects) and trovafloxacin mesylate will be compared in a separate report. Approximately 150 subjects were planned to be enrolled per treatment group. Subjects returned for Evaluation 2 within 48 to 72 hours after initiation of therapy and within 72 hours after the last dose for Evaluation 3. Subjects returned once during Study Days 14-21 (Evaluation 4) for a Test-of-Cure Visit. The efficacy evaluation included clinical, bacteriological, serological, antigen, and radiographic response to treatment. Safety was evaluated throughout the study by physical examinations, vital signs, laboratory tests, concomitant medications, and monitoring of adverse events.		

Number of Subjects (planned and analyzed)	Clarithromycin IR	[redacted]	Trovafloxacin
Number of Subjects Planned	150		150
Number of Subjects Randomized and Treated	95		86
Intent-to-Treat Analyses	95		86
Clinically Evaluable Analyses	85		66
Excluded from Clinically Evaluable Analyses	10		20
Clin./Bact. Evaluable Analyses	54		30
Excluded from Clin./Bact. Evaluable Analyses	41		56
Subjects Included in the Safety Analyses	95		86

Diagnosis and Main Criteria for Inclusion:
Males and females 18 to 75 years of age inclusive were enrolled if they had a clinical diagnosis of CAP confirmed by a positive chest x-ray, supported by appropriate clinical signs and symptoms and a qualified Gram stain.

Test Product, Dose and Mode of Administration, Batch Number:

Test Product	Dose	Mode of Administration	Finishing Lot Batch Number
Clarithromycin IR tablets	1 x 250 mg BID	Oral	45-755-S2

Reference Therapy, Dose and Mode of Administration, Batch Number:

Comparator	Dose	Mode of Administration	Finishing Lot Batch Number
Trovafloxacin tablets in capsules	1 x 200 mg QD	Oral	46-844-S2

Duration of Treatment: 7 days

Criteria for Evaluation (Evaluated before unblinding):
Clinically Evaluable Analyses: All of the following criteria were to be 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 from 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 Analyses: In addition to the above conditions, subjects must have had a qualified pretreatment Gram stain and at least one target pathogen was isolated from the pretreatment culture or identified by serology (or antigen) testing.

Clinically Evaluable Analyses (continued): **Intent-to-Treat Analyses:** 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 analyses. **All-Treated Subjects Safety Analyses:** All subjects who received at least one dose of study medication were included in the All-Treated Subjects safety analyses.
Statistical Methods: Statistical tests were based on two-tailed tests with the 0.05 significance level and 95% confidence interval (CI). The primary treatment comparison was clarithromycin IR (1 x 250 mg BID) vs. trovafloxacin (1 x 200 mg QD) in the clinically evaluable population. The primary efficacy variable was clinical outcome at Evaluation 4 in the clinically evaluable subject population. Secondary efficacy variables were bacteriological response, radiographic response, and the change from baseline in clinical signs and symptoms.

Investigative Sites

Investigative sites were selected by Abbott Laboratories and [redacted] Fifty-eight investigators were approved to receive study drug and 35 of these investigators enrolled subjects into the study. A total of 181 subjects were enrolled by 35 investigators in the clarithromycin IR 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 broken for any subject who was receiving study drug, so that subjects on trovafloxacin could be immediately discontinued from treatment; three subjects were unblinded, of whom two were receiving trovafloxacin and one was receiving clarithromycin IR. The two subjects who were receiving trovafloxacin were prematurely terminated from the study.

The methods for this study are presented for all three study groups while the result section pertains to the clarithromycin IR and trovafloxacin groups only. Results of this study will be submitted to support a claim for adding *H. influenzae* to the BIAXIN® label for CAP. A separate report will present data from the clarithromycin ER and trovafloxacin groups.

The distribution of All-Treated Subjects in the clarithromycin IR and trovafloxacin groups for each investigator is presented in the table below:

Distribution of All-Treated Subjects by Investigator					
Investigator	Clarithromycin IR	Trovafloxacin	Investigator	Clarithromycin IR	Trovafloxacin
Acampora	2	2	Navarro	4	2
Bundy	1	2	Patel	20	20
Cronic	0	1	Perlman	4	4
Degarmo	2	3	Pierone	0	1
Duff	0	2	Pinto	4	4
Foley	1	0	Scheinberg	2	0
Gaman	2	3	Schneider	1	2
Garrity	2	1	Schrenker	1	2
Hall	1	2	Sheikh	1	0
Harrison	8	7	Sokol	3	2
Hilmi	1	0	Spiotta	1	1
Honsinger	3	2	Stein	2	0
Hosko	4	2	Strauss	1	0
Hutchins	0	1	Sullivan	10	9
Jones (Oregon)	3	3	Tarshis	6	4
Jones (Utah)	2	0	Vrooman	1	2
Meyerhoff	1	0	Wilhelm	0	1
Nadeemullah	1	1	**Total**	**95**	**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.

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, and a 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)	OR	clarithromycin ER tablets 2 x 500 mg QD for 7 days (plus placebo for clarithromycin IR and trovafloxacin)	OR	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 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 below:

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

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.
b Study Day 1 was the day the first dose was administered.
c If culturable material was available.
d If clinically indicated.
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.
f Only if subject prematurely withdrew from the study.

Inclusion Criteria

The subject had to meet all of the following criteria:

- Subject had a chest x-ray consistent with pneumonia. If a recent radiograph (within 48 hours before therapy) was available, the infiltrate must have been a new one and there must have been no intercurrent procedures or antimicrobial treatment.
- Subject presented with a recent respiratory illness that, upon consideration of signs and symptoms after physical examination, was consistent with the diagnosis of CAP.

  Subjects who required immediate study drug therapy before culture results were known could have entered with a presumptive diagnosis based on a chest radiograph which was positive for pulmonary infiltrate(s) and at least two of the following signs and symptoms:

  - cough;
  - hypoxemia with $PO_2 < 60$ mm Hg while subject was breathing on room air;
  - purulent sputum production or a change in the character of the sputum;
  - fever (oral temperature > 38.0°C or > 100.4°F);
  - development of, or increase in, dyspnea or tachypnea (elevated respiratory rate ≥ 30/min);
  - auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (i.e., dullness on percussion, bronchial breath sounds [crackles, rhonchi, wheezes, or egophony]); and/or
  - an elevated total peripheral white blood cell count (WBC > 10,000/mm^3); or >15% immature neutrophils (bands), regardless of total peripheral WBC count; or leukopenia with WBC < 4500/mm^3.

  Other clinical findings to be recorded, if present were:
  - development of, or increase in, chest discomfort (pain) and/or congestion; and
  - rigors or shaking chills.
- A pretreatment purulent sputum was to be obtained within 48 hours pretherapy for Gram stain and routine bacterial culture with susceptibility testing. Specimens obtained by deep expectoration were to be screened microscopically prior to culture. To qualify as a purulent sputum, the specimens must have had < 10 squamous epithelial cells and > 25 leukocytes per low power field (100X).
- Pretreatment blood and urine samples were to be obtained within 48 hours pretherapy for serologic and antigen assays.
- If culture results were known before study treatment began, the pathogen(s) must not have been resistant to the assigned study drug(s).

- A female with childbearing potential could have been enrolled provided she:
  - had a negative urine human chorionic gonadotropin (HCG) pregnancy test (this included subjects with tubal ligation).
  - was using an effective method of birth control. Examples of methods of birth control to prevent pregnancy were:
    - condoms, IUD, contraceptive foams, contraceptive jellies, cervical cap, or
    - oral contraceptives or hormone replacement therapy for a period of 3 months prior to study start until completion of study drug administration.
  - did not attempt to become pregnant during the study period.
- Able to swallow tablets and capsules intact and be a suitable candidate for oral antibiotic therapy.
- The subject (or legal representative) voluntarily signed the informed consent form after the nature of the study had been explained, prior to initiation of any study-related procedures.

Exclusion Criteria

Subjects were excluded from study participation if they met any of the following criteria:

- History of hypersensitivity or allergic reactions to macrolide or quinolone antimicrobials.
- Prior hospitalization within previous 4 weeks or residence at a chronic care facility.
- Females who were pregnant or lactating.
- Subjects who had:
  - evidence of active tuberculosis (or other mycobacterial infections), empyema, lung abscess, pulmonary embolism, edema, cystic fibrosis, tumor (primary or metastatic) involving the lung, bronchial obstruction, a history of postobstructive pneumonia (not including chronic obstructive pulmonary disease), or known or suspected *Pneumocystis carinii* pneumonia.
  - evidence of uncontrolled clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurological or endocrine disease, malignancy, or other abnormality (other than CAP).
  - any infection that required the use of a concomitant antimicrobial agent, in addition to study drug, or use of systemic antimicrobial therapy or long-acting antimicrobial therapy within 2 weeks or 4 weeks, respectively, prior to the study.

- treatment with a long-acting injectable antimicrobial agent (e.g., penicillin G benzathine) within 4 weeks or other systemic antibiotics within 2 weeks prior to study drug administration.
- evidence of alcohol abuse, illegal drug use, or drug abuse within 12 months before starting the study.
- known significant renal or hepatic impairment or disease indicated by recent chemistries:

  serum creatinine ≥ 2.0 mg/dL;

  AST/SGOT >3 X the upper limit of the reference range;

  ALT/SGPT >3 X the upper limit of the reference range;

  alkaline phosphatase > 2 X the upper limit of the reference range; and/or

  total bilirubin >2 X the upper limit of the reference range.
- previous treatment in this study.
- treatment with an investigational drug within 8 weeks prior to study drug administration.

- Subjects who had any underlying condition or disease state that would interfere with the completion of the study procedures and evaluations or absorption of study drug:
  - compromised host status, e.g., granulocytes ≤ 1,000/mm^3;
  - other significant underlying condition, e.g., life-threatening infection or positive blood culture with associated shock or multiple organ failure, metastatic tumor;
  - a history of heart failure and/or cardiac arrhythmia;
  - a severely compromised respiratory rate; and/or
  - any other condition likely to interfere with the evaluation of response to treatment.
- Subjects who were currently receiving or who were likely to require any of the following medications during the period between Evaluation 1 (initial presentation to office/clinic) and within 48 hours after the last dose of treatment:
  - [redacted]astemizole (Hismanal®), cisapride (Propulsid®), or pimozide (Orap®); and/or
  - Vitamins or minerals containing iron, aluminum-base or magnesium-base antacids, antacids containing citric acid buffered with sodium citrate, or sucralfate.

- Subjects who were currently receiving or who were likely to require any of the following medications during the period between Evaluation 1 (initial presentation to office/clinic) and Evaluation 4 (Study Day 21-28):
  - Oral or parenteral steroid at a dose equivalent to or ≥ 10 mg/day of prednisone.
  - Any immunosuppressant drug.
  - Other systemic antimicrobial therapy.
  - Intravenous morphine.
  - Concomitant theophylline (or any theophylline analog), carbamazepine, [redacted] dihydroergotamine, triazolam, diazepam, disulfiram, digoxin, [redacted] phenytoin, or [redacted] unless clinically monitored for signs and symptoms of toxicity.
  - Concomitant warfarin therapy unless prothrombin time could adequately be monitored.

- Immunocompromised subjects (e.g., neutropenic subjects), subjects receiving immunosuppressive agents, or subjects with known HIV infection.

Removal of Subjects from Therapy or Assessment

A subject was withdrawn from the study immediately if any of the following occurred:

- Clinically significant deterioration of the subject's medical status.
- Subject's response to therapy was unsatisfactory (>72 hours after start of treatment):
  - Persistence of pyrexia, increase or no trend to decline.
  - Persistence or worsening of clinical symptoms and/or respiratory status.
  - Chest radiographs indicated worsening pulmonary status.
- Clinically significant abnormal pretreatment laboratory result which included:
  - Alkaline phosphatase > 2X the upper limit of the reference range;
  - AST/SGOT and/or ALT/SGPT > 3X the upper limit of the reference range;
  - Total bilirubin > 2X the upper limit of the reference range; and/or
  - Serum creatinine ≥ 2.0 mg/dL.
- The investigator decided that discontinuation was in the best interest of the subject.
- The subject or legal guardian requested withdrawal from the study.
- Selection criteria violations were noted after the subject started study drug.

A subject who was prematurely withdrawn from study drug was instructed to return to the investigator's office within 72 hours of the last dose of study drug for completion of Evaluation 4 procedures. A clinical evaluation was to be performed and sputum (if the subject was still producing sputum), blood, and urine samples were to be obtained for microbiologic and serologic assays. The Evaluation 4 procedures were to be completed prior to the institution of another antibiotic or other

appropriate therapy, but were not in any way to delay institution of any new treatments or therapeutic modalities, which, in the investigator's opinion, were necessary to treat the subject's condition.
If the subject discontinued from the study after the full course of therapy, but prior to the completion of all study procedures, samples for microbiologic testing were to be obtained if possible. Subjects who prematurely discontinued were not replaced.

Treatments Administered

Treatment assignment was determined by the randomization schedule such that equal numbers of subjects were assigned to each of the three treatment regimens, as outlined in the table below:

Treatments Administered		
Regimen	**Morning Dose[a]**	**Evening Dose[a]**
Clarithromycin immediate-release (IR)	one 250-mg tablet of clarithromycin IR two placebo tablets for clarithromycin ER	one 250-mg tablet of clarithromycin IR one placebo capsule for trovafloxacin
Clarithromycin extended-release (ER)	one placebo tablet for clarithromycin IR two 500-mg tablets for clarithromycin ER	one placebo tablet for clarithromycin IR one placebo capsule for trovafloxacin
Trovafloxacin mesylate	one placebo tablet for clarithromycin IR two placebo tablets for clarithromycin ER	one placebo tablet for clarithromycin IR one 200-mg tablet of trovafloxacin in a capsule
a Morning and evening doses were to be administered with food.		

Subjects were instructed to take their study medication twice each day (morning and evening) for each of the 7 days. On the first day (Study Day 1), all tablets and capsules were to be taken together, with food. On Study Days 2-7, the daily regimen consisted of three tablets in the morning and one capsule with one tablet in the evening. Study medication was to be taken with food.

Blinding

The investigator, study coordinator, and subject remained blinded to each subject's treatment throughout the course of the study. The randomization schedule, which assigned subject treatment by subject number, was computer-generated by Abbott Laboratories Department of Clinical Statistics prior to study start. The subjects were randomized in a 1:1:1 ratio in a block of six to receive either clarithromycin IR tablets and placebo for clarithromycin ER and trovafloxacin, or clarithromycin ER tablets and placebo for clarithromycin IR and trovafloxacin, or trovafloxacin mesylate and placebo for clarithromycin IR and clarithromycin ER. All subjects were assigned identification

numbers in ascending numerical sequence as they were enrolled into the study; subject numbers were pre-printed on each blister card label. A sealed envelope for each subject, containing the drug assignment, was provided to the investigator and retained in a locked secure area. The study blind envelope could have been opened if, in the opinion of the investigator, it was in the subject's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) was to be notified before breaking the blind unless identification of the study drug was required for emergency therapeutic measures. The sponsor was then notified within 48 hours of the blind being broken. The date, time, and reason that the blind was broken were recorded on the appropriate CRF. All opened and unopened envelopes were retained with the CRF and returned to Abbott Laboratories at the end of the study.

Prior and Concomitant Therapy

Any medications (including over-the-counter medication) taken by the subject within 48 hours, systemic antibiotics taken within 2 weeks, and long-acting antibiotics taken within 4 weeks prior to study start were recorded on the appropriate CRF.
Because of the potential interaction with clarithromycin, subjects were not allowed to take [redacted] astemizole, cisapride, or pimozide while on study medication. For the same reason, subjects were not allowed to take theophylline (or any theophylline analog), carbamazepine, ergotamine, dihydroergotamine, triazolam, diazepam, disulfiram, digoxin, [redacted] phenytoin, or [redacted] unless the subject was clinically monitored for signs and symptoms of toxicity. While on study medication, subjects were not allowed to take concomitant warfarin therapy unless prothrombin time could be adequately monitored.
Subjects were to be advised that vitamins or minerals containing iron, aluminum-base or magnesium-base antacids, antacids containing citric acid buffered with sodium citrate, or sucralfate should not be taken during treatment with the study drug. Co-administration of intravenous morphine was not allowed during the study (Study Days 1 to 28).
Subjects were not to receive any oral or parenteral steroids at a dose equivalent to or greater than 10 mg/day of prednisone, any immunosuppressant drug, other systemic antimicrobial therapy, or other investigational agent until after Evaluation 4. If the administration of any concurrent medication was necessary during the course of this study, dosage information, dates of administration, and indication for use were recorded on the CRF. In the event that any surgical or diagnostic procedure (other than those described in the protocol) was performed during the course of the study, the date, time, and description of the procedure(s), as well as all perioperative medications, anesthetics and clinical findings, were recorded on the CRF.

Treatment Compliance

In order to document compliance with the treatment regimen, subjects were instructed to return the blister-pack card (full, partial, or empty) at Evaluation 2 to the study coordinator, who inspected the contents of the card and returned it to the subject. The study blister-pack cards were retained by the study coordinator at Evaluation 3.

Compliance with each study medication was documented by the study coordinator on the appropriate CRF. The exact start and stop date, the number of tablets (capsules) taken, and the number of tablets (capsules) remaining were recorded on the CRF. If the number of tablets (capsules) taken and the number of tablets (capsules) returned did not add up to the number of tablets (capsules) dispensed, an explanation was provided on the CRF. An overall accountability of study medication was performed and verified by the [redacted] monitor or designee throughout the study and at the site close-out visit.

Efficacy and Safety Variables

Efficacy and Safety Measurements Assessed

Clinical assessments of the signs and symptoms of CAP were performed at Evaluations 1, 2, 3 and 4, and a clinical response to therapy was assigned by the investigator at Evaluation 4 (Test-of-Cure Visit). Cultures for isolation of pathogens from purulent sputum were obtained at Evaluation 1 to identify the presence of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Legionella* spp. and other pathogens. Cultures were also obtained at Evaluations 2, 3 and/or 4 for microbiological testing (if the subject was still producing purulent and qualified sputum at the time of subsequent Evaluation visits). Blood samples for serologic testing of *M. pneumoniae*, *C. pneumoniae*, and *Legionella* spp. and urine samples for urine antigen assays for *Legionella* spp. were also collected at Evaluations 1 (Pre-Therapy Visit) and 4 (Test-of-Cure Visit).
Adverse events and concomitant medications were monitored throughout the study. A complete physical examination with vital signs was performed at Evaluations 1 and 4, while vital signs were assessed at Evaluations 2 and 3. Any clinically abnormal observation arising during the study treatment period was followed to a satisfactory resolution. Hematology and serum chemistry tests were performed at Evaluations 1 and 3.

Efficacy Procedures

Efficacy in this study was assessed by resolution of clinical signs and symptoms of CAP and bacteriological eradication of pathogens.

Clinical Signs and Symptoms

Clinical signs and symptoms of the subject's current episode of CAP were assessed at Evaluations 1, 2, 3 and 4, with a clinical response to therapy assigned by the investigator at Evaluation 4 (Test-of-Cure Visit). The assessment categories for each clinical sign and symptom are presented in the table below:

Assessment of Clinical Signs and Symptoms of Current Episode of CAP	
Clinical Sign/Symptom	Assessment
Cough	absent mild: does not interfere with normal activities moderate: interferes with normal activities or sleep severe: causes chest pain and dizziness
Sputum Production	absent*, mild, moderate, severe
Sputum Production Volume (in the last 24 hours)	<1 oz; 1-2 oz, 2-3 oz, >3 oz
Sputum Appearance: None Mucoid Mucopurulent Purulent Hemoptic	 Subject not producing sputum. Clear mucous material with egg white appearance, which may contain isolated flecks (traces) of pus. Mucoid material with many thick green or yellow opaque purulent areas (≤ ½ pus). Almost uniform yellow or green thick opaque material with the appearance of pus (more than ½ pus). Blood-stained sputum.
Respiratory Rate (tachypnea)	< 30/min or ≥ 30/min
Dyspnea	absent mild: not enough to interfere with normal activities moderate: interferes with normal activities to some degree severe: prevents normal activities
Rales/Crackling	absent, present
Rhonchi/Wheezing	absent, present
Egophony and/or dullness	absent, present
Rigors or shaking chills	absent, present
Pleuritic Chest Pain	absent, present
Fever (>100.4° F or >38.0° C)	absent, present
Oxygenation	PO_2 < 60 mm Hg or ≥ 60 mm Hg
Peripheral WBC Count	< 4500/mm^3, 4500/mm^3- 10,000/mm^3, or > 10,000/mm^3
* Subjects had to be producing purulent sputum at Evaluation 1 to be eligible for enrollment	

Chest X-Ray

A chest x-ray was obtained within 48 hours prior to administration of study drug(s) from all subjects. The chest x-ray was to be positive for an acute pulmonary infiltrate consistent with CAP in order for the subject to be enrolled into the study. Both posterior-anterior (PA) and lateral view x-rays were performed whenever possible at Evaluation 1. If initial x-rays were borderline (not clearly positive for infiltrate), adequate hydration was provided for approximately 24 hours and the x-rays were repeated. The final full report of the pretherapy (and post-therapy) chest radiograph by the radiologist was entered on the CRF page, and a copy of the report was included with the CRF. If there was a discrepancy in the reading between the investigator and the radiologist, the reading of the investigator always took precedence. The investigator entered the evidence (or

reason) for re-evaluation of the chest x-ray on the CRF page. The chest x-ray was repeated at Evaluations 2 and 3, only if clinically indicated. The chest x-ray was to be repeated at Evaluation 4 to determine if infiltrates had lessened or resolved. Subsequent radiographs (if available) were compared to the pretherapy radiograph.

Sputum Sample

Purulent sputum samples for Gram stain (microscopy) and culture and susceptibility testing were obtained within 48 hours before initiation of therapy and at Evaluations 2, 3 and 4 (if the subject was still producing a qualified purulent sputum specimen). Sputum samples were to be obtained by deep, spontaneous expectoration. If induced expectoration was utilized for obtaining a sputum sample, only normal saline without preservative was to be used as the vehicle; bacteriostatic vehicles were not permitted. If the subject was unable to produce a sputum specimen, the unavailability of culturable material was to be documented on the CRF.

Gram Stain

The investigator prepared four sputum smears that were air-dried for Gram stain evaluation. Each slide was clearly identified with the study number, subject number, subject initials, and date the specimen was obtained. Two slides were stained, one of which was examined to determine that the sputum was "qualified" and retained by the site as part of the CRF. The second Gram-stained slide, along with the two unstained slides, was sent to [redacted] Only Gram stain specimens which contained < 10 squamous epithelial cells and > 25 leukocytes per low power field (100X) were regarded as fully qualified sputum acceptable for culture and susceptibility testing.

Culture and Susceptibility Testing

Sputum specimens were collected into a container, then transferred to transport media and clearly labeled with the subject number, subject initials, source of specimen, method of collection, and collection date. Qualified sputum samples were sent to the central laboratory for culture and susceptibility testing for *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *Legionella* spp., and other pathogens. *In vitro* susceptibilities of the isolates to clarithromycin and trovafloxacin were determined using the broth microdilution method, with measurement of the minimum inhibitory concentrations (MIC) in micrograms per milliliter (µg/mL), and the [redacted] disk zone diameter, with measurement of the zone of inhibition in millimeters (mm). Using the National Committee for Clinical Laboratory Standards (NCCLS) guidelines, susceptibility of the isolates to the antibiotics was recorded as susceptible, intermediate or resistant, as shown in the tables below:

Susceptibility Criteria for Clarithromycin						
	Minimum Inhibitory Concentration (µg/mL)			Zone Diameter (mm)		
Pathogen	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
H. influenzae@	≤8	16	≥32	≥13	11-12	≤10
S. pneumoniae	≤0.25	0.5	≥1	≥21	17-20	≤16
M. catarrhalis#	≤2	4	≥8	≥18	14-17	≤13
S. aureus	≤2	4	≥8	≥18	14-17	≤13
@ *H. influenzae* breakpoints apply to other *Haemophilus* spp. # *S. aureus* breakpoints were used for *M. catarrhalis*.						

Susceptibility Criteria for Trovafloxacin						
	Minimum Inhibitory Concentration (µg/mL)			Zone Diameter (mm)		
Pathogen	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
H. influenzae@	≤1	-	-	≥22	-	-
S. pneumoniae	≤1	2	≥4	≥19	16-18	≤15
M. catarrhalis#	≤2	4	≥8	≥17	14-16	≤13
S. aureus	≤2	4	≥8	≥17	14-16	≤13
@ *H. influenzae* breakpoints apply to other *Haemophilus* spp. # Label breakpoints for non-fastidious aerobes were used.						

All pretherapy and subsequent pathogens were frozen in appropriate media and shipped to Abbott Laboratories for storage.

Atypical Pathogens

Blood samples were obtained from all subjects at Evaluations 1 and 4 for serologic assays of *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. Sputum and urine samples were collected for culture and urine antigen testing, respectively, for *Legionella* spp.

Safety Procedures

The safety of the study medication was monitored throughout the study by physical examinations, including vital signs, concomitant medications, and the assessment of adverse events. Chest x-rays and laboratory evaluations were performed prior to treatment (Evaluation 1) to assess the subject's medical status at baseline. Subjects were instructed to call the investigator, or to return to the study site at any time during the treatment period if they felt progress was unsatisfactory or if signs and symptoms of infection worsened.

Laboratory Procedures

Laboratory tests (hematology and serum chemistry) were performed by [redacted] This laboratory is accredited by the College of American Pathologists. All blood samples were collected in accordance with accepted laboratory procedures. Specimens were obtained at Evaluations 1 and 3 for the following tests listed in the table below:

Clinical Laboratory Tests	
Hematology Tests	**Serum Chemistry Tests**
Hemoglobin	Blood Urea Nitrogen (BUN)
Hematocrit	Creatinine
White Blood Cell Count (WBC) with Differential	Total Bilirubin
Red Blood Cell Count (RBC)	Direct Bilirubin
Platelet Count	Alkaline Phosphatase
	AST/SGOT
	ALT/SGPT

If an unexpected laboratory value(s) outside the normal range occurred, the investigator was to repeat the laboratory test(s) as judged appropriate to ensure the validity of the abnormal result(s). Liver and renal function test(s) were to be repeated if one or more of the following was observed:

- AST/SGOT >3 X the upper limit of the reference range;
- ALT/SGPT >3 X the upper limit of the reference range;
- Alkaline phosphatase >2 X the upper limit of the reference range;
- Total bilirubin > 2 X the upper limit of the reference range;
- Creatinine ≥2.0 mg/dL (if, in the investigator's opinion, the creatinine was elevated due to pretreatment dehydration, the serum creatinine could have been repeated after rehydration of the subject);

If test results were not within the limits specified upon repeat testing, the subject could be continued in the study only at the discretion of the investigator with concurrence of the sponsor.
Any significantly abnormal laboratory result was to be followed until it resolved, stabilized, or became explainable due to other known causes (i.e., concurrent condition or medication) and clinical judgment indicated that further studies were not warranted.
The investigator assessed the etiology of any significantly abnormal results. Subjects were to be prematurely discontinued from the study if abnormal laboratory values were verified, deemed clinically significant, and were study drug-related. Clinically significant abnormal laboratory results that were considered to be adverse events were also recorded on the adverse events CRF.

Other Drug Levels

If the subject was receiving digoxin, theophylline (or a theophylline analog), or other allowed drug(s), subjects were to be clinically monitored for signs and symptoms of toxicity. Since this was a medical practice and not part of this study, the results were not reported.

Pregnancy Test

If a subject was female and of childbearing potential (postmenopausal for less than 1 year or without a hysterectomy), a negative urine HCG pregnancy test result was required within two days prior to enrollment.

Medical History

A complete medical history was obtained at pretreatment (Evaluation 1) including:

- duration of signs and symptoms of the current infection
- number of lower respiratory tract infections within the past 12 months (including current infection)
- any prior medical evaluation for the current infection
- any prior medical treatment (prescription drug) for the current infection
- any underlying pulmonary or other clinically significant medical conditions
- history of chronic bronchitis, CAP, or other pulmonary diseases (including hospitalizations)
- concurrent illnesses
- social history (including tobacco and alcohol use).

Physical Examination

A complete physical examination was performed at Evaluations 1 and 4, including the following vital signs assessments:

- blood pressure (after sitting 3 minutes)
- pulse (30 seconds)
- respiration rate

- oral temperature
- height (Evaluation 1 only) and weight

Only vital signs were measured at Evaluations 2 and 3.

Adverse Events

Adverse events (AEs) were defined as any unexpected event(s) such as sign(s), symptom(s), and/or laboratory finding(s) associated with the use of drugs in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject, occurring between the start of the study (i.e., signing of consent form) through 30 days from the end of therapy.
Subjects were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken. The investigator assessed any adverse event and recorded information in detail onto the adverse event section of the CRF. The report of the adverse event included the date and time of onset, description, severity, date of resolution (or duration of event if <24 hours), unifying diagnosis/syndrome (if known), alternate etiology, investigator's assessment of relationship to the study drug, any actions taken, and whether or not the adverse event met the criteria for a serious adverse event. Any adverse events or abnormal laboratory results that were considered clinically significant were followed to a satisfactory resolution, or until they became stable or could be explained due to other known causes (i.e., concurrent condition or medication) and clinical judgment indicated that further evaluation was not warranted.

The investigator used the following definitions to rate the severity of each adverse event:

Mild	The adverse event was transient and easily tolerated by the subject.
Moderate	The adverse event caused the subject discomfort and interrupted the subject's usual activities.
Severe	The adverse event caused considerable interference with the subject's usual activities and may have been incapacitating or life-threatening.

The possible relationship of the adverse event to the study drug was assessed using the following definitions:

Probable	An adverse event had a strong temporal relationship to study drug or recurred on rechallenge and another etiology was unlikely or significantly less likely.
Possible*	An adverse event had a strong temporal relationship to study drug and an alternative etiology was equally or less likely compared to the potential relationship to study drug.
Probably Not*	An adverse event had little or no temporal relationship to the study drug and/or a more likely alternative etiology existed.
Not Related*	An adverse event was due to an underlying or concurrent illness or effect of another drug and was not related to the study drug (e.g., had no temporal relationship to study drug or had a much more likely alternative etiology).

* An alternate etiology was to be specified for these assignments of relationship to study drug.

Serious Adverse Events

Any adverse event that resulted in any of the criteria listed in the table below was considered a "serious" adverse event (SAE):

Table 9.5e Criteria for a Serious Adverse Event
If the Adverse Event Resulted in:
A Persistent or Significant Disability/Incapacity
A Congenital Anomaly
A Hospitalization
Prolongation of Hospitalization
A Medical or Surgical Intervention to Prevent Serious Outcome
A Life-Threatening Situation (defined as the subject being at immediate risk of death from the event as it occurred)
Death of the Subject

An SAE included any adverse drug experience occurring at any dose that resulted in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not have resulted in death, been life-threatening or required hospitalization could have been considered serious when, based upon appropriate medical judgment, they jeopardized the subject and could have required medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
If a study subject had a miscarriage/spontaneous abortion or had an elective abortion during the study, this event was also to be reported as an SAE for Abbott Laboratories.

Serious adverse events that occurred within 30 days after the discontinuation of study drug were to be collected. Any SAE that occurred after 30 days posttreatment and was spontaneously reported to Abbot Laboratories by the investigator or reporter was also to be collected.

Deaths

Any death that occurred during the study or within 30 days of discontinuation from the study was reported as a serious adverse event. Copies of the death certificate and autopsy report were to be submitted when available.

Appropriateness of Measurements

All clinical/microbiology and laboratory procedures used in this study are standard and generally accepted.

Efficacy Variables

Primary Variable

The primary efficacy variable in this study was the clinical cure rate, defined as the percentage of subjects who had a clinical response of "cure" (Draft Guideline, Food and Drug Administration, Center for Drug Evaluation and Research, July 1998).

Clinical Response Definitions

The investigator compared the clinical findings and x-ray results at Evaluation 4 to the findings prior to study treatment for each subject and assigned a clinical response. Bacteriological results were not considered when assigning clinical response. The clinical response was rated using the following definitions:

Clinical Cure	(Evaluation 4 only) Complete resolution of all (or improvement in) signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on chest radiograph, or no pneumonia or extrapulmonary infection requiring antimicrobial therapy other than or in addition to the study drug as assessed at the Test-of-Cure Visit (Evaluation 4).
Clinical Failure	(all Evaluations) The subject was considered to be a therapy failure under the following conditions: 1) Persistence or worsening in signs and symptoms of the acute process after 3 to 5 days of therapy or requirement of additional antibiotic for initial pneumonia; 2) Failure to show improvement in at least three of the clinical findings after 3 days of therapy; 3) Initial improvement in at least three of the clinical signs and symptoms followed by clinically significant worsening in one or more of these clinical findings after 3 to 5 days of therapy; 4) Development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy other than or in addition to the study drug;

5) Persistence or progression of chest radiographic abnormalities;
6) Death due to pneumonia.

Indeterminate — (Evaluation 4 only) The evaluation was not possible (e.g., disallowed medication used, no follow-up examination); the reason was recorded on the CRF.

Secondary Efficacy Variables

The secondary efficacy variables for this study were the bacteriological response, radiographic response, and the change from baseline in signs and symptoms. Two bacteriological outcomes (the subject bacteriological cure rate and the pathogen eradication rate) and two radiographic outcomes (the radiographic resolution rate and the radiographic success rate) were analyzed, as defined in the table below:

Definitions of Bacteriological and Radiographic Outcomes

Response Variable	Definition
The Subject Bacteriologic Cure Rate	The percentage of bacteriologically evaluable subjects (i.e., subject with at least one evaluable pathogen at Evaluation 1) who demonstrated eradication of all evaluable pathogens.
The Pathogen Eradication Rate	Two definitions were examined: 1) for each pretreatment pathogen, the percent of subjects in whom the pathogen was eradicated; 2) the percentage of all evaluable pretreatment pathogens eradicated (regardless of number of subjects).
The Radiographic Resolution Rate	The percentage of evaluable subjects who demonstrated complete clearing of chest x-ray evidence of pneumonia.
The Radiographic Success Rate	The percentage of evaluable subjects who demonstrated resolution or improvement in the chest x-ray evidence of pneumonia compared to the pretreatment x-ray.

Bacteriological Response Definitions

The bacteriological response was assigned by Abbott Laboratories for each valid pretreatment pathogen by assessing the culture (susceptibility), serologic, and/or antigen test results at appropriate evaluation visits before breaking the blind. The response categories for evaluation of culture results were as follows:

Presumed Eradication* — In the absence of sputum production, the initial pathogen(s) was presumptively eradicated if the definition of clinical cure was met.

Eradication	The absence of the original pathogen(s) from a repeat sputum culture performed at Evaluation 4.
Presumed Persistence*	In the absence of a repeat sputum culture, the original pathogen(s) was presumed persistent if the definition of clinical failure was met.
Persistence	The presence of the original pathogen(s) at Evaluation 4 culture(s) or at the time of discontinuation of study therapy.
Superinfection	Presence of a new pathogen(s) in Evaluation 4 culture in a symptomatic subject.
Indeterminate	The evaluation was not possible (e.g., subject did not return).
Recurrence	Isolation of the original pathogen(s) from a culture taken after Evaluation 4.
New Infection	Isolation of a new pathogen from a culture taken after Evaluation 4 in a symptomatic subject.
Colonization	Isolation of an organism at Evaluation 4 culture in an asymptomatic subject.

*Presumed eradication and presumed persistence were interpreted from serological results for atypical pathogens.

Radiological Response Definitions

The investigator compared chest x-ray findings obtained at Evaluation 4 (and Evaluations 2 and 3, if clinically indicated) to the findings at Evaluation 1. The radiographic response was rated using the following definitions:

Resolution	Complete clearing of chest x-ray evidence of pneumonia.
Improvement	Reduction in the chest x-ray evidence of pneumonia in comparison to the pretreatment x-ray.
No Change	No change in the chest x-ray evidence of pneumonia in comparison to the pretreatment x-ray.
Worsening	Worsening of the chest-x-ray evidence of pneumonia in comparison to the pretreatment x-ray.
Indeterminate	The evaluation was not possible (e.g., no follow-up x-ray).

Diagnosis of Infection Due to Atypical Pathogens

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**

- a single Legionella titer ≥1:256.
- a fourfold increase in Legionella titer from the Pretherapy Visit to the Test-of-Cure Visit; the titer was to be > 1:128 to be considered significant for acute disease.

- positive at enrollment for *L. pneumophila* from sputum specimen.
- a positive *Legionella* urine antigen result.

***Chlamydia pneumoniae* Test Results**

- A single immunoglobulin M (IgM) titer ≥ 1:32 or a fourfold increase or decrease in titer from the Pretherapy Visit to the Test-of-Cure Visit.
- A single immunoglobulin G (IgG) titer > 1:512.

***Mycoplasma pneumoniae* Test Results**

- a single IgM titer ≥ 1:16 or a fourfold increase or decrease in titer from the Pretherapy Visit to the Test-of-Cure Visit.
- a single IgG titer ≥ 1:128 or a fourfold increase or decrease in titer from the Pretherapy Visit to the Test-of-Cure Visit.

Drug Concentration Measurements

Drug concentration measurements for the study medications were not performed for this study.

Statistical Methods Planned in the Protocol and Determination of Sample Size

Statistical and Analytical Plans

All statistical tests were two-tailed with the significance level of 0.05. All p-values were rounded to three decimal places.

Data Sets Analyzed

Enrolled subjects were evaluated and assigned to an appropriate data set for analysis: clinically and bacteriologically evaluable, clinically evaluable (only for clinical responses), Intent-to-Treat and/or All-Treated Subjects. The Clinically and Bacteriologically Evaluable data set, Clinically Evaluable data set, and Intent-to-Treat data set were used for the efficacy analyses. The All-Treated Subjects data set was used for the safety analysis.

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristic variables were analyzed to assess the comparability of the three treatment groups provided by randomization. Quantitative variables, such as age and other pertinent baseline characteristics, were analyzed by a

one-way analysis of variance (ANOVA), while categorical variables, such as gender, race and other pertinent baseline characteristics, were analyzed by the extension of Fisher's exact test to RxC tables.

Efficacy Analyses

The primary treatment comparisons were clarithromycin extended-release (1000 mg QD) versus trovafloxacin (200 mg QD) and clarithromycin immediate-release (250 mg BID) versus trovafloxacin (200 mg QD) regarding the clinical cure rate in the clinically evaluable population. The clinical cure rate, the radiographic resolution/improvement rate, the subject bacteriological eradication rate, and the pathogen eradication rate were analyzed using Fisher's exact test comparing the three treatment groups. Binomial 95% confidence intervals, based on normal approximation for the binomial distribution, were computed for the difference of the above rates between the treatment groups.
In addition, the clinical cure rate, the radiographic resolution rate, and the subject bacteriologic eradication rate were summarized by treatment group according to subgroups such as gender, race, age, tobacco use, and other pertinent factors. Treatment groups were further compared using the Cochran-Mantel-Haenszel test with stratifications by the above variables and by investigator sites. Treatment by investigator sites interaction was also examined; sites with very small numbers of subjects could be combined by regions, as appropriate.
Changes from Evaluation 1 (pretreatment) to Evaluations 2, 3 and 4 in each clinical sign and symptom were summarized by treatment group. The three treatment groups were compared with respect to the percentage of subjects who showed either resolution or improvement in the sign and symptom among the subjects presenting with the sign and symptom. The analysis was performed using Fisher's exact test.
If clinical response and bacteriological response could not be determined due to any reason (for example, missing visits), these subjects were treated as failures in the Intent-to-Treat data set analyses.

Safety Analyses

Subjects who took at least one dose of study drug were included in the safety analyses.
A treatment-emergent adverse event was defined as any adverse event that began or worsened after the first dose of study medication. Treatment-emergent adverse events were summarized by treatment group and compared using Fisher's exact test. The incidence rates were summarized separately for all adverse events and for adverse events excluding those with no relationship to study drugs.
Potentially clinically significant laboratory values were summarized and reviewed by the Abbott medical monitor. Mean changes from baseline for vital signs were summarized.

Determination of Sample Size

The three treatment groups were expected to have comparable efficacy. Assuming the clinical cure rates for the three treatment groups were approximately 85%, 360 Clinically Evaluable Subjects would provide at least 80% power to assure that the two-tailed 95% confidence intervals around the difference in response rate remained within -0.15 or less [clarithromycin IR (1 x 250 mg BID) vs. trovafloxacin (1 x 200 mg QD) or clarithromycin ER (2 x 500 mg QD) vs. trovafloxacin (1 x 200 mg QD)]. Assuming 80% clinical evaluability, approximately 450 subjects were needed, with subject dropouts not being replaced. The -0.15 lower bound was chosen based on "Issues Regarding Adequacy of Trials, Division of Anti-Infective Drug Products, Points to Consider".

Statistical Methods Changes

Restrictions issued by the FDA on June 9, 1999, regarding the use of trovafloxacin, resulted in the premature termination of the study; the anticipated enrollment had not yet been attained.

[redacted] changed the laboratory criteria for *C. pneumoniae* acute infection from a single IgM titer ≥1:32 to a single IgM titer ≥1:10.

Sufficient *H. influenzae* isolates were obtained in this study to support a claim for adding *H. influenzae* to the BIAXIN label for CAP. Subjects assigned to clarithromycin immediate-release and trovafloxacin were compared in this report.

Study Subjects

Disposition of Subjects

One hundred eighty-one (181) subjects were randomized, 95 to clarithromycin immediate-release (IR) and 86 to trovafloxacin.

Overall, 14% (25/181) of the treated subjects prematurely discontinued from the study; 12% (11/95) of subjects discontinued from study in the clarithromycin IR 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 (three clarithromycin IR subjects and two trovafloxacin subjects), insufficient improvement (three clarithromycin IR subjects and one trovafloxacin subject), lost to follow-up (two subjects in each group), noncompliance (one trovafloxacin subject), and "other" reasons (three clarithromycin IR subjects [one subject each withdrew consent, used a confounding antibiotic, and had elevated baseline liver function test results] 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, 7% (12/181) of the subjects prematurely discontinued treatment; 7% (7/95) of subjects discontinued study drug in the clarithromycin IR group and 6% (5/86) of

subjects discontinued study drug in the trovafloxacin group. Three subjects in the clarithromycin IR group and one subject in the trovafloxacin group prematurely discontinued treatment due to adverse events. One subject in the clarithromycin IR group was lost to follow-up. Additionally, three subjects in the clarithromycin IR group and four 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 table below:

Subjects Whose Treatment Was Prematurely Discontinued

Primary Reason for Discontinuation	Investigator	Subject #	Age (years)	Sex	Days on Therapy
Clarithromycin IR Group					
Adverse Event	Jones	1027	37	F	2
	Nadeemullah	1254	49	M	3
	Patel	1069	75	M	1
Lost to Follow-Up	Scheinberg	1063	18	M	unknown
Other	Hosko	1325[a]	39	M	3
	Pinto	1407[b]	56	M	7
	Tarshis	1584[c]	39	M	1
Trovafloxacin Group					
Adverse Event	Degarmo	1087	61	F	5
Other	Gaman	1411[d,e]	24	F	3
	Pinto	1408[d]	49	F	3
	Vrooman	1383[d]	31	M	5
	Patel	1361[c]	39	M	1

a Liver function tests elevated at baseline.
b Another physician prescribed additional antibiotic.
c Patient withdrew consent.
d Sponsor terminated the study.
e Blind not broken.

The treatment assignment blind was broken for four subjects during the study . The blinding envelope for one clarithromycin IR subject (Investigator Perlman, Subject 1360) was opened in error, disclosing the subject's study drug assignment to the study coordinator and staff nurse but not the Principal Investigator. The remaining three subjects (clarithromycin IR: Investigator Perlman, Subject 1420; trovafloxacin: 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. Subjects 1408 and 1383 discontinued prematurely because they were receiving trovafloxacin; however, Subject 1420 continued with protocol-directed study drug and procedures.

Subject 1360 in the clarithromycin IR group was assigned a clinical failure by the investigator but no target pathogen was isolated at pretreatment. Subject 1420 in the clarithromycin IR group was assigned a clinical cure and *C. pneumoniae*, *L. pneumophila*, and *H. parainfluenzae* were isolated at pretreatment; presumed eradication was assigned by Abbott Laboratories.

Efficacy Evaluation

Data Sets Analyzed

Four data sets were analyzed. A "Clinically and Bacteriologically Evaluable" subject population, a "Clinically Evaluable" (clinical outcomes only) subject population, and an Intent-to-Treat subject population were analyzed for efficacy. An "All-Treated Subjects" population was analyzed for safety. Subjects were classified to each of the populations before unblinding.

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.