PROPOSED INDICATIONS:

Treatment of Acute Maxillary Sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae.*

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

Related Material:

NDAs – 50-662; 50-697; 50-698; 50-721

SUBMISSION REVIEWED:

The submission consists of 97 volumes, and the clinical data are contained in volumes 22 to 97 inclusive.

Chemistry, Manufacturing and Controls:

Refer to the chemistry review by Dr. Suresh Pagay.

Human Pharmacokinetics and Bioavailability:

Refer to the pharmacokinetics review by Dr. He Sun.

Microbiology:

Refer to the microbiology review by Dr. Dick King dated July 21, 1999.

Statistical:

Refer to the statistical review by Dr. Joel Jiang.

MEDICAL OFFICER'S REVIEW:

Five randomized, open-label, crossover (two, three, or four period) Phase 1 trials were conducted in the United States to assess the bioavailability of clarithromycin extended-release tablets. These studies have been reviewed by Dr. He Sun. (Please refer to his review)

Two adequate, well-controlled, double-blind clinical trials comparing the efficacy and safety of clarithromycin ER (2X500 mg QD) and clarithromycin IR (500 mg BID) were conducted in the United States and Canada, one in subjects with Acute Exacerbation of Chronic Bronchitis (M97-756) and one in subjects with Acute Maxillary Sinusitis (M97-667). Each of these studies will be reviewed for efficacy and safety.

Clarithromycin Immediate Release

Clarithromycin (A-56268, TE-031) is a novel macrolide antibiotic discovered by Taisho Pharmaceutical Company, Japan, and developed worldwide by Abbott Laboratories. It has a broad spectrum of activity *in vitro* against clinically important gram-positive and gram-negative aerobes and anaerobes, including *Staphylococcus* spp., *Streptococcus* spp., *Haemophilus* spp., *Helicobacter pylori, Neisseria gonorrhoeae, Legionella pneumophila, Campylobacter* spp., *Mycoplasma* spp., *Moraxella catarrhalis,* and *Chlamydia* spp. The *in vitro* activity of clarithromycin is generally 1 $_{\log}2$ dilution more potent than that of erythromycin. In addition, clarithromycin is more acid stable than erythromycin.

The 14-hydroxy metabolite is usually 1 $_{\log}2$ dilution less active than the parent compound except against *Haemophilus influenzae* where it is actually twofold more active. As a result, the 14-OH metabolite appears to significantly contribute to the overall activity of clarithromycin. Therefore, when investigating the tissue disposition of clarithromycin, it is imperative to delineate the respective tissue concentrations of the parent compound and its 14-OH metabolite.

Clarithromycin is active against a variety of organisms that are responsible for acute maxillary sinusitis. In studies conducted at Abbott Laboratories, the minimum inhibitory concentrations (MIC) of the parent drug and the 14-hydroxy metabolite of clarithromycin *in vitro* for 90% minimum inhibitory concentrations (MIC_{90}) of isolates for some of these species were:

Clarithromycin MICs for Upper Respiratory Tract Infection (URTI) Pathogens		
Organism	MIC_{90} (µg/mL) Clarithromycin	MIC_{90} (µg/mL) 14-OH metabolite
Haemophilus influenzae	8.0	4.0
Moraxella catarrhalis	0.03	0.03
Staphylococcus aureus (macrolide susceptible)	0.25	0.25
Streptococcus pneumoniae	0.015	0.015
Streptococcus pyogenes	0.06	0.03

The clinical susceptibility of the target pathogens, particularly in the case of pathogens such as *Haemophilus influenzae*, does not reflect the biological activity of the 14-hydroxy metabolite of clarithromycin, the major circulating active metabolite in man. The 14-hydroxy metabolite is actually twofold more active than clarithromycin against *H. influenzae* and has been shown to exert an additive or synergistic effect against *H. influenzae* in concert with the parent compound. Consequently, the effective MICs of clarithromycin required to inhibit the growth of many of these pathogens *in vivo* are lower than suggested by the *in vitro* findings. When tested in 50% serum *Haemophilus* test medium, the MIC_{90} for clarithromycin and the 14-hydroxy metabolite at their most active combination was 1.0 µg/mL and 0.5 µg/mL, respectively.

Clarithromycin (Biaxin®) has been approved by the FDA/HPB for use in adults for the treatment of mild to moderate infections in the conditions listed below:

> Upper Respiratory Tract Infections (URTI) - Pharyngitis/tonsillitis due to *Streptococcus pyogenes*. Acute maxillary sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis*.
>
> Lower Respiratory Tract Infections (LRTI) - Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae, Moraxella catarrhalis*, or *Streptococcus pneumoniae*. Pneumonia due to *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae*, or *Chlamydia pneumoniae* (TWAR).
>
> Uncomplicated skin and skin structure infections due to *Staphylococcus aureus* or *Streptococcus pyogenes* (abscesses usually require surgical drainage).
>
> Disseminated mycobacterial infections due to *Mycobacterium avium* and *Mycobacterium intracellular*.

BIAXIN®Filmtab® tablets in combination with PRILOSEC®/LOSEC® (omeprazole) capsules are indicated for the treatment of subjects with an active duodenal ulcer associated with *Helicobacter pylori* infection. The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence. An additional approved

therapy for this indication includes Biaxin in combination with lansoprazole plus amoxicillin.

Clarithromycin has been administered in clinical trials to over 10,000 subjects worldwide. At doses of 250 to 500 mg twice daily, clarithromycin has been shown to be safe and effective in the treatment of upper and lower respiratory tract infections as well as skin infections. The most common adverse events observed in the use of clarithromycin in adults included headaches, abnormal taste, dyspepsia, abdominal pain, nausea and diarrhea.

Clarithromycin Extended Release

Clarithromycin immediate release (IR) tablets are currently administered on a twice a day basis for treatment of a variety of infectious diseases. Abbott has developed an extended release (ER) formulation that will provide sufficient clarithromycin throughout the day to treat the same infections but allows the dose to be administered only once per day. The formulation in this study is of a matrix-type extended release tablet, which relies on a polymer to control the rate of drug release over time. The development of the extended release clarithromycin tablet is based upon the premise that once-a-day dosing will facilitate dosing compliance in a patient population.

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal dose of immediate-release clarithromycin tablets (500 mg twice daily), clarithromycin ER tables (2 x 500 mg once daily) provide lower and later steady-state peak plasma concentrations but equivalent 24-hour AUCs for both clarithromycin and its microbiologically active metabolite, 14(R)-hydroxy-clarithromycin. In healthy human subjects, steady-state peak plasma clarithromycin concentrations of approximately 2 to 3 μg/mL were achieved about 5 to 8 hours after oral administration of 2 x 500 mg clarithromycin ER tablets once daily. For 14(R)-hydroxy-clarithromycin, steady-state peak plasma concentrations of approximately 0.8 μg/mL were attained about 6 to 9 hours after oral administration of 2 x 500-mg clarithromycin ER tablets once daily.

In a previous sinusitis study, M90-417, clarithromycin IR had a clinical cure rate of 64% and an improvement rate of 33%, a bacteriological cure rate of 87%, and a radiological success rate (resolution or improvement) of 88% [NDA 50-662 (S-004)]. In this study, the clinical efficacy (clinical cure) and safety of clarithromycin extended release tablets were compared with those of clarithromycin immediate release tablets in the treatment of acute maxillary sinusitis.

In previous AECB Studies M90-418, M90-434, and M90-435, clarithromycin IR had a clinical cure rate of 51%, a clinical improvement rate of 44%, and a bacteriological cure rate of 90% [NDA 50-662 (S-004)]. In this study, the efficacy and safety of clarithromycin extended release tablets were compared with those of clarithromycin immediate release tablets in the treatment of AECB.

Review of Study M97-667:

Comparative Study of the Safety and Efficacy of Clarithromycin Immediate Release and Clarithromycin Extended Release in the Treatment of Acute Maxillary Sinusitis in Adults

Study Identification:	M97-667
Study Phase:	3
Name of Drug:	Clarithromycin Extended Release (Abbott-56268)
Indication:	Acute Maxillary Sinusitis
Structure:	Randomized
Blinding:	Double-Blind
Duration of Therapy:	14 days, clarithromycin extended release (ER); 14 days, clarithromycin immediate release (IR)
Investigators:	37 investigators (multicenter) United States (US) and Canada
Method of Subject Assignment:	Subjects were randomly assigned in a 1:1 ratio to receive either clarithromycin extended release tablets, 1 gram (2-500 mg tab) once a day (QD) for 14 days, or clarithromycin immediate release tablets, 1 gram, 500 mg twice a day (BID) for 14 days.
Study Initiation:	March 13, 1998
Study Completion:	October 1, 1998.

Synopsis

Name of Company: Abbott Laboratories		
Name of Finished Product: Clarithromycin Extended Release (ER) (A-56268)		
Name of the Active Ingredient: 6-0-methylerythromycin A		
Title of Study: Comparative Study of the Safety and Efficacy of Clarithromycin Immediate Release and Clarithromycin Extended Release Tablets in the Treatment of Acute Maxillary Sinusitis in Adults		
Investigator(s): 37 investigator sites enrolled subjects.	**Study Center:**	
Publication (reference): N/A		
Study Period (years): Date of First Enrollment: March 13, 1998 Date of Last Completed: October 1, 1998	**Phase of Development:** 3	

Objectives: The objective of this study was to compare the safety and efficacy of orally administered clarithromycin immediate release and clarithromycin extended release (ER) in the treatment of subjects with acute maxillary sinusitis who were suitable candidates for oral antibiotic therapy.

Methodology:
This was a Phase 3, double-blind, randomized, controlled, multicenter study in outpatient subjects with acute maxillary sinusitis. Subjects were randomly assigned in a 1:1 ratio to receive either:
clarithromycin extended release (ER) tablets, 500 mg x 2 QD for 14 days, or
clarithromycin immediate release (IR) tablets, 500 mg BID for 14 days.

Approximately 132 subjects were planned to be enrolled per treatment group. Subjects were contacted by telephone once during Study Days 3 to 5 to assess their status and decide if a during-treatment visit (Visit 2) was necessary. Subjects returned for Visit 3 within 48 hours posttreatment. Subjects returned once during Study Days 24-31 (Visit 4) for a test-of-cure visit. If the subject did not have a Visit 4 procedure completed or signs and symptoms had improved but clinical cure could not be assigned at Visit 4, the subject returned 4 weeks after the last dose of study drug for Visit 5. Safety was evaluated throughout the subject's study participation by periodic laboratory tests, posttreatment physical examination, and monitoring of adverse events.

Number of Subjects (planned and analyzed):	Clarithromycin ER	Clarithromycin IR
Number of Subjects Planned	132	132
Number of Subjects Randomized and Treated	142	141
Subjects Included in the Intent-to-Treat Analyses	138	136
Subjects Excluded from Intent-to-Treat Analyses	4	5
Subjects Included in the Clinically Evaluable Analyses	122	123
Subjects Excluded from Clinically Evaluable Analyses	20	18
No clinical evaluation at Test-of-Cure Visit	9	7
Selection criteria not met		
Chronic maxillary sinusitis	2	3
Negative sinus x-ray at pretreatment	1	1
Diagnosis of frontal, ethmoid, or sphenoid sinusitis	1	1
Other (e.g., noncompliance, confounding meds, etc.)	7	6
Subjects Included in the Safety Analyses	142	141

Name of Company: Abbott Laboratories		
Name of Finished Product: Clarithromycin Extended Release (ER) (A-56268)		
Name of the Active Ingredient: 6-0-methylerythromycin A		

Diagnosis and Main Criteria for Inclusion:
Males and females 12 years of age or older were enrolled if they had a presumptive diagnosis of acute maxillary sinusitis which was suitable for oral antibiotic therapy, with at least one of the following clinical signs and symptoms (facial pain/pressure/tightness typically over the maxillary sinuses; purulent nasal discharge) which had been present at least 7 days but no longer than 28 days, and diagnosis was confirmed by sinus x-ray.

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

Test Product	Dose	Mode of Administration	Finishing Lot Batch Number USA	Finishing Lot Batch Number Canada
Clarithromycin extended release tablets	500 mg x 2 QD for 14 days	Oral	33-266-S2 40-304-S2	40-313-S2

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

Test Product	Dose	Mode of Administration	Finishing Lot Batch Number USA	Finishing Lot Batch Number Canada
Clarithromycin immediate release tablets	500 mg BID for 14 days	Oral	36-643-S2 40-306-S2	40-315-S2

Duration of Treatment: 14 days of treatment

Criteria for Evaluation:
Clinically Evaluable Analysis: All of the following criteria were to be satisfied for a subject to be considered eligible for clinical efficacy analysis:

- The subject had taken study drug for a minimum of 3 full days to be a clinical failure; to be a clinical cure, the subject had taken at least 80% of prescribed study medication.
- The subject did not take any antimicrobial therapy from 21 days prior to study initiation up through the last posttreatment evaluation, unless the subject was a clinical failure or the antimicrobial was not considered to have an effect on the sinus infection before unblinding.
- The subject did not receive any interfering therapeutic procedures or any other potentially confounding intervention during the study, unless the subject was considered a clinical failure.
- Sinus x-ray and signs/symptoms of infection were evaluated at least 7 days posttreatment, unless the subject was considered a clinical failure.
- The subject did not violate any selection criteria, unless the violation was considered not to affect the efficacy evaluation before unblinding.

Intent-to-Treat Analysis: All subjects who took at least one dose of study medication, had at least one sign or symptom of sinusitis, had a confirmed diagnosis of acute maxillary sinusitis by radiographic examination, and had no evidence of chronic maxillary sinusitis were included in the intent-to-treat population.

All Treated Subjects Analysis: All subjects who received at least one dose of study medication were included in the all treated subjects safety analyses.

Name of Company: Abbott Laboratories		
Name of Finished Product: Clarithromycin Extended Release (ER) (A-56268)		
Name of the Active Ingredient: 6-0-methylerythromycin A		
Statistical Methods: Statistical tests between treatment groups were two-tailed with the 0.05 significance level. Exact binomial 95% confidence intervals (CI) were constructed for the two treatment groups for each efficacy variable. Binomial 95% CI were computed for the difference between treatment groups (extended release – immediate release) in efficacy variables. Clinical cure rates were the primary efficacy variable. Radiographic resolution responses and clinical signs/symptoms were secondary efficacy variables.		

Investigative Sites

Abbott Laboratories [redacted] selected investigative sites. A total of 44 investigators in the US and Canada were recruited to perform the study and receive study drug supplies; 37 of these investigators enrolled subjects into the study. The distribution of all enrolled subjects for each investigator is presented in table below:

Distribution of All Enrolled Subjects by Investigator[a]

	Clarithromycin Group			Clarithromycin Group	
Investigator	Extended Release	Immediate Release	Investigator	Extended Release	Immediate Release
Alwine	1	0	Matz	7	8
Audet	2	2	McCarty	3	3
Barnes	2	2	McCluskey	8	8
Blatter	2	3	McNellis	3	2
Blattner	2	2	Miller	2	0
Cohen	2	2	Murray	6	7
Dixon	12	12	Pappas	6	4
Dorfner	0	1	Rabinowitz	2	2
Douglas	0	1	Sack	3	3
Fidelholtz	1	2	Schultz	4	3
Ganier	6	7	Schworer	18	18
Gilman	1	1	Settipane	1	1
Gray	4	2	Shah	3	2
Gugenheim	0	2	Smith	6	7
Halverson	1	0	Sokolowski	1	1
Herron	3	4	Solomon	10	11
Hopland	6	6	Sperling	2	2
Imam	4	3	Wald	5	5
Lentnek	3	2	**Total**	**142**	**141**

a One additional subject (6219) from site 13577 (Smith) was enrolled but did not take any study drug and was excluded from all analyses.

Study Objectives

The study objective was to compare the safety and efficacy of orally administered clarithromycin immediate release and clarithromycin extended release (ER) in the treatment of adult subjects with acute maxillary sinusitis who were suitable candidates for oral antibiotic therapy.

Investigational Plan

Overall Study Design and Plan - Description

This was a Phase 3, randomized, double-blind, multicenter study in outpatients. Approximately 45 investigators were to enroll approximately 264 subjects (132 subjects per treatment group). Subjects were randomly assigned in a 1:1 ratio to receive for 14 days either 2 X 500 mg of clarithromycin extended release once a day (QD) plus placebo for clarithromycin immediate release or 500 mg of clarithromycin immediate release twice a day (BID) plus placebo for clarithromycin extended release. In addition, all subjects were supplied with 0.05% oxymetazoline nasal spray to be used in conjunction with clarithromycin during the first 3 days of study drug therapy.

The nature of the study was explained to subjects (or the parents/legal guardians of minor subjects) who presented with clinical signs and symptoms of acute maxillary sinusitis. After informed consent was obtained, a sinus x-ray was performed to confirm the diagnosis. If x-ray results were positive, the subject was enrolled in the study, a medical history was obtained, and physical examination, vitals signs assessment, and laboratory evaluations were performed.

Clinical and radiologic assessments were performed prior to initiating study drug. The severity of the clinical signs and symptoms of acute maxillary sinusitis was documented. Eligible subjects were randomly assigned in a 1:1 ratio to receive either:

clarithromycin extended release tablets 500 mg x 2 QD for 14 days (plus clarithromycin immediate release placebo)	OR	clarithromycin immediate release tablets 500 mg BID for 14 days (plus clarithromycin extended release placebo)

Subjects were contacted by telephone for interview by the investigator or study coordinator once during Study Days 3 to 5 to determine whether signs and symptoms of maxillary sinusitis had improved or if a during-treatment visit (Visit 2) was necessary. Subjects returned to the clinic within 48 hours posttreatment (Visit 3) and once during Study Days 24 to 31 (Visit 4). Clinical response was assessed at Visit 4 (Test-of-Cure). If the subject's signs and symptoms had improved at Visit 4 but clinical cure could not be assigned or if Visit 4 procedures were missing, the subject was to return 4 weeks after the last dose of study drug (Visit 5) for final assessments. Safety was evaluated through

periodic laboratory tests, posttreatment physical examination, and monitoring of adverse events.

The total duration of each subject's participation in the study was approximately 4 to 6 weeks, depending on whether or not Visit 5 was required. The total duration of the study from first enrollment to last subject follow-up was approximately 8 months.

No long-term follow-up beyond Visit 4 or Visit 5 was planned unless there was an unresolved adverse event. In the case of an unresolved adverse event at the final scheduled visit, the subject was followed until resolution of the event or the investigator determined that resolution was unlikely (i.e., event was chronic) and the event was stable.

Assuming a clinical evaluability rate of 90%, approximately 264 subjects were to be enrolled to obtain 240 eligible subjects.

A complete study schematic is presented in Table below:

Study Schematic

Evaluation Procedure	Visit 1 (Study Day 1)#	Telephone Contact (Study Days 3 to 5)	Visit 2 (Study Days 3 to 5) (if clinically indicated by telephone contact)	Visit 3 (Within 48 hours post-treatment) (Termination Visit if indicated by Visit 2)	Visit 4 Study Day 24-31 (Test-of-Cure)	Visit 5 4 Weeks After Last Dose If Subject Did Not Have Visit 4
Informed Consent	X					
Pregnancy Test	X					
Medical History	X					
Complete Physical Examination	X			X		
Vital Signs	X			X	X	X
Clinical Signs and Symptoms	X		X	X	X	X
Sinus X-ray	X		X*	X*	X	X
Clinical Laboratory Tests	X			X&		
Compliance Check				X		
Monitor Concomitant Medications	X	X	X	X	X	X
Subject Number and Assignment to Treatment Regimen	X					
Dispense Study Drug	X					
Subject Instructions	X					
Monitor Adverse Events	X	X	X	X	X	X
Schedule Next Visit		X*			X^	
Assign Clinical Response					X	X
Subject Status		X				

Screening procedures could have been performed within 48 hours prior to study drug administration.
* If clinically indicated.
& Clinically significantly abnormal laboratory values were followed until they normalized, stabilized or became explicable due to a non-therapy problem.
^ The investigator instructed the subject to return for Visit 5 evaluation if the subject did not have Visit 4 procedures completed or if signs and symptoms had improved but clinical cure could not be assigned at Visit 4.

Inclusion Criteria

The subject had to meet all of the following criteria:

- Diagnosed as having acute maxillary sinusitis, which was suitable for oral antibiotic therapy. The diagnosis must have been based on the following evidence:
  - A sinus x-ray performed within 72 hours pretreatment confirming the diagnosis of acute maxillary sinusitis.
  - At least one of the following clinical signs and symptoms of acute maxillary sinusitis the onset of which had been at least 7 days prior to but no longer than 28 days before the screening visit: facial pain/pressure/tightness typically over the maxillary sinuses, a purulent nasal discharge.
  - Subject could have had cough, headache, nasal obstruction, bad breath, change in perception of smell, toothache, tearing, periorbital swelling.
- Twelve years of age or older, and weighing at least 34 kilograms (75 pounds).
- 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, and
    - 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.
- The subject had voluntary signed the Informed Consent Form after the nature of the study had been explained, prior to the performance of any study-related procedure. Subjects between 12 and 18 years of age also required written consent from a parent or legal guardian.

Exclusion Criteria

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

- Chronic maxillary sinusitis (i.e., subjects with three or more episodes of sinusitis in the preceding 12 months, or with symptoms lasting longer than 28 days prior to screening).
- Females who were pregnant or lactating.
- Diagnosis of frontal, ethmoid or sphenoid sinusitis.
- Subjects who had:
  - History of hypersensitivity to sympathomimetic amines (e.g., oxymetazoline HCl or phenylephrine) or any condition which contraindicated the use of oxymetazoline nasal spray.
  - Concurrent treatment with a systemic decongestant and/or antihistamine other than as specified in this protocol.
  - Any infection which necessitated the use of a concomitant antibiotic.
  - Subject who had a history of hypersensitivity or allergy to macrolides.

  - Treatment with a systemic antibiotic within 3 weeks prior to study drug administration or treatment with a long-acting injectable antibiotic (e.g., penicillin [redacted] within 30 days prior to study drug administration.
  - Treatment with an investigational drug within 4 weeks prior to study administration.
  - Concomitant warfarin therapy unless prothrombin times could be adequately monitored.
  - Previous treatment in this study.
  - Immunocompromised host status.
  - Any anatomical abnormalities of significant sinuses.
  - Subjects residing at chronic care facilities.
- Subjects who were currently receiving or who were likely to require any of the following medications:
  - Concomitant theophylline or any theophylline analog, carbamazepine, diazepam, warfarin, ergotamine, phenytoin, or digoxin unless clinically monitored for signs and symptoms of toxicity during the study.
  - [redacted] astemizole (Hismanal®), cisapride (Propulsid®), or primozide (Orap®) until 48 hours after last dose of study drug.
  - Any other investigational agent.
  - Intra-nasal steroid use. Dermal use was allowed.
  - Oral or parenteral steroid (at a dose equivalent to prednisone ≥10 mg) and, if the subject's dose was <10 mg, the dose must have been stable, had not changed in the last 6 weeks, and the subject would not require an increase during the period of study. Orally inhaled steroids were allowed.
  - Any immunosuppressant drug.
  - Other systemic antimicrobial therapy.
- Subjects with one of the following concurrent illnesses:
  - Severe or complicated lower respiratory tract infection (LRTI).
  - Pneumonia (positive chest x-ray at screening).
  - Positive chest x-ray evidence of active tuberculosis, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, pleural effusion or consolidation.
  - Severe compromised respiratory status.
  - Clinically significant abnormal pretreatment laboratory result.
  - Known significant renal or hepatic impairment.

Removal of Subjects from Therapy

If study drug therapy was prematurely discontinued, the primary reason for discontinuation was to be recorded on the appropriate CRF.

A subject was withdrawn from the study immediately if any of the following occurred:
- There was insufficient improvement in the subject's sinusitis. The clinical response of the subject was rated as a "Clinical Failure" if the subject had at least 3 days of therapy.
- The investigator decided that discontinuation was in the best interest of the subject.
- Pretreatment laboratory result was clinically significantly abnormal.
- Selection criteria were violated after the subject started study drug.

- The subject or parent/guardian requested withdrawal from the study.

A subject who was prematurely withdrawn from the study was instructed to return to the investigator's office for a posttreatment evaluation within 48 hours of the last dose of study drug. A clinical response to therapy was assigned. This evaluation was to be made prior to the institution of any new therapeutic modalities, but was not in any way to delay institution of any new therapeutic modalities which, in the investigator's opinion, were necessary.

If the subject discontinued from the study after the full course of therapy, but prior to the completion of all study procedures, the reason for the discontinuation was to be recorded on the appropriate CRF.

Subject dropouts were to be documented on the appropriate CRF. Post-study physical examination and laboratory analysis were obtained as soon as possible after study discontinuation. Dropouts 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 two treatment regimens. Subjects received either a 500 mg tablet of clarithromycin immediate release BID (and extended release placebo) or 2 X 500 mg (two 500-mg tablets) of clarithromycin extended release QD (and immediate release placebo). The anticipated duration of therapy was 14 days. The medication was to be taken under fed conditions, within 2 hours after eating or within 1 hour before eating.

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 ratio to receive either clarithromycin immediate release tablets and extended release placebo or clarithromycin extended release tablets and immediate release placebo. All subjects were assigned identification numbers in ascending numerical sequence as they were enrolled into the study. A label, which contained the drug assignment for each subject, was provided to the investigator in a separate sealed envelope. The sealed envelope was retained by the study coordinator as part of the CRF. 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 24 hours of the blind being broken. The date, time, and reason that the blind was broken were to be recorded on the appropriate CRF.

Prior and Concomitant Therapy

If any medication (including over-the-counter medication) was taken during the course of the study, it was to be recorded on the appropriate CRF along with dosage information, dates of administration, and reason for use. This included any medication taken within 4 weeks prior to the first dose through the last visit.

Any diagnostic, therapeutic, or surgical procedure, such as sinus drainage, was to be recorded including the date, time, indication, description of the procedure, and any clinical findings.

Subjects were instructed not to take any medication other than study drug until after Visit 4 (if it was the last visit) or Visit 5. Because of the potential interaction with clarithromycin, subjects were not allowed to take astemizole, pimozide, or cisapride while on study medication. For the same reason, subjects were not allowed to take theophylline, carbamazepine, diazepam, ergotamine, dihydroergotamine, triazolam, phenytoin, cyclosporin, hexobarbital, unless the subject was clinically monitored for signs and symptoms of toxicity. While on study medication, subjects were also not allowed to take concomitant warfarin therapy unless prothrombin time could be adequately monitored.

Treatment Compliance

In order to document compliance with the treatment regimen, subjects were instructed to return the bottles of medication (even if empty) to the study coordinator. The study drug bottles were retained by the study coordinator for both treatment groups. Compliance with each study medication was documented by the study coordinator on the appropriate CRF. An exact start and stop date and the number of tablets remaining were recorded on the CRF. If the number of tablets taken and the number of tablets returned did not add up to the number of tablets dispensed, an explanation was to be provided on the CRF.

An overall accountability of study medication was performed and verified by the 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 acute sinusitis, sinus x-ray, and assignment of clinical and radiographic response were performed. Visit 4 was designated the Test-of-Cure Visit. If subjects were not seen at Visit 4, or subjects had improvement in signs and symptoms at Visit 4 but clinical cure could not be assigned, Visit 5 was scheduled. Adverse events and concomitant medications were monitored throughout the study. A complete physical examination with vital signs was performed at Visits 1 and 3. Vital signs were also assessed at Visits 4 and 5. Any clinically abnormal observations arising during the treatment period were followed to resolution. Hematology and serum chemistry tests were performed at Visits 1 and 3.

Efficacy Procedures

Sinus X-ray

An x-ray of the sinus(es) (three projections) was obtained at pretreatment (Visit 1) within 72 hours prior to initiation of study drug therapy to confirm the diagnosis of acute maxillary sinusitis and also at Visit 4 (Visit 5 if scheduled). X-ray findings interpreted by the investigator were accepted. If clinically indicated, x-ray was also performed at Visit 2 and Visit 3.

The following x-ray findings were reported on the CRF as absent or present:

- clear (subjects with clear sinus x-rays were not eligible for enrollment)
- opacification
- mucosal thickening
- air fluid level

The investigator indicated the involved sinus (i.e., left and/or right) and summarized the x-ray findings on the CRF. In addition, the investigator assigned a radiographic response at Visit 4 or Visit 5 (if radiographic response was not assigned at Visit 4).

Clinical Signs and Symptoms

The investigator asked the subject to classify the severity of sinus headache, pain and tenderness as absent, mild, moderate or severe. In addition, the clinical signs and symptoms of facial erythema, nasal congestion, facial swelling, fever, and purulent nasal discharge were classified as absent or present at Visit 1. The investigator assessed the subject's clinical signs and symptoms and assigned a clinical response based on the criteria at Visit 4 or Visit 5.

Telephone Contact

One time during Study Days 3 to 5, the investigator (or study coordinator) was to contact the subject by telephone to assess and record the subject's status by having the subject answer the following questions:

1. Had the subject's condition changed since Visit 1? (improved/no change/ worsened)
2. Had the subject complied with dosing procedures? (yes/no)
3. Had the subject experienced any adverse events? (record adverse event data)
4. Had the subject taken any concurrent medications? (record concurrent medication data)

At this time the investigator decided if a during-treatment visit (Visit 2) was necessary.

Safety Procedures

The safety of the study drugs was monitored throughout the study by concomitant medications, vital signs, and assessment of adverse events. Physical examination and

laboratory evaluations were performed prior to treatment (Visit 1) and within 48 hours posttreatment (Visit 3). Subjects were reminded to contact the investigator if they felt their condition had not improved.

Laboratory Procedures

Laboratory evaluations (hematology and serum chemistry) were performed by [redacted] All blood samples were collected and handled in accordance with accepted laboratory procedures.

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

Any clinically significantly abnormal value was to be followed until it returned to normal, stabilized, or became explainable due to a nontherapy problem.

Other Drug Levels (If Applicable)

Subjects who were receiving theophylline, carbamazepine or other allowable drug(s) were clinically monitored for signs and symptoms of toxicity. Since this was medical practice and not part of this study, the levels were not reported.

Pregnancy Test (If Applicable)

If the subject was female and of childbearing potential (postmenopausal for less than 1 year or had not had a hysterectomy), a negative urine HCG pregnancy test result was required within 2 days prior to enrollment.

Medical History
A complete medical history was obtained at pretreatment including:

- history of nasal polyps
- history of deviated septum
- history of allergic rhinitis
- number of sinus infections in the past 12 months (including the present infection; subjects with three or more sinus infections in the preceding 12 months were not enrolled in the study)
- history of gastrointestinal disturbances
- history of any otorhinolaryngological procedure.

Physical Examination
A complete physical examination was performed, including the following vital signs:

- blood pressure (after sitting 3 minutes)
- pulse (30 seconds)
- body temperature
- height (Visit 1 only) and weight.

Adverse Events
Adverse events were defined as any unexpected event(s) such as sign(s), symptom(s), and/or laboratory finding(s) associated with the use of a drug 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 through the final visit (Visit 5).

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), 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, which were considered clinically significant, were followed to a satisfactory resolution.

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 could 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 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).

Serious Adverse Events
Any adverse event that resulted in any of the following criteria was considered a serious adverse event (SAE):

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

A serious adverse event was any 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 may have been considered a serious adverse experience when, based upon appropriate medical judgment, they jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above, i.e. 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. Examples of such medical events included allergic bronchospasm

requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did 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.

Deaths
Any death that occurred during the study or within 30 days of discontinuation from the study was to be 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 and laboratory procedures that were used in this study are standard and generally accepted.

Efficacy Variables

Primary Variable

The primary efficacy variable for this study was the clinical cure rate. The following definition was used to define the primary efficacy variable:

Clinical Cure Rate — Percentage of evaluable subjects who had a response of clinical cure.

Assignment of Clinical Response

At Visit 4 or Visit 5 (if applicable) the investigator compared the clinical signs and symptoms with those obtained at Visit 1 and assigned a clinical response. Radiographic results were also considered when assigning a clinical response. The clinical response was rated using the following definitions:

Clinical Cure — (Applicable for Visit 4 and Visit 5) The pretreatment signs and symptoms of the infection resolved/improved and at least improvement was observed in the radiographic appearance of the sinuses and no further antibiotic therapy was required.

Clinical Failure — (Applicable for Visit 4 and Visit 5) The pretreatment signs and symptoms of the infection did not improve or worsened, including the appearance of new symptoms, and the subject was treated with additional antimicrobials. If a subject was classified a failure at the on-therapy or end-of-therapy visit, this evaluation of failure was carried forward into the final visit outcome; that is, for the purpose of calculating outcome rates, once a failure, always a failure.

Indeterminate	Clinical response to therapy could not be determined. A reason was indicated on the CRF.

Investigator Additional Assessment of Clinical Response

Principal investigators were sent a letter (October 14, 1998) requesting an additional assessment of subject clinical response, using a modified definition of clinical cure for acute maxillary sinusitis based on updated FDA guidelines (July 1998). The following definition of clinical cure was used for the additional assessment:

Clinical Cure	The pretreatment signs and symptoms of the infection resolved/ improved and at least no worsening (no change) was observed in the radiographic appearance of the sinuses and no further antibiotic therapy was required.

Secondary Variables

The secondary efficacy variables for this study were the radiographic resolution rate and the radiographic success rate. The following definitions were used to define the secondary efficacy variables:

Radiographic Resolution Rate	Percentage of evaluable subjects who had a response of radiographic resolution.
Radiographic Success Rate	Percentage of evaluable subjects who had a response of radiographic resolution or improvement.

Assignment of Radiographic Response

The investigator compared the x-ray findings during and post-study (test-of-cure) with those obtained at Visit 1 and assigned a radiographic response using the following definitions:

Resolution	Complete clearing of x-ray evidence of acute maxillary sinusitis.
Improvement	Reduction in the x-ray evidence of acute maxillary sinusitis in comparison to the Visit 1 (pretreatment) x-ray.
No Change	No change in the x-ray evidence of acute maxillary sinusitis in comparison to the Visit 1 (pretreatment) x-ray.
Worsening	Worsening of x-ray evidence of acute maxillary sinusitis in comparison to the Visit 1 (pretreatment) x-ray. Subjects who exhibited x-ray evidence worse than at pretreatment were immediately discontinued from the study.

In addition, at posttreatment the investigator compared each clinical sign and symptom of maxillary sinusitis with those documented at pretreatment and determined if the sign and symptom had resolved or improved. These signs and symptoms could have included sinus headache, sinus pain, sinus tenderness, facial erythema, nasal congestion, facial swelling, purulent nasal discharge, and fever.

Drug Concentration Measurements

Drug concentrations were not measured in 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. The primary comparison was clarithromycin extended release versus clarithromycin immediate release. 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 evaluable, intent-to-treat, and/or all treated subjects. The clinically evaluable data set was used for the primary efficacy analysis, with the intent-to-treat population supporting the efficacy results. 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 two 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 Fisher's exact test, or its extension to RxC tables.

Efficacy Analyses

The primary efficacy variable was the clinical cure rate and the secondary efficacy variables were the radiographic resolution rate and radiographic success rate. These variables were analyzed using Fisher's exact test comparing the two treatment groups. Binomial 95% confidence intervals, based on normal approximation for the binomial distribution, were computed for the difference of the above rates (extended release - immediate release) between the treatment groups.

In addition, the efficacy variables were summarized by treatment group according to subgroups such as country, investigator site, gender, race, age, weight, nasal exam result, infection status at pretreatment, overall clinical condition at pretreatment, number of

acute sinus infections within the past 12 months, treatment duration, and treatment compliance. Treatment groups were further compared using the Cochran-Mantel-Haenszel test with stratifications by the above variables. Treatment by investigator sites interaction was also examined but no formal statistical test was used; sites with very small numbers of subjects were planned to be combined by regions, as appropriate.

Changes from pretreatment to posttreatment visits in each clinical sign and symptom were summarized by treatment group. The two 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 analyses were performed with Fisher's exact test.

If clinical response could not be determined due to any reason (for example, missing visits), it was treated as a failure in the intent-to-treat subjects data set analysis and was excluded from the clinically evaluable data set.

Safety Analyses

Subjects who took at least one dose of study drug were included in the safety analyses.

Adverse Events

All treatment-emergent adverse events (i.e., those that began or worsened in severity after randomized drug was administered) were mapped to the COSTART III dictionary. Subjects reporting more than one adverse event for a particular COSTART term were counted only once for that term using the most severe incident. If more than one type of event occurred within a body system for a subject, the subject was counted only once when summarizing by body system. Adverse event incidence rates, with and without concurrent conditions (i.e., events which were judged not related or probably not related to study drug), were summarized by treatment group and compared using Fisher's exact test. In addition, serious adverse events and discontinuations due to adverse events were summarized by treatment group.

Laboratory Data

Clinical laboratory data were collected at Visit 1 and Visit 3. Results were listed for each subject and values outside the laboratory reference range were identified. Potentially clinically significant laboratory values were summarized within each treatment group.

Vital Signs

Mean changes from baseline in vital signs data were summarized within each treatment group. No formal statistical tests were performed.

Determination of Sample Size

The two treatment groups were expected to have comparable efficacy. Assuming the clinical cure rates for both treatments were approximately 65% (based on Study M90-417, NDA 50-662 [S-004]), 240 clinically evaluable subjects would provide 80%

power to assure that two-tailed 95% confidence intervals around the difference in response rate crossed zero and remained within a lower bound of -0.20 or less. A -20% lower bound was chosen based on Issues Regarding Adequacy of Trials, Division of Anti-Infective Drug Products, Points to Consider. Assuming 90% evaluability, approximately 264 subjects were needed.

Statistical Methods

Because of an update to the FDA Guidelines for Industry (July 1998) regarding the Clinical Cure Definition for Acute Maxillary Sinusitis, principal investigators were asked to complete an additional evaluation of subjects, using the following revised definition of clinical cure (letter to principal investigators, October 14, 1998):

> The pretreatment signs and symptoms of the infection resolved/improved and at least no worsening (no change) is observed in the radiographic appearance of the sinuses and no further antibiotic therapy is required.

This additional clinical cure rate was analyzed in the same way as the original defined clinical response. In addition, since no obvious treatment by site interaction was observed, sites with small numbers of subjects were not combined.

Study Subjects

Disposition of Subjects

A total of 284 subjects were randomized in the study and a total of 283 subjects took study drug; 142 subjects took clarithromycin extended release (ER) and 141 subjects took clarithromycin immediate release (IR).

Overall, 18% (52/283) of the subjects prematurely discontinued from the study; 23 (16%) subjects discontinued from the clarithromycin ER group and 29 (21%) subjects discontinued from the clarithromycin IR group. The most frequent reason for discontinuation from the study in both treatment groups was adverse event, cited by 4% (6/142) of subjects in the clarithromycin ER group and 8% (11/141) of subjects in the clarithromycin IR group. Other reasons for discontinuation in the clarithromycin ER and clarithromycin IR groups included lost to follow-up (six subjects and four subjects, respectively), investigator request (five subjects and two subjects, respectively), "other" reasons (two subjects and four subjects, respectively), subject noncompliance (two subjects and three subjects, respectively), subject request (one subject and three subjects, respectively), and insufficient improvement (one subject and two subjects, respectively). In addition, one subject was discontinued from the clarithromycin IR group because it was discovered that selection criteria were violated after enrollment.

Overall, 10% (28/283) of the subjects prematurely discontinued treatment; nine (6%) subjects in the clarithromycin ER group and 19 (13%) subjects in the clarithromycin IR group. The most frequent reason for discontinuation from both treatment groups was

adverse event, cited by 4% (6/142) of the subjects in the clarithromycin ER group and 8% (11/141) of the subjects in the clarithromycin IR group. One subject (Lentnek, Subject 6176) returned for all scheduled visits after premature discontinuation from treatment. Three subjects in the clarithromycin ER group and one subject in the clarithromycin IR group were lost to follow-up. Seven additional subjects discontinued treatment in the clarithromycin IR group: three subjects requested withdrawal, two subjects were discontinued due to noncompliance, and one subject each discontinued due to insufficient improvement and violation of selection criteria after enrollment.

The details of the subjects who prematurely discontinued treatment are presented by treatment group in Table below:

Subjects Whose Treatment Was Prematurely Discontinued					
Primary Reason for Discontinuation	Subject #	Age (years)	Sex	Days on Therapy	Investigator
Clarithromycin Extended Release Group					
Adverse Event	6304	28	F	4	Dixon
	6284	41	M	8	McCluskey
	6220	63	M	5	Smith
	6314	33	F	9	Smith
	6232	48	M	6	Solomon
	6352	76	M	6	Solomon
Lost to Follow-Up	6464	23	M	3	McCarty
	6150	33	F	3	Schultz
	6446	58	M	12	Sokolowski
Clarithromycin Immediate Release Group					
Adverse Event	6303	69	F	7	Dixon
	6543	37	F	4	Dixon
	6546	25	M	3	Dixon
	6254	43	M	3	Imam
	6176	20	F	5	Lentnek
	6265	33	M	3	Matz
	6147	24	F	12	McCluskey
	6238	37	M	7	McNellis
	6235	35	F	1	Solomon
	6351	17	M	2	Solomon
	6590	30	F	10	Wald
Lost to Follow-Up	6120	57	F	15	Pappas
Subject Request	6424	32	F	6	Blattner
	6218	45	F	6	Smith
	6311	35	F	8	Smith
Subject Noncompliance	6292	58	F	16	Murray
	6317	52	F	8	Murray
Insufficient Improvement	6102	16	M	4	Solomon
Selection Criteria Violated After Enrollment	6288	37	M	9	Murray

Sixteen of the 17 subjects who were discontinued from treatment were classified as evaluable for the clinically evaluable data set, and they were considered to be clinical failures. One subject (6176) was classified as not evaluable for the clinically evaluable data set, and the subject's response was considered to be indeterminate. Lentnek Subject 6176 took less than 80% of study drug, and returned for Visit 4 at Study Day 35 with

clinical resolution of signs and symptoms and radiographic resolution of acute maxillary sinusitis.

The study blind was not broken for any subject during the study.

Efficacy Evaluation

Data Sets Analyzed

Three data sets were analyzed. A "clinically evaluable" subject population and an "intent-to-treat" subject population were analyzed for efficacy. An "all treated subjects" population was analyzed for safety.

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 taken study drug for a minimum of 3 full days to be a clinical failure; to be a clinical cure, the subject had taken at least 80% of prescribed study medication.
- The subject did not take any antimicrobial therapy from 21 days prior to study initiation up through the last posttreatment evaluation, unless the subject was a clinical failure or the antimicrobial was not considered to have an effect on the sinus infection before unblinding.
- The subject did not receive any interfering therapeutic procedures or any other potentially confounding intervention during the study, unless the subject was considered a clinical failure.
- Sinus x-ray and signs/symptoms of infection were evaluated at least 7 days posttreatment, unless the subject was considered a clinical failure.
- The subject did not violate any selection criteria, unless the violation was considered not to affect the efficacy evaluation before unblinding.

Intent-to-Treat Subject Population

All subjects who took at least one dose of study medication, had at least one sign or symptom of sinusitis, had a confirmed diagnosis of acute maxillary sinusitis by radiographic examination, and had no evidence of chronic maxillary sinusitis were included in the intent-to-treat population.

All Treated Subjects Population

All subjects who took at least one dose of study medication and had available data were included in the all treated subjects population.

Disposition of Subjects by Data Set

A total of 142 subjects were randomized to and received clarithromycin ER and 141 were randomized to and received clarithromycin IR. A total of 38 (20 clarithromycin ER and

18 clarithromycin IR) subjects were excluded from the clinically evaluable analyses. Of these, 16 subjects did not have a clinical evaluation at the Test-of-Cure Visit, nine subjects did not meet selection criteria, four subjects were noncompliant with the treatment regimen, four subjects had no sinus x-ray at the Test-of-Cure Visit, three subjects used confounding medications prior to the Test-of-Cure Visit, and two subjects were missing the time of the Test-of-Cure Visit.

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

Disposition of Subjects by Data Set

	Clarithromycin	
	ER	IR
Total Randomized (All Treated Subjects Population)	142	141
Intent-to-Treat Population	138	136
Selection criteria not met	4	5
Chronic maxillary sinusitis	2	3
Negative sinus x-ray at pretreatment	1	1
Diagnosis of frontal, ethmoid or sphenoid sinusitis	1	1
Subjects Included in the Clinically Evaluable Efficacy Analyses:	122	123
Subjects Excluded from the Clinically Evaluable Efficacy Analyses	20	18
Clinical evaluation not performed at Test-of-Cure Visit	9	7
Selection criteria not met	4	5
Chronic maxillary sinusitis	2	3
Negative sinus x-ray at pretreatment	1	1
Diagnosis of frontal, ethmoid or sphenoid sinusitis	1	1
Noncompliance with treatment regimen	2	2
No sinus x-ray at Test-of-Cure Visit	1	3
Confounding medications	3	0
Missing time of Test-of-Cure Visit	1	1

Demographic and Other Baseline Characteristics

Demographics

There were no statistically significant differences between treatment groups in sex, race, age, or weight. The majority of the subjects were females (64%) and white (87%). The

mean age of all subjects was 41.4 years, and age ranged from 13 to 78 years. The table below presents the demographic information for all treated subjects.

Demographic Information (All Treated Subjects Population)

Demographic Characteristic	Number of Subjects by Treatment Group: Clarithromycin ER		Clarithromycin IR		P-value[a]
Total Treated	142		141		0.622
Sex					
Female	93	(65%)	88	(62%)	
Male	49	(35%)	53	(38%)	
Race[b]					0.158
White	119	(84%)	127	(90%)	
Black	17	(12%)	10	(7%)	
Other	6	(4%)	4	(3%)	
Age (years)					0.572
<40	68	(48%)	67	(48%)	
40 - <65	66	(46%)	68	(48%)	
≥65	8	(6%)	6	(4%)	
Mean (SD)	41.9	(13.6)	41.0	(13.0)	
Range	13 - 78		15 - 73		
Weight (kg)					0.728
<45	2	(1%)	0	(0%)	
45 - <70	49	(35%)	50	(35%)	
≥70	90	(63%)	90	(64%)	
Missing	1	(1%)	1	(1%)	
Mean (SD)	79.8	(22.2)	78.9	(18.0)	
Range	43 - 159		51 - 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: white and all other races combined.

Presenting Conditions, Medical History, and Diagnoses

There were no statistically significant differences between treatment groups in diagnoses or presenting conditions. The table below summarizes the presenting conditions, medical history, and diagnoses for all treated subjects.

Summary of Presenting Conditions, Medical History, and Diagnoses (All Treated Subjects Population)

	Number of Subjects by Treatment Group				
	Clarithromycin ER		Clarithromycin IR		P-value[a]
Total Treated	142		141		
Number of Infections [b]					0.297
1	86	(61%)	79	(56%)	
2	55	(39%)	59	(42%)	
≥3	1	(<1%)	3	(2%)	
Mean (SD)	1.4	(0.5)	1.5	(0.6)	
Range					
Underlying Nasal Diseases[c]					Not computed
Nasal polyps	3	(2%)	3	(2%)	
Deviated septum	25	(18%)	22	(16%)	
Allergic rhinitis	50	(35%)	60	(43%)	
Other	14	(10%)	11	(8%)	
Any of the above	71	(50%)	69	(49%)	Not computed
None of the above	71	(50%)	72	(51%)	
Infection Status					0.457
Mild	28	(20%)	23	(16%)	
Moderate	114	(80%)	118	(84%)	
Overall Clinical Condition					0.904
Good	114	(80%)	114	(81%)	
Fair	28	(20%)	27	(19%)	

a P-values are from ANOVA for difference between treatment groups for number of infections and from Cochran-Mantel-Haenszel test comparing the treatment groups for infection status and overall clinical condition.
b Number of sinus infections within the past 12 months, including present infection.
c A subject may have more than one disease/condition.

Pretreatment Signs and Symptoms

Among all treated subjects at pretreatment, the most frequently reported signs or symptoms in both treatment groups were nasal congestion (98%), sinus pain (90%), and purulent nasal discharge (90%). A statistically significant difference was observed between treatment groups in nasal congestion at pretreatment. All subjects (100%) in the clarithromycin ER group and 96% of the clarithromycin IR group reported nasal congestion (p=0.013); this difference was not considered to be clinically meaningful.

The table below presents the pretreatment signs and symptoms of all treated subjects.

Summary of Pretreatment Signs and Symptoms (All Treated Subjects Population)

	Number of Subjects by Treatment Group				
	Clarithromycin ER		Clarithromycin IR		P-value[a]
Total Treated	142		141		
Sinus Headache					0.568
Absent	21	(15%)	18	(13%)	
Mild	33	(23%)	44	(31%)	
Moderate	69	(49%)	63	(45%)	
Severe	19	(13%)	16	(11%)	
Sinus Pain					0.628
Absent	14	(10%)	13	(9%)	
Mild	44	(31%)	48	(34%)	
Moderate	73	(51%)	60	(43%)	
Severe	11	(8%)	20	(14%)	
Sinus Tenderness					0.670
Absent	14	(10%)	19	(13%)	
Mild	61	(43%)	56	(40%)	
Moderate	58	(41%)	57	(40%)	
Severe	9	(6%)	9	(6%)	
Facial Erythema					0.329
Absent	108	(76%)	100	(71%)	
Present	34	(24%)	41	(29%)	
Nasal Congestion					0.013*
Absent	0	(0%)	6	(4%)	
Present	142	(100%)	135	(96%)	
Facial Swelling					0.500
Absent	81	(57%)	86	(61%)	
Present	61	(43%)	55	(39%)	
Purulent Nasal Discharge					0.438
Absent	16	(11%)	12	(9%)	
Present	126	(89%)	129	(91%)	
Fever					0.524
Absent	113	(80%)	107	(76%)	
Present	29	(20%)	33	(23%)	
Missing	0	(0%)	1	(1%)	

a P-values are from a Cochran-Mantel-Haenszel test comparing treatment groups.
* Indicates statistical significance at the 0.05 level.

Pretreatment Sinus X-Ray

Per protocol, all clinically evaluable subjects demonstrated acute maxillary sinusitis by sinus x-ray at pretreatment except two subjects (Smith Subject 6215, Smith Subject 6311) whose x-rays were misread initially and were later confirmed not to have acute maxillary

sinusitis. The majority (56%) of subjects had involvement in both sinuses. There were no statistically significant differences between treatment groups in opacification, mucosal thickening, or air fluid level.

The table below presents the results of the pretreatment sinus x-ray for all treated subjects.

Summary of Pretreatment Sinus X-Ray (All Treated Subjects Population)

	Number of Subjects by Treatment Group				
	Clarithromycin ER		Clarithromycin IR		P-value[a]
Total Treated	142		141		
Clear					Not computed
Yes	0	(0%)	0	(0%)	
No	142	(100%)	141	(100%)	
Opacification					0.096
Absent	80	(56%)	65	(46%)	
Present	62	(44%)	76	(54%)	
Mucosal Thickening					0.253
Absent	27	(19%)	35	(25%)	
Present	115	(81%)	106	(75%)	
Air Fluid Level					0.374
Absent	117	(82%)	110	(78%)	
Present	25	(18%)	31	(22%)	
Involved Sinus					Not computed
Left	37	(26%)	34	(24%)	
Right	22	(15%)	31	(22%)	
Left/Right	83	(58%)	76	(54%)	

a P-values are from Fisher's exact test comparing the treatment groups.

Concurrent Medications

Use of medications at pretreatment was similar between the treatment groups for the all treated subjects population; 73% of subjects in the clarithromycin ER group and 70% of the subjects in the clarithromycin IR group were taking medications at pretreatment. Overall, the most frequently used classifications of medication at pretreatment were sympathomimetic agents (27%), H_1-receptor antagonists (18%), estrogens (18%),

nonsteroidal anti-inflammatory agents (16%), and analgesics, antipyretics, and anti-inflammatory drugs (14%).

During the study, 82% of the subjects in the clarithromycin ER group and 79% of the subjects in the clarithromycin IR group used concurrent medications.
The high incidence of concurrent medication use during the study resulted from use of drugs generally administered for treatment of fevers, colds, coughs, and other symptoms associated with sinusitis. Overall, 30% of all subjects used sympathomimetic agents, 22% used H_1-receptor antagonists, 20% used nonsteroidal anti-inflammatory agents, and 19% used analgesics, antipyretics, and anti-inflammatory agents during the study; in addition, 18% used estrogens. The most frequently used concomitant medications were acetaminophen (17%) and loratadine (12%).Prior to the Test-of-Cure Visit, three subjects in the clarithromycin ER group received disallowed concomitant medication that affected the assessment of clinical response and were excluded from the clinically evaluable analysis of efficacy. Details of each of the subjects are presented in the table below:

Subjects Excluded From Clinically Evaluable Efficacy Analyses Due to Confounding Antibiotics

Investigator/ Subject Number	Concomitant Antibiotic	Reason for Use	Day Started (Days Post)	Clinical Response	Radiographic Response
Subjects Excluded From Clarithromycin ER Group					
Dixon/6542	Dexamethasone	Congestion	16 (2)	Indeterminate	Resolution
Hopland/6561#	Amoxil®	Abscessed tooth	16 (1)	Indeterminate	Resolution
Hopland/6758	Sulfatrim DS®	Urinary tract infection	16 (1)	Indeterminate	Resolution
Subjects Excluded From Clarithromycin IR Group					
None					

Subject prematurely discontinued the study.

Measurement of Treatment Compliance

The majority of subjects in both treatment groups completed at least 11 days of treatment (≥92%) and were at least 80% complaint with the treatment regimen (≥91%). Duration of treatment and study drug compliance for the clinically evaluable population are presented in the table below:

Duration of Treatment and Study Drug Compliance (Clinically Evaluable Population)

	Clarithromycin ER		Clarithromycin IR		P-value[a]
Total	122		123		
Duration of Treatment (Days)					0.200
<3	0	(0%)	2	(2%)	
3 - <11	6	(5%)	8	(7%)	
≥11	116	(95%)	113	(92%)	
Mean (SD)	14.0	(1.92)	13.6	(2.92)	
Min – Max	4 - 19		1 - 16		
Compliance (percentage)[b]					0.093
<20	0	(0%)	4	(3%)	
20 - <80	5	(4%)	7	(6%)	
≥80	116	(96%)	112	(91%)	
Unknown	1				
Mean (SD)	97.0	(11.75)	93.5	(20.22)	
Min – Max	28.6 - 100		7.1 - 100		

a P-value for F-test testing equality of treatment means.
b Subjects who did not return study drug containers but reported full compliance were included as 100% compliant.

For both the intent-to-treat and all treated subjects populations, >95% of the clarithromycin ER group and >86% of the clarithromycin IR group were at least 80% compliant. The difference in compliance between the two treatment groups was statistically significant in both the intent-to-treat (p=0.018) and all treated subjects (p=0.005) populations. The mean duration of treatment was slightly higher in the clarithromycin ER group than in the clarithromycin IR group in both the intent-to-treat (13.7 and 13.4 days, respectively) and all treated subjects (13.8 and 13.3 days, respectively) populations.

Efficacy Results and Tabulations of Individual Subject Data

Analysis of Efficacy

Primary Efficacy Variable

No statistically significant differences were observed between the treatment groups in clinical cure rates at the Test-of-Cure Visit. Among clinically evaluable subjects, 84% of

the clarithromycin ER group and 78% of the clarithromycin IR group were considered to be cured. The 95% confidence interval (CI) for the difference between clinical cure rates (clarithromycin ER - clarithromycin IR) demonstrated that the two treatments were equivalent. A summary of the clinical cure rates for the clinically evaluable population is presented in the table below:

Clinical Cure Rates at the Test-of-Cure Visit (Clinically Evaluable Population)

	Clarithromycin ER n/N (%) [95% CI][a]	Clarithromycin IR n/N (%) [95% CI][a]	P-value[b] [95% CI][c]
Clinical Cure Rate	102/121* (84%) [76.6, 90.3]	94/121** (78%) [69.2, 84.8]	0.251 [-3.2, 16.5]

a Exact binomial confidence interval.
b P-value is from a Fisher's exact test comparing treatment groups.
c Binomial confidence interval based on normal approximation.
* One subject had an indeterminate clinical response and was not included in the calculation of cure rate.
** Two subjects had indeterminate clinical responses and were not included in the calculation of cure rate.

Clinical cure rates at the Test-of-Cure Visit were also compared using Cochran-Mantel-Haenszel methodology adjusting for country, investigator, sex, race, age, weight, overall clinical condition, infection status, number of sinus infections in the past 12 months, nasal polyps, deviated septum, allergic rhinitis, other nasal abnormality, any of the nasal abnormalities, study drug duration, and study drug compliance. After adjusting for each factor, no statistically significant differences were observed between the two treatment groups.

Clinical responses were assigned at Visit 4 for most subjects; only 14 subjects, five in the clarithromycin ER group and nine in the clarithromycin IR group, had their responses assigned at Visit 5. Of the five subjects in the clarithromycin ER group, three were considered to be cures and two were considered to be failures. Of the nine subjects in the clarithromycin IR group, four subjects each were considered to be cures and failures, and one subject's response was indeterminate.

Among clinically evaluable subjects, 85% of the clarithromycin ER group in the USA, 50% of the clarithromycin ER group in Canada, 78% of the clarithromycin IR group in the USA, and 50% of the clarithromycin IR group in Canada were considered to be cured.
Results in the intent-to-treat population also demonstrated that the two treatments were equivalent. Clinical cure rates at the Test-of-Cure Visit were 76% in the clarithromycin ER group and 71% in the clarithromycin IR group. No statistically significant