CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-784 / S-004, S-006

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW OF NDA 50-784/S-004
Acute Bacterial Sinusitis

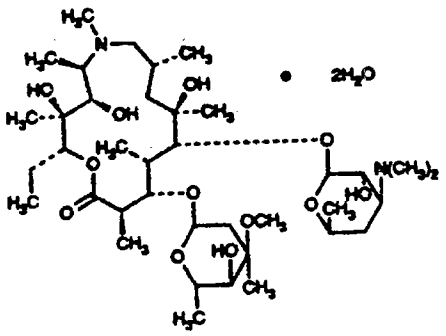
Date Submitted: March 17, 2003.
MOR Initiated: August 11, 2003.
MOR Completed: January 11, 2004.

APPLICANT: Pfizer, Inc.,
235 East 42nd Street
New York, NY 10017

DRUG: **Generic:** Azithromycin
Trade: Zithromax®
Formulation: 500 mg Oral Tablets
Chemical Structure:

The chemical name of Azithromycin is (*2R,3S,4R,5R,8R, 10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L-ribo*-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3- (dimethylamino)-β-*D-xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

The chemical structure of azithromycin is:



Related Material:

NDA 50-670
NDA 50-710
NDA 50-711
IND 24,999

SUBMISSION REVIEWED:

The submission consists of one DLT electronic tape, 4.36 gigabytes in size, with 2,152 files and 219 folders. An electronic regulatory review aid containing a Word 97 version of the proposed labeling and CRF (Case Report Form) tabulations for protocols A0661036 and A0661057, which provide evidence of safety and efficacy in this supplement have also been provided.

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EXECUTIVE SUMMARY

I. Recommendations:

A. Recommendation on Approvability

In sNDA 50-784 (S-004), the Applicant submitted two studies to assess the administration of azithromycin 500 mg/day for 3 days for patients with acute bacterial sinusitis, a total dose of 1.5 gm.
The efficacy and safety data in this supplemental NDA provides satisfactory evidence of efficacy and safety of azithromycin at 500 mg/day for 3 days for patients with acute bacterial sinusitis.
The reviewing Medical Officer recommends an action of **Approval** for sNDA 50-784/s-004 for the use of azithromycin at 500 mg/day for 3 days for patients with acute bacterial sinusitis.
Azithromycin at 500 mg/day for 3 days achieved the goal of noninferiority to the comparator and there were no new safety issues identified to alter the risk benefit profile for Azithromycin®.

B. Recommendations on Postmarketing Studies and/or Risk Management Steps

The Medical Officer does not have any specific recommendations for postmarketing studies related to this supplemental NDA.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

Two studies, A0661036 and A0661057, support the claim of azithromycin, administered as 500 mg/day for 3 days, for the treatment of acute bacterial sinusitis.

One (A0661036) of the two studies supporting the claim of azithromycin in the treatment of acute bacterial sinusitis was a double-blind, double-dummy comparative study versus amoxicillin/clavulanate, and the other (A0661057) was an open-label, non-comparative bacteriology study. Both studies included two treatment durations for azithromycin. One group received 500 mg/day for three days, while another group received the same daily dose of azithromycin for six days.
In these two pivotal studies, 593 subjects received a 3-day treatment course and 566 subjects received a 6-day treatment course of azithromycin. Amoxicillin/clavulanate was given to 313 subjects in the comparative study.

B. Efficacy

Study A0661036:
Nine hundred twenty subjects (307 azith 3-day; 306 azith 6-day; 307 amox/clav) were included in the clinical MITT analyses. The 97.5% confidence intervals for the difference between the success rates for amoxicillin/clavulanate versus each of the azithromycin treatment groups (azith 3-day; azith 6-day) demonstrated equivalence at both EOT (End-of-Treatment; Visit 3) and EOS (End-of-Study; Visit 4). The clinical cure rates at EOS were 71.5%, 74.1%, and 71.5% in the azithromycin 3-day, azithromycin 6-day and amox/clav groups, respectively. The 97.5% confidence interval (CI) for the treatment difference between azi 3-day and amox/clav was (-8.4, 8.3). The 97.5% CI for the treatment difference between azi 6-day and amox/clav was (-5.6, 10.9).

Eight hundred twenty-four subjects (280 azi 3-day; 281 azi 6-day; 263 amox/clav) were included in the clinically evaluable analyses. Of these 824 subjects, 799 subjects (269 azi 3-day; 271 azi 6-day; 259 amox/clav) were included in the EOT analysis and 794 subjects (272 azi 3-day; 271 azi 6-day; 251 amox/clav) were included in the EOS analysis. The 97.5% confidence intervals for the difference between the success rates for amoxicillin/clavulanate versus each of the azithromycin treatment groups (azith 3-day; azith 6-day) demonstrated equivalence at both EOT (Visit 3) and EOS (Visit 4).
The clinical cure rates at EOS were 88.8%, 89.3%, and 84.9% in the azithromycin 3-day, azithromycin 6-day and amox/clav groups, respectively. The 97.5% confidence interval (CI) for the treatment difference between azi 3-day and amox/clav was (-8.5, 9.2). The 97.5% CI for the treatment difference between azi 6-day and amox/clav was (-6.7, 10.9).

The results from the clinical evaluable analyses and clinical MITT analyses were consistent.

For both the clinical MITT and clinical evaluable analyses, in all treatment groups, the success rates at EOT and EOS were comparable for subjects with and without baseline allergic rhinitis. For both the MITT and clinical evaluable analyses, protocol specified signs and symptoms (i.e., post-nasal purulent discharge, facial pain, hyposmia, jaw pain with mastication, headache, halitosis, and nasal congestion) improved throughout the course of the study in all treatment groups.

The incidence of radiological findings (i.e., opacification, air fluid level, and mucosal thickening of 6 mm or greater) decreased throughout the course of the study in all treatment groups for both the MITT and clinical evaluable analyses.

Safety Results: The following safety results are from the comparative study. There were 312, 311, and 313 subjects evaluable for safety in the azithromycin 3-day, azithromycin 6-day, and amox/clav groups, respectively.
Treatment-emergent adverse events (TEAE) were reported in 159, 167, and 210 subjects in the azithromycin 3-day, azithromycin 6-day, and amox/clav groups, respectively. Treatment related TEAE were reported in 97, 117, and 160 subjects in the azithromycin 3-day, azithromycin 6-day, and amox/clav groups, respectively. There were no serious adverse events reported in the two azithromycin groups. Two serious adverse events were

reported in the amox/clav subjects. Treatment-related TEAE led to discontinuation of study drug in 7, 11 and 28 subjects in the azithromycin 3-day, azithromycin 6-day, and amox/clav groups, respectively.

The incidence of treatment-emergent adverse events (TEAE), irrespective of relationship to study drug, was higher in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups (51.0% azi 3-day subjects, 53.7% azi 6-day subjects, and 67.1% amox/clav subjects). The incidences of both diarrhea (17.3% azi 3-day; 23.2% azi 6-day; 33.2% amox/clav) and nausea (7.7% azi 3-day; 9.3% azi 6-day; 12.8% amox/clav) were higher in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups. Diarrhea was the most frequently occurring adverse event across all treatment groups and was the only TEAE that occurred at a 5% or higher difference in rate between the azithromycin treatment groups and the amoxicillin/clavulanate treatment group. The incidences of diarrhea, nausea, and abdominal pain were slightly higher in the azithromycin 6-day treatment group compared with the azithromycin 3-day treatment group.
A higher percentage of amoxicillin/clavulanate-treated subjects (51.1%) experienced treatment-related TEAE than did azithromycin-treated subjects (31.1% azith 3-day; 37.6% azith 6-day). Diarrhea, abdominal pain, nausea, and flatulence were the only treatment-related TEAEs that occurred in 5% or more of subjects. Diarrhea (17% azith 3-day; 21.2% azith 6-day; 32.3% amox/clav) and nausea (7.4% azith 3-day; 8.7% azith 6-day; 12.1% amox/clav) occurred at a higher rate in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups. Flatulence (5.4% azith 3-day; 3.5% azith 6-day; 1.9% amox/clav) occurred at a higher rate in the azithromycin treatment groups than in the amoxicillin/clavulanate treatment group. The incidences of diarrhea, nausea, and abdominal pain were slightly higher in the azithromycin 6-day treatment group compared with the azithromycin 3-day treatment group.

There were more subjects who discontinued study drug due to adverse events in the amoxicillin/clavulanate treatment group (32 subjects) than in either of the two azithromycin treatment groups (10 subjects in the azith 3-day group and 13 subjects in the azith 6-day group).

Two subjects in the amoxicillin/clavulanate treatment group experienced serious adverse events. The first subject experienced a cardiac arrest on Day 13 and died. The second subject was hospitalized for an intentional drug overdose. The investigator considered both of these adverse events to be unrelated to study drug. There were no serious adverse events in the azithromycin treatment groups.

Summary and Conclusions:

Based on the results of this study the following conclusions can be made:

- In this comparative study, it was observed that administration of azithromycin at 500 mg/day for 3 days was equivalent in efficacy to amoxicillin/clavulanate administered at 1500 mg amoxicillin/375 mg clavulanate per day for 10 days. This was true at both the EOT and EOS time points for both the MITT and clinical evaluable subgroup analyses.

- Treatment with azithromycin (500 mg/day) for 3 days was better tolerated compared with 10 days of 1500 mg amoxicillin/375 mg clavulanate per day as shown by a reduction in the overall rate of adverse events, gastrointestinal-related adverse events, and subject discontinuations due to adverse events.
- Treatment with azithromycin (500 mg/day) for 6 days was also equivalent in efficacy to 10 days of 1500 mg amoxicillin/375 mg clavulanate per day, and better tolerated.
- Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall clinical success rates appeared similar whether azithromycin was administered over 3 or 6 days.

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Study A0661057:

Efficacy Results: Five hundred thirty-five subjects (281 azi 3-day; 254 azi 6-day) were included in the clinical MITT analyses. Clinical response rates at EOS were 77.5% and 84.7% with the azithromycin 3-day and azithromycin 6-day groups, respectively. The clinical success was higher for subjects in the azithromycin 6-day treatment group than for subjects in the azithromcyin 3-day treatment group.

For the clinically evaluable analysis, 490 subjects (257 azi 3-day; 233 azi 6-day) were included in the EOT analysis and 484 subjects (254 azi 3-day; 230 azi 6-day) were included in the EOS analysis. Clinical cure rates at EOS were 76.8% and 83.9% with the azithromycin 3-day and azithromycin 6-day groups, respectively.
The results from the clinical evaluable analyses and clinical MITT analyses were consistent.

One hundred sixty-six subjects (74 azi 3-day; 92 azi 6-day) were included in the bacteriological MITT analyses. These were the subjects in the MITT population with pathogen isolated by baseline sinus puncture. The clinical cure rates at EOS in the bacteriological MITT population were 83.3% and 83.7% in the azi 3-day and azi 6-day groups, respectively.

Comparable cure rates were seen in the two azithromycin treatment groups for subjects with specific pathogens. For *H. influenzae*, the clinical cure rates were 25/32 (78.1%) and 24/28 (85.7%) in the azi 3-day and azi 6-day groups, respectively. For *S. pneumoniae*, the clinical cure rates were 21/25 (84%) and 34/42 (81.0%) in the azi 3-day and azi 6-day groups, respectively. For *M. catarrhalis*, the clinical cure rates were 13/15 (92.9%) and 15/19 (78.9%) in the azi 3-day and azi 6-day groups, respectively. Few patients had *S. aureus* as a baseline pathogen, two in the azi 3-day and six in the azi 6-day group. All were cured at EOS.

As would be expected based on the small number of postbaseline cultures obtained during the study, bacteriological response by baseline pathogen correlated very closely with clinical response by pathogen for both azithromycin 3-day and azithromycin 6-day treatment groups. For both the clinical MITT and clinical evaluable analyses, in both treatment groups, the success rates at EOT were comparable for subjects with and without baseline allergic rhinitis. At EOS, the success rates were slightly higher for subjects without baseline allergic rhinitis than for subjects with baseline allergic rhinitis. The signs and symptoms present at baseline were consistent with acute bacterial sinusitis and comparable between the azithromycin treatment groups. At baseline, a majority of the clinical MITT subjects had moderate or severe post-nasal purulent discharge (77.2% azi 3-day; 82.7% azi 6-day), facial pain (68.7% azi 3-day; 75.2% azi 6-day), headache (68.0% azi 3-day; 72.8% azi 6-day), and nasal discharge (87.9% azi 3-day; 87.8% azi 6-day). The results were similar for the clinically evaluable population.

For the clinical MITT population, subjects in the two azithromycin treatment groups were comparable with respect to their radiological findings at baseline (air fluid level: 28.1%

azi 3-day; 29.1% azi 6-day; opacification: 53.7% azi 3-day; 58.7% azi 6-day). Baseline radiological findings were consistent with a diagnosis of acute bacterial sinusitis. Radiological findings for the clinically evaluable population were consistent with those for the clinical MITT population.

Safety Results: There were 281 azi 3-day subjects and 255 azi 6-day subjects evaluated for safety in this non-comparative trial.
Treatment-emergent adverse events (TEAE) were reported in 109 (39%) and 98 (38%) of subjects in the azithromycin 3-day and azithromycin 6-day groups, respectively. Treatment related TEAE were reported in 58 (21%) and 45 (17.6%) of subjects in the azithromycin 3-day and azithromycin 6-day groups, respectively. There were two serious adverse events reported, one in each of the azithromycin groups. Treatment-related TEAE led to discontinuation of study drug in 2 subjects each in the azithromycin 3-day and azithromycin 6-day groups.

The incidence of treatment-related treatment-emergent adverse events (TEAEs) was 20.6% in the azithromycin 3-day group and 17.6% in the azithromycin 6-day group. Diarrhea, abdominal pain, and nausea were the most frequently reported treatment-related TEAEs. The majority of the treatment-related TEAEs were mild or moderate in severity.

Six subjects (3 azith 3-day; 3 azith 6-day) discontinued (study drug and/or study) due to adverse events. Of these 6 subjects, 2 subjects in the azith 3-day group and all 3 subjects in the azith 6-day group discontinued study drug.

Two subjects (one subject in each treatment group) experienced serious adverse events. The first subject (azith 3-day) experienced suicidal ideation on Day 6. The second subject (azith 6-day) was hospitalized for septicemia on Day 26. Both these events resolved and the investigator considered these events to be unrelated to study drug.

Summary and Conclusions:

Based on the results of this study the following conclusions can be made:

- The efficacy of azithromycin at 500 mg/day administered for either 3 or 6 days was demonstrated in subjects with documented infections caused by *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.
- In subjects with *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* isolated at Baseline, the clinical and bacteriological success rates were generally high (azi 3-day: 87%-93% at EOT and 73-93% at EOS; azi 6-day: 93%-100% at EOT and 77%-86% at EOS). Although no statistical comparisons were conducted between the two azithromycin treatment groups, the clinical and bacteriological success rates in subjects with *H. influenzae* appeared slightly higher when azithromycin was administered for 6 days.
  Overall success rates in subjects with baseline pathogens appeared similar whether azithromycin was administered over 3 or 6 days.
- In all subjects, those with or without documented baseline pathogens, the clinical success rates were also high (azi 3-day: 89% at EOT and 77-78% at EOS; azi 6 day:

94%-95% at EOT and 84%-85% at EOS). Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall success rates appeared to be slightly higher when azithromycin was administered over 6 days as compared with 3 days.

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CLINICAL REVIEW

I. Introduction and Background

General

Azithromycin is a well-established antibacterial agent and is the first of a class of antibiotics designated chemically as "azalides." Members of this class of drug possess amphiphilic cationic properties. Azithromycin is a broad-spectrum antibiotic with activity against a wide variety of Gram-positive and Gram-negative bacteria. The mechanism of action of azithromycin is by inhibition of protein synthesis by binding to 50s bacterial ribosomal subunits and thereby interfering with translocation of the growing peptide chain from one side of the ribosome to the other. Nucleic acid synthesis is not affected.

Additional attributes of azithromycin include prolonged serum and tissue half-lives, and high concentrations in tissues.

Preclinical investigations of the pharmacokinetics of azithromycin *in vitro* and in rats and dogs demonstrated several unique features: firstly, a very high affinity for tissues with tissue to serum concentration ratios of up to 100-fold and more; secondly, uptake and concentration in phagocytic cells without impairing their function; and thirdly, a prolonged serum and tissue half-life of up to 160 hours in dogs after multiple dosing.

Azithromycin has been shown *in vitro* and *in vivo* to concentrate in phagocytic cells, a phenomenon possibly related to its amphiphilic cationic properties. The uptake of azithromycin into macrophages, without impairing their function, is of potential benefit leading to increased delivery of the drug to infection sites and also possibly greater activity against pathogens absorbed into macrophages but not killed, such as *Staphylococcus aureus*. Once inside the cell, azithromycin remains active within storage lysosomes and is delivered directly to the bacteria when the lysosomes merge with phagosomes containing bacteria.

Pharmacokinetic studies with oral azithromycin in animals showed serum concentrations to be proportional to dose. However, tissue concentrations up to several hundred times those in serum were achieved, with a half life that varied from 26 to 160 hours after dosing from 1 to 10 days, respectively, in dogs. Additionally, initial radio-labeled studies in rats and dogs recovered only 64% and 57% of the drug after 7 days collection. These findings are markedly different from other antibiotics.

NDA 50-784 for ZITHROMAX® (azithromycin) 500-mg tablets was approved on May 24, 2002 for a dosing regimen of 500 mg once daily for 3 days to treat acute bacterial exacerbations of chronic bronchitis in adults. This supplemental NDA provides for the addition of a new indication, acute bacterial sinusitis, using the same dosing regimen of 500 mg once daily for 3 days in adults.

II. Chemistry & Manufacturing, Animal Pharmacology & Toxicology.

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

Microbiology.

The reader is referred to the microbiology review by Mr. Harold Silver.

Biostatistics.

The reader is referred to the biostatistical review by Dr. Scott Komo.

III. Human Pharmacokinetics and Pharmacodynamics.

The reader is referred to the biopharmaceutics review by Dr. Charles Bonapace.

IV. Description of Clinical Data and Sources.

A. The safety and efficacy data submitted were gathered from two pivotal randomized clinical trials (A0661366 and A0661057) which, in combination, meet the criteria for development of antibiotics for acute bacterial sinusitis as defined in the 1998 Draft Guidance Document.

Study A0661036 was a randomized, double-blind, multicenter comparative trial of azithromycin (500 mg/day) for 3 days (1.5 grams), azithromycin (500 mg/day) for 6 days (3.0 grams) and amoxicillin/clavulanate (500 mg amoxicillin/125 mg clavulanate three times a day) for 10 days for the treatment of acute bacterial sinusitis. Study A0661057 was an open-label, multicenter, study evaluating oral therapy with azithromycin (500 mg/day) for 3 days (1.5 grams) and for 6 days (3.0 grams) in the treatment of acute bacterial sinusitis. In Study A0661057, samples of sinus fluid were obtained at baseline by antral puncture and pathogens were isolated by culture.

In addition to the adult claim, the sponsor is making a claim for use of a 3-day regimen of azithromycin in treatment of pediatric subjects 6 months and older with acute bacterial sinusitis at 10 mg/kg/day. This pediatric claim is based on the fact that safety and efficacy of the 3-day regimen have been established in the present sNDA in adults with acute bacterial sinusitis and that comparable 3-day pediatric dosing has been shown to be safe and effective in treating acute otitis media (NDA 50-710/S-009). The microbiology of acute bacterial sinusitis in children is similar to that seen in adults, with the primary pathogens being *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. The same pathogens are the most frequent cause of bacterial acute otitis media in children. The claim is also based upon a similar pathophysiology for acute bacterial sinusitis in pediatric patients and adults.

V. Clinical Review Method

A. How the review was conducted

The applicant has submitted two clinical trials in support of the indication for acute maxillary sinusitis in adults. Data from these trials were reviewed for efficacy and safety.

B. Overview of Materials consulted in Review

The applicant has submitted an electronic copy of the supplemental NDA. The electronic submission contains final study reports for the two clinical studies, all case report forms, integrated summaries of efficacy and safety, and the proposed draft package insert.

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

The Division of Scientific Investigations audited selected sites for the study. The Medical Officer is not aware of any serious problems found in the DSI inspection of selected study sites and their principal investigators. In addition, the Medical Officer has reviewed a random sample of 10% of the enrolled patient population for each study. The Medical Officer agrees with the applicant's analysis.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The studies submitted in support of the indication sought were conducted with an approved formulation of azithromycin. The studies were conducted under an IND, and were submitted to FDA for protocol review. All investigators conducted the trials in accordance with good clinical practices.

E. Evaluation of Financial Disclosure

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

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The efficacy of azithromycin at 500 mg/day administered for either 3 or 6 days was demonstrated in subjects with documented acute bacterial sinusitis caused by *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.

In subjects with *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* isolated at baseline, the clinical and bacteriological success rates were generally high (azithromycin 3-day: 87%-93% at EOT and 73-93% at EOS; azithromycin 6-day: 93%-100% at EOT and 77%-86% at EOS). Although no statistical comparisons were conducted between the two azithromycin treatment groups, the clinical and bacteriological success rates in subjects with *H. influenzae* appeared slightly higher when azithromycin was administered for 6 days (78.1% vs. 85.7%).

Overall success rates in subjects with baseline pathogens appeared similar whether azithromycin was administered over 3 or 6 days.

In all subjects, those with or without documented baseline pathogens, the clinical success rates were also high (azith 3-day: 89% at EOT and 77-78% at EOS; azith 6 day: 94%-95% at EOT and 84%-85% at EOS). Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall success rates appeared to be slightly higher when azithromycin was administered over 6 days as compared with 3 days.

In the comparative trial, nine hundred twenty subjects (307 azi 3-day; 306 azi 6-day; 307 amox/clav) were included in the clinical MITT analyses and 824 subjects (280 azi 3-day; 281 azi 6-day; 263 amox/clav) were included in the clinical evaluable analyses. The results from the clinical MITT analyses and the clinically evaluable analyses demonstrated that clinical success rates for azithromycin administered for 3 days or 6 days were equivalent to that of amoxicillin/clavulanate administered for 10 days.

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

The applicant has submitted two studies in support of the acute maxillary sinusitis indication.

Study	Design	Dose of Azithromycin	Treatment Duration	Comparator
A0661036	Double-Blind Comparative	500 mg/day	3 days and 6 days	Amoxicillin/ Clavulanate, 625 mg tid for 10 days
A0661057	Open-Label Non-Comparative	500 mg/day	3 days and 6 days	None

This document describes the efficacy and safety data from these studies in detail. Final conclusions and recommendations are made based upon the requested draft labeling submitted by the applicant.

C. Detailed Review of Trial by Indication
Indication Reviewed – Acute Bacterial Sinusitis

a). REVIEW OF STUDY A0661036.

Title of the study: *A randomized double-blind, multicenter trial comparing oral therapy with Zithromax® (Azithromycin) 500 mg/day for 3 days, Zithromax® 500 mg/day for 6 days and oral Augmentin® (Amoxicillin/Clavulanate) 500/125 mg t.i.d. for 10 days for the treatment of acute bacterial sinusitis.*

Investigative Sites

A total of 59 investigators in the US were recruited and received study drug supplies to conduct this study. A total of 941 subjects were enrolled. The study was conducted between 29 January 2001 and 7 March 2002.

Study Objectives

Primary Objective

The primary objective of this study was to evaluate the clinical efficacy of oral Zithromax® (azithromycin) administered as 500 mg/day for 3 days or 500 mg/day for 6 days compared with oral Augmentin® (amoxicillin/clavulanate) administered as 1500 mg amoxicillin/375 mg clavulanate per day for 10 days in the treatment of subjects with acute bacterial sinusitis.

Secondary Objective
A secondary objective was to compare the safety and toleration of these regimens.

INVESTIGATIONAL PLAN

Details of the investigational plan, efficacy and safety evaluability criteria can be found in Appendix I.

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STUDY PATIENTS

Disposition of Patients

Principal Investigators:

R. Bettis, MD	J. M. Bundy, MD	H. Chipman, III, MD
S. Coleman, MD	D. Creager, MD	B. Cromar, MD
A. Dahdul, MD	C. Deabate, MD@	M. Diamond, MD
J. Durden, MD	P. English, MD	T. File, Jr., MD
D. Freeman, MD	D. Fried, MD	J. Hedrick, MD
A. Heller, MD	D. Henry, MD	P. Huang, MD
K. Kim, MD	E. Lane, MD	B. Matthews, MD
D. McCarron, MD	G. McCulloch, MD	P. Miller, MD
J. Parker, MD	A. Patel, MD	H. Pillsbury, III, MD*
L. Pizzo, MD	A. Puopolo, MD	G. Raphael, MD
H. Resnick, MD	E. Riffer, MD	J. Robinson, MD
J. Rosen, MD	D. Russell, MD	H. Ryback, MD
B. Samuels, MD	N. Schultz, MD*	W. Sokol, MD
E. Solomon, MD	M. Sperling, MD	R. Sterling, MD
R. Stoltz, MD	J. Sullivan, MD	G. Tarshis, MD
R. Watson, MD	S. Weakley, MD*	A. White, MD
E. Wilson, MD	D. Young, MD	R. Zuckerman, MD

*No subjects were randomized.
@ 16 patients enrolled by this disqualified investigator – all patients excluded from efficacy analysis

Evaluation Groups: Nine hundred forty-one subjects (316 azithromycin 3-day; 311 azithromycin 6-day; 314 amoxicillin/clavulanate) were randomized to double-blind treatment. Nine hundred thirty-six subjects (312 azithromycin 3-day; 311 azithromycin 6-day; 313 amoxicillin/clavulanate) were treated with study drug. Of the 936 treated subjects, 297 subjects (95.2%) in the azithromycin 3-day group, 292 subjects (93.9%) in the azithromycin 6-day group, and 282 subjects (90.1%) in the amoxicillin/clavulanate group completed treatment. The following table shows the number of subjects evaluable for efficacy and safety analysis by treatment group.

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Table C-1
Subject Evaluation Groups

	Azi 3-Day N (%)	Azi 6-Day N (%)	Amox/clav N (%)
Randomized	316	311	314
Treated	312	311	313
Completed Study	297 (95.2)	292 (93.9)	282 (90.1)
Discontinued Study	15 (4.8)	19 (6.1)	31 (9.9)
Analyzed for Efficacy			
Clinical MITT	307 (98.4)	306 (98.4)	307 (98.1)
Clinical Evaluable			
Visit 3	269 (86.2)	271 (87.1)	259 (82.7)
Visit 4	272 (87.2)	271 (87.1)	251 (80.2)
Analyzed for Safety			
Adverse Events	312 (100.0)	311 (100.0)	313 (100.0)
Laboratory Data	308 (98.7)	300 (96.5)	296 (94.6)

Study Discontinuations

Discontinuations from study are presented in Table C-2

Table C-2: Discontinuations

	Azithromycin 3-Day		**Azithromycin 6-Day**		**Amox/Clav**	
Number (%) of Subjects	**312**		**311**		**313**	
Subject Died	0		0		1	(0.3)
Related to Study Drug	**1**	**(0.3)**	**6**	**(1.9)**	**11**	**(3.5)**
Adverse event	0		4	(1.3)	10	(3.2)
Lack of efficacy	1	(0.3)	2	(0.6)	1	(0.3)
Not Related to Study Drug	**14**	**(4.5)**	**13**	**(4.2)**	**19**	**(6.1)**
Adverse event	1	(0.3)	2	(0.6)	0	
Other	2	(0.6)	2	(0.6)	5	(1.6)
Subject defaulted	11	(3.5)	9	(2.9)	14	(4.5)
Total	**15**	**(4.8)**	**19**	**(6.1)**	**31**	**(9.9)**

Medical Officer's Comments:

Sixty-five subjects (15 azithromycin 3-day; 19 azithromycin 6-day; 31 amox/clav) discontinued from the study. The most frequent reason for discontinuation in all treatment groups was "Subject Defaulted" which included "Lost to Follow-up" and "Withdrawn Consent". Seventeen subjects (1 azithromycin 3-day; 6 azithromycin 6-day; 10 amox/clav) discontinued from the study due to adverse events.

Protocol Deviations

Three hundred seventy-five subjects (123 azi 3-day; 122 azi 6-day; 130 amox/clav) deviated from the protocol. The protocol deviations are summarized in the following table.

Table C-3 : Summary of Protocol Deviations

	Azi 3-day	**Azi 6-Day**	**Amox/Clav**
	N	**N**	**N**
No. of Subjects With a Protocol Deviation@	**123**	**122**	**130**
General Categories of Protocol Deviations			
Antibiotic use During Study for Condition Other Than Sinusitis	8	6	7
Concomitant Antihistamine Use	26	47	38
Concomitant Corticosteroid Use	10	19	13
Concomitant Pseudoephredrine Taken Within 24 h Prior to Visits 3 or 4	4	3	2
History of Sinus Surgery	1	0	2
Inclusion/Exclusion Criteria	23	17	25
Missed or out-of-Window Visits 3 or 4	37	35	47
Other Protocol Deviations	26	17	19
Received <80% or >120% of Required Active Study Medication Doses	5	3	20
Required Safety lab or Test not Done	21	18	18
X-ray Not Done and Not a Failure	14	15	27

@Subjects may have had more than one protocol deviation.

Demography and Baseline Characteristics

Demography

Sex, age, race, weight, and height are summarized for safety evaluable subjects in Table C-4:

Table C-4: Demography

	Azithromycin 3-Day			Azithromycin 6-Day			Amox/Clav		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
Number of Subjects	123	189	312	124	187	311	134	179	313
Age (years):									
18-44	80	123	203	74	122	196	79	109	188
45-64	34	56	90	44	48	92	46	60	106
>= 65	9	10	19	6	17	23	9	10	19
Mean	40.5	39.9	40.2	41.9	41.0	41.3	42.7	42.2	42.4
SD	13.3	13.4	13.4	13.3	15.4	14.6	13.9	13.9	13.9
Range	18.0-76.0	18.0-73.0	18.0-76.0	18.0-80.0	18.0-80.0	18.0-80.0	18.0-78.0	18.0-84.0	18.0-84.0
Race:									
WHITE	113	158	271	107	154	261	114	160	274
BLACK	5	15	20	7	11	18	10	9	19
ASIAN	0	2	2	2	7	9	1	2	3
HISPANIC	3	10	13	7	14	21	7	7	14
OTHER	2	4	6	1	1	2	2	1	3
Weight (kg):									
Mean	91.3	77.0		88.6	75.2		90.0	74.2	
SD	18.6	20.3		13.8	18.1		15.8	18.3	
Range	51.7-163.3	39.0-142.4		61.0-132.9	35.4-154.2		57.6-149.7	45.4-137.0	
N	123	187		124	185		133	178	
Height (cm):									
Mean	179.1	164.3		179.4	164.1		179.2	165.4	
SD	7.2	7.1		7.4	10.7		8.2	6.5	
Range	152.0-201.0	144.0-183.0		160.0-211.0	53.0-183.0		155.0-206.0	150.0-180.0	
N	123	188		124	185		132	179	

Medical Officer's Comments:

The majority of subjects in the 3 treatment groups were female and white. Subjects in the azithromycin treatment groups were comparable with subjects in the amoxicillin/clavulanate treatment group with respect to age, weight, and height.

Primary Diagnoses and Durations

The primary diagnoses and durations of present episode are summarized by treatment group in Table C-5. The mean duration of signs and symptoms prior to presentation was similar between the two azithromycin treatment groups and the amoxicillin/clavulanate treatment group: 12.9 days for azi 3-day and azi 6-day subjects; 13.0 days for amox/clav subjects.

Table C-5: Primary Diagnosis and Durations – Safety Population

	Azi 3-Day	Azi 6-Day	Amox/Clav
Number of Subjects	**312**	**311**	**313**
Primary Diagnosis ACUTE BACTERIAL SINUSITIS			
Duration Since First Signs/Symptoms (days)			
Mean	12.9	12.9	13.0
Range			
Unspecified (N)	0	0	0

Medical History

The percentage of subjects with past or present diseases/syndromes was similar between the two azithromycin treatment groups and the amoxicillin/clavulanate treatment group. The most common medical diseases/syndromes that occurred in at least 10% of subjects in any treatment group and were present at study entry are shown in the following table.

Table C-6: Medical Diseases/Syndromes That Occurred in ≥10% of Subjects in any Treatment Group and Were Present at Study Entry

	Azi 3-Day N	Azi 6-Day N	Amox/Clav N
Total Number of Subjects	**312**	**311**	**313**
Allergic Rhinitis due to Other Allergen	31	33	37
Allergic Rhinitis due to Pollen	46	55	66
Allergic Rhinitis, cause Unspecified	41	45	49
Asthma, Unspecified	25	34	31
Depressive Disorder, not Elsewhere Classified	34	41	52
Unspecified Essential Hypertension	42	58	45

A subject may have had more than one type of rhinitis.

Prior Drug Treatments

The percentage of subjects who used drug treatments (excluding antibiotics) was similar between the two azithromycin treatment groups and the amoxicillin/clavulanate treatment group: 63.8% azi 3-Day; 69.1% azi 6-Day; 67.7% amox/clav. Prior drug treatments used by 10% or more subjects are shown in the following table.

Table C-7:
Drug Treatments Other Than Antibiotics Used by ≥ 10% of Subjects in any Treatment Group

	Azi 3-Day N (%)	Azi 6-Day N (%)	Amox/Clav N (%)
Total Number of Subjects	**312(100.0)**	**311(100.0)**	**313(100.0)**
Drugs Used in Rheumatic Diseases & Gout	55 (17.6)	60 (19.3)	51 (16.3)
Antidepressant Drugs	39 (12.5)	50 (16.1)	54 (17.3)
Contraceptives	33 (10.6)	44 (14.1)	38 (12.1)
Sex Hormones	34 (10.9)	37 (11.9)	37 (11.8)
Antihypertensive Drugs	28 (9.0)	33 (10.6)	34 (10.9)
Analgesics	30 (9.6)	34 (10.9)	25 (8.0)
Vitamins	29 (9.3)	23 (7.4)	33 (10.5)

Medical Officer's Comments:

Twelve subjects (5 [1.6%] azi 3-Day; 2 [0.6%] azi 6-Day; 5 [1.6%] amox/clav) used antibiotics prior to the start of the study. These antibiotics included antileprotic drugs, macrolides, metronidazole and tinidazole, penicillins and quinolones. Of these antibiotics, penicillins were the most frequently used drugs (2 azi 3-day subjects; 1 azi 6-day subject; 2 amox/clav subjects). Of the 12 subjects, only 2 subjects (1 azi 3-Day; 1 amox/clav) received systemic antibiotic for more than 24 hours within 2 weeks prior to the baseline visit. Both these subjects were considered to be protocol deviators and were excluded from the clinical evaluable analyses.

Concomitant Medications and Non-drug Treatments

The incidence of concomitant medication use was similar between the two azithromycin treatment groups and the amoxicillin/clavulanate treatment group (78.2% [244/312] azi 3-day; 83.6% [260/311] azi 6-day; 85.3% [267/313] amox/clav). General categories of concomitant medications used by 10% or more subjects in any treatment group are shown in the following table.

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Table C-8: Concomitant Medications Other than Antibiotics by ≥ 10% of Subjects in any Treatment Group

	Azi 3-Day N (%)	Azi 6-Day N (%)	Amox/Clav N (%)
Systemic Treatment of Symptoms of URT Infections	105 (33.7)	108 (34.7)	115 (36.7)
Drugs Used in Rheumatic Diseases & Gout	76 (24.4)	85 (27.3)	83 (26.5)
Analgesics	57 (18.3)	61 (19.6)	49 (15.7)
Antidepressant Drugs	43 (13.8)	55 (17.7)	58 (18.5)
Contraceptives	33 (10.6)	45 (14.5)	38 (12.1)
Sex Hormones	34 (10.9)	37 (11.9)	38 (12.1)
Vitamins	30 (9.6)	25 (8.0)	34 (10.9)
Antihypertensive Drugs	29 (9.3)	37 (11.9)	36 (11.5)

In all treatment groups, the most frequently used concomitant medications other than antibiotics were: drugs taken for the systemic treatment of symptoms of URT infections, drugs used in rheumatic diseases and gout, analgesics, and antidepressants.

One hundred eighty-one subjects (20.2% [63/312] azi 3-day; 17.4% [54/311] azi 6-day; 20.4% [64/313] amox/clav) used concomitant antibiotics during the study. The most frequently used class of antibiotics were quinolones (38 azi 3-day; 25 azi 6-day; 30 amox/clav), penicillins (9 azi 3-day; 7 azi 6-day; 12 amox/clav), and cephalosporins, cephamycins, and other beta-lactams (7 azi 3-day; 10 azi 6-day; 10 amox/clav). Of the subjects who used concomitant antibiotics, 21 subjects received antibiotics for the treatment of conditions other than sinusitis and were considered to be protocol deviators. All subjects receiving antibiotics for the treatment of sinusitis, or conditions related to sinusitis received a clinical response of failure.

Medical Officer's Comments:

The use of concomitant non-drug treatment was similar between the two azithromycin treatment groups and the amoxicillin/clavulanate treatment group. Overall, 8.0% (25/312) azi 3-day subjects, 7.7% (24/311) azi 6-day subjects, and 8.3% (26/313) amox/clav subjects had at least one non-drug treatment. There were no important differences among the treatment groups in the use of concomitant non-drug treatments.

Drug Administration

The duration of exposure to active treatment is presented in Table C-9:

Table C-9: Duration of Active Treatment – Safety Population

	Azi 3-Day	Azi 6-Day	Amox/Clav
Number of Subjects	**312**	**311**	**313**
Duration Category (Days)			
<=1	2	1	2
2	1	4	9
3	309	2	5
4	0	5	8
5	0	7	6
6	0	292	3
7	0	0	9
8	0	0	5
9	0	0	7
10	0	0	121
11	0	0	136
12	0	0	0
13	0	0	0
14	0	0	2
15	0	0	0

Medical Officer's Comments:

The median duration of exposure was 3 days (range 1-3 days) for azi 3-day subjects, 6 days (range 1-6 days) for azi 6-day subjects, and 10 days (range 1-14 days) for amox/clav subjects.

EFFICACY EVALUATION

Data Sets Analyzed

Four subjects in the azi 3-day group and one subject in the amox/clav group did not take any study medication. These subjects are not included in the efficacy or safety analysis.

Two populations were analyzed for efficacy: the modified intent-to-treat (MITT) and the clinically evaluable populations. Of the 936 subjects treated, 920 subjects (307 [98.4%] azi 3-day; 306 [98.4%] azi 6-day; 307 [98.1%] amox/clav) were included in the clinical MITT population. The clinical evaluable population consisted of 799 subjects (269 [86.2%] azi 3-day; 271 [87.1%] azi 6-day; 259 [82.7%] amox/clav) at EOT and 794 subjects (272 [87.2%] azi 3-day; 271 [87.1%] azi 6-day; 251 [80.2%] amox/clav) at EOS.

Clinical MITT Analyses

Of the 936 subjects treated, 16 subjects (5 azi 3-day; 5 azi 6-day; 6 amox/clav) were excluded from the clinical MITT analyses. All of these subjects were enrolled at Site 1007, which was considered ineligible by the FDA. The investigator at this site has been disqualified based on failed inspections with other NDAs. These subjects were also excluded from the clinical evaluable analyses.

Clinically Evaluable Analyses

One hundred twenty-seven subjects (42 azi 3-day; 35 azi 6-day; 50 amox/clav) were excluded from the clinically evaluable analyses at EOT (Visit 3). Most of these subjects did not meet entry criteria, nor had visits outside of the specified time window. One subject in the azithromycin 3-day treatment group was excluded from the analyses for using a concomitant systemic antibiotic for an intercurrent illness.

One hundred thirty-four subjects (40 azi 3-day; 35 azi 6-day; 59 amox/clav) were excluded from the clinical evaluable analyses at EOS (Visit 4). Most of these subjects did not meet entry criteria, had visits outside of the specified time window, radiographs were not done and the clinical outcome was not a failure, or had a missing/unknown clinical response evaluation at Visit 4. Seven subjects (2 azi 3-day; 2 azi 6-day; 3 amox/clav) were excluded from the analyses for using concomitant systemic antibiotics for intercurrent illnesses.

Efficacy Results

Efficacy results are discussed with respect to two analyses, MITT and clinically evaluable.

MITT Analyses

Nine hundred twenty subjects (307 azi 3-day; 306 azi 6-day; 307 amox/clav) were included in the MITT analyses. Twenty-eight subjects (4 azi 3-day; 8 azi 6-day; 16 amox/clav) had missing/unknown outcomes at EOT and 40 subjects (9 azi 3-day; 12 azi 6-day; 19 amox/clav) had missing/unknown outcomes at EOS. In this analysis, subjects with a missing/unknown clinical outcome were not included in the calculation of success rates. The 97.5% confidence intervals for the difference between the success rates for amoxicillin/clavulanate versus each of the azithromycin treatment groups (azi 3-day; azi 6-day) demonstrated equivalence at both EOT (Visit 3) and EOS (Visit 4). The clinical outcomes at the EOT and EOS time points are shown in the following table.

Table C-10: Clinical Response – MITT Population

				97.5 % CI	
	Azi 3D	Azi 6D	A/C	Azi 3D-A/C	Azi 6D-A/C
EOT (N [% Success])[a]	268(88.4%)	265(88.9%)	248(85.2%)	(-3.0, 9.4)	(-2.5, 9.9)
EOS (N [% Cure])[b]	213(71.5%)	218(74.1%)	206(71.5%)	(-8.4, 8.3)	(-5.6, 10.9)

Azi 3D = azithromycin 3-day; Azi 6D = azithromycin 6-day; A/C = amoxicillin/clavulanate.
EOT success = Cure + Improvement, EOS success = Cure.
[a]Visit 3
[b]Visit 4

Medical Officer's Comments:

The sponsor submitted the above table. However, the statistical reviewer, Dr. Scott Komo, performed a sensitivity analysis where Unknowns were classified as failures. The effect of this change does not substantially change the results of the analyses. In fact, because the amoxicillin/clavulanate arm has more unknowns than either of the

azithromycin arms, its response rate is decreased more than the azithromycin arms so the lower bound of the confidence interval is farther away from the noninferiority margin. The revised results are presented below:

Table C-11: Revised Clinical Response Rates in the MITT Population

Time	#Subjects w/o a clinical response or classified as Unknown			N (%)			97.5 % CI (%)	
	Azi 3-Day	Azi 6-Day	A/C	Azi 3-Day	Azi 6-Day	A/C	Azi 3D – A/C	Azi 6D – A/C
EOT	4	8	16	268 (87.3%)	265 (86.6%)	248 (80.8%)	(-0.1, 13.1)	(-0.8, 12.5)
EOS	9	12	19	213 (69.4%)	218 (71.2%)	206 (67.1%)	(-6.1, 10.7)	(-4.2, 12.5)

EOT Success = Cure + Improvement; EOS Success = Cure

Clinical Response Stratified by Presence or Absence of Allergic Rhinitis at Baseline (Clinical MITT Population)

Clinical response at EOT (Visit 3) and EOS (Visit 4) stratified by baseline allergic rhinitis is presented in Table C-12:

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Table C-12: Clinical Response Stratified by Allergic Rhinitis Status at Baseline - MITT Population

		Azithromycin 3-Day	Azithromycin 6-Day	Amox/Clav
With Allergic Rhinitis	Subjects Evaluable at End of Therapy	108	112	117
	Success	95 (88.0%)	101 (90.2%)	98 (83.8%)
	Cure	39	40	32
	Improvement	56	61	66
	Failure	13 (12.0%)	11 (9.8%)	19 (16.2%)
	Subjects Evaluable at End of Study	107	110	116
	Cure	79 (73.8%)	80 (72.7%)	77 (66.4%)
	Failure	28 (26.2%)	30 (27.3%)	39 (33.6%)
Without Allergic Rhinitis	Subjects Evaluable at End of Therapy	195	186	174
	Success	173 (88.7%)	164 (88.2%)	150 (86.2%)
	Cure	88	79	65
	Improvement	85	85	85
	Failure	22 (11.3%)	22 (11.8%)	24 (13.8%)
	Subjects Evaluable at End of Study	191	184	172
	Cure	134 (70.2%)	138 (75.0%)	129 (75.0%)
	Failure	57 (29.8%)	46 (25.0%)	43 (25.0%)

Unknown responses are not included in the analysis

Medical Officer's Comments:

Across all treatment groups, the success rates at EOT were comparable for subjects with and without baseline allergic rhinitis. Similarly, at EOS the success rates were comparable for subjects with and without baseline allergic rhinitis. There were no clinically meaningful differences between the two azithromycin treatment groups and the amoxicillin/clavulanate treatment group.

Clinically Evaluable Analyses

Eight hundred twenty-four subjects (280 azi 3-day; 281 azi 6-day; 263 amox/clav) were included in the clinical evaluable analyses. Of these 824 subjects, 799 subjects (269 azi 3-day; 271 azi 6-day; 259 amox/clav) were included in the EOT analysis and 794 subjects (272 azi 3-day; 271 azi 6-day; 251 amox/clav) were included in the EOS analysis. The 97.5% confidence intervals for the difference between the success rates for amoxicillin/clavulanate versus each of the azithromycin treatment groups (azi 3-day; azi 6-day) demonstrated equivalence at both EOT (Visit 3) and EOS (Visit 4). The clinical outcomes at the EOT and EOS time points are shown in the following table.

Table C-13: Clinical Response – Clinically Evaluable Population

	Azi 3D	Azi 6D	A/C	97.5 % CI Azi 3D-A/C	97.5 % CI Azi 6D-A/C
EOT (N [% Success])[a]	239(88.8%)	242(89.3%)	220(84.9%)	(-2.7, 10.5)	(-2.2, 10.9)
EOS (N [% Cure])[b]	195(71.7%)	199(73.4%)	179(71.3%)	(-8.5, 9.2)	(-6.7, 10.9)

Azi 3D = azithromycin 3-day; Azi 6D = azithromycin 6-day; A/C = amoxicillin/clavulanate.
[a]Visit 3
[b]Visit 4
EOT success = Cure + Improvement; EOS success = Cure.

Medical Officer's Comments:

The results from the clinically evaluable analyses and MITT analyses were consistent.

Clinical Response Stratified by Presence or Absence of Allergic Rhinitis at Baseline (Clinically Evaluable Population)

Clinical response at EOT (Visit 3) and EOS (Visit 4) stratified by baseline allergic rhinitis is presented in Table C-14 for the clinical evaluable population.

Table C-14: Clinical Response Stratified by Allergic Rhinitis Status at Baseline – Clinically Evaluable Population

		Azithromycin 3-Day	Azithromycin 6-Day	Amox/Clav
With Allergic Rhinitis	Subjects Evaluable at End of Therapy	95	100	102
	Success	84 (88.4%)	92 (92.0%)	85 (83.3%)
	Cure	38	39	28
	Improvement	46	53	57
	Failure	11 (11.6%)	8 (8.0%)	17 (16.7%)
	Subjects Evaluable at End of Study	97	101	96
	Cure	72 (74.2%)	74 (73.3%)	64 (66.7%)
	Failure	25 (25.8%)	27 (26.7%)	32 (33.3%)
Without Allergic Rhinitis	Subjects Evaluable at End of Therapy	174	171	157
	Success	155 (89.1%)	150 (87.7%)	135 (86.0%)
	Cure	76	73	59
	Improvement	79	77	76
	Failure	19 (10.9%)	21 (12.3%)	22 (14.0%)
	Subjects Evaluable at End of Study	175	170	155
	Cure	123 (70.3%)	125 (73.5%)	115 (74.2%)
	Failure	52 (29.7%)	45 (26.5%)	40 (25.8%)

Medical Officer's Comments:

Similar to the MITT population, the success rates at EOT and EOS were comparable for subjects with and without baseline allergic rhinitis across all treatment groups. There

were no clinically meaningful differences between the two azithromycin treatment groups and the amoxicillin/clavulanate treatment group.

Findings in Special Subgroups:

Gender, Age and Race:

The sponsor did not submit any analyses that examined any gender, race or age differences in the primary endpoint. The statistical reviewer, Dr. Scott Komo, has calculated the following results based on the sponsor's MITT population.
In the both the MITT and CE populations for the EOS assessment, clinical response did not differ much for the three treatment groups by gender. Similarly, for age, the clinical response rates did not differ much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few subjects in this group. Finally, because most of the subjects were Caucasian, it was not possible to determine if the clinical response rates varied by ethnic group.

Table C-15: Clinical Response Rates for the MITT Population for the EOS Assessment

Subgroup	n/N (%)		
	Azi 3-Day	Azi 6-Day	A/C
Gender			
Female	128/186 (68.8)	128/187 (68.4)	124/179 (69.3)
Male	85/121 (70.2)	90/119 (75.6)	82/128 (64.1)
Age			
18-44	142/200 (71.0)	143/196 (73.0)	121/186 (65.0)
45-64	60/88 (68.2)	59/87 (67.8)	72/102 (70.6)
>=65	11/19 (57.9)	16/23 (69.6)	13/19 (68.4)
Ethnicity			
Asian	1/2 (50.0)	8/9 (88.9)	1/3 (33.3)
Black	8/15 (53.3)	10/16 (62.5)	10/14 (71.4)
Hispanic	9/13 (69.2)	14/21 (66.7)	7/7 (100.0)
Other	3/6 (50.0)	1/2 (50.0)	2/3 (66.7)
White	192/271 (70.8)	185/258 (71.7)	186/273 (68.1)

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Table C-16: Clinical Response Rates for the CE population at the EOS Assessment

Subgroup	n/N (%)		
	Azi 3-Day	Azi 6-Day	A/C
Gender			
Female	115/161 (71.4)	116/167 (69.5)	105/152 (69.1)
Male	80/111 (72.1)	83/104 (79.8)	74/99 (74.8)
Age			
18-44	128/175 (73.1)	132/173 (76.3)	105/149 (70.5)
45-64	57/80 (71.2)	53/79 (67.1)	65/88 (73.9)
>=65	10/17 (58.8)	14/19 (73.7)	9/14 (64.3)
Race			
Asian	1/1 (100.0)	7/8 (87.5)	1/2 (50.0)
Black	8/13 (61.5)	9/15 (60.0)	7/9 (77.8)
Hispanic	8/11 (72.7)	13/20 (65.0)	6/13 (46.2)
Other	3/5 (60.0)	1/2 (50.0)	2/3 (66.7)
White	175/242 (72.3)	169/226 (74.8)	163/224 (72.8)

Signs and Symptoms

The signs and symptoms present at baseline were comparable between the azithromycin treatment groups and the amoxicillin/clavulanate treatment group. In both the MITT and clinically evaluable populations, of the signs and symptoms present at baseline, post-nasal purulent discharge, facial pain, headache and nasal congestion were predominantly moderate in intensity across all treatment groups. At EOT (Visit 3), these signs and symptoms along with hyposmia, jaw pain with mastication, and halitosis, improved and were not present in the majority of subjects in all treatment groups. At EOS (Visit 4), all the signs and symptoms continued to improve and individual signs and symptoms were not present in 60% to 98% of subjects. There were no clinically meaningful differences between the azithromycin treatment groups and the amoxicillin/clavulanate treatment group.

Radiological Findings

Radiological findings for both the MITT population and for the clinically evaluable population are presented in Tables C-17 and C-18:

Table C-17: Radiological Findings – MITT Population

		Azi 3-Day		Azi 6-Day		Amox/Clav	
Baseline Visit	Number of Subjects*	307		306		307	
	Opacification						
	Present	184	(59.9%)	164	(53.6%)	171	(55.7%)
	Absent	120	(39.1%)	140	(45.8%)	134	(43.6%)
	Not Done / Missing	3	(1.0%)	2	(0.7%)	2	(0.7%)
	Air Fluid Level						
	Present	98	(31.9%)	82	(26.8%)	89	(29.0%)
	Absent	206	(67.1%)	222	(72.5%)	216	(70.4%)
	Not Done / Missing	3	(1.0%)	2	(0.7%)	2	(0.7%)
	>=6 mm Mucosal Thickening						
	Present	197	(64.2%)	221	(72.2%)	208	(67.8%)
	Absent	107	(34.9%)	83	(27.1%)	97	(31.6%)
	Not Done / Missing	3	(1.0%)	2	(0.7%)	2	(0.7%)
End of Therapy (Visit 3)	Number of Subjects*	303		297		291	
	Opacification						
	Present	15	(5.0%)	18	(6.1%)	29	(10.0%)
	Absent	26	(8.6%)	25	(8.4%)	23	(7.9%)
	Not Done / Missing	262	(86.5%)	254	(85.5%)	239	(82.1%)
	Air Fluid Level						
	Present	4	(1.3%)	8	(2.7%)	14	(4.8%)
	Absent	37	(12.2%)	35	(11.8%)	37	(12.7%)
	Not Done / Missing	262	(86.5%)	254	(85.5%)	240	(82.5%)
	>=6 mm Mucosal Thickening						
	Present	22	(7.3%)	23	(7.7%)	29	(10.0%)
	Absent	19	(6.3%)	20	(6.7%)	22	(7.6%)
	Not Done / Missing	262	(86.5%)	254	(85.5%)	240	(82.5%)
	Comparison To Baseline						
	Worse Than At Baseline	6	(2.0%)	7	(2.4%)	12	(4.1%)
	Same As Baseline	12	(4.0%)	13	(4.4%)	10	(3.4%)
	Better Than Baseline	20	(6.6%)	16	(5.4%)	26	(8.9%)
	Complete Resolution	3	(1.0%)	3	(1.0%)	3	(1.0%)
	Not Done	262	(86.5%)	258	(86.9%)	240	(82.5%)

Table C-17: Radiological Findings – MITT Population (cont.)

		Azi 3-Day		Azi 6-Day		Amox/Clav	
End of Study (Visit 4)	Number of Subjects*	293		286		278	
	Opacification						
	Present	84	(28.7%)	74	(25.9%)	81	(29.1%)
	Absent	196	(66.9%)	194	(67.8%)	177	(63.7%)
	Not Done / Missing	13	(4.4%)	18	(6.3%)	20	(7.2%)
	Air Fluid Level						
	Present	29	(9.9%)	19	(6.6%)	21	(7.6%)
	Absent	250	(85.3%)	249	(87.1%)	237	(85.3%)
	Not Done / Missing	14	(4.8%)	18	(6.3%)	20	(7.2%)
	>=6 mm Mucosal Thickening						
	Present	108	(36.9%)	97	(33.9%)	101	(36.3%)
	Absent	172	(58.7%)	171	(59.8%)	156	(56.1%)
	Not Done / Missing	13	(4.4%)	18	(6.3%)	21	(7.6%)
Comparison To Baseline							
Worse Than At Baseline		15	(5.1%)	11	(3.8%)	15	(5.4%)
Same As Baseline		54	(18.4%)	42	(14.7%)	57	(20.5%)
Better Than Baseline		135	(46.1%)	119	(41.6%)	106	(38.1%)
Complete Resolution		75	(25.6%)	93	(32.5%)	78	(28.1%)
Not Done		14	(4.8%)	21	(7.3%)	22	(7.9%)

*: Totals may not match the clinical response tables due to subjects with unknown responses recoded to failure.

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Table C-18: Radiological Findings – Clinically evaluable Population

		Azi 3-Day		Azi 6-Day	Amox/Clav
Baseline Visit	Number of Subjects*	280		281	263
	Opacification				
	Present	176	(62.9%)	156 (55.5%)	149 (56.7%)
	Absent	104	(37.1%)	125 (44.5%)	114 (43.3%)
	Air Fluid Level				
	Present	94	(33.6%)	78 (27.8%)	78 (29.7%)
	Absent	186	(66.4%)	203 (72.2%)	185 (70.3%)
	>=6 mm Mucosal Thickening				
	Present	188	(67.1%)	210 (74.7%)	186 (70.7%)
	Absent	92	(32.9%)	71 (25.3%)	77 (29.3%)
End of Therapy (Visit 3)	Number of Subjects*	269		270	257
	Opacification				
	Present	12	(4.5%)	15 (5.6%)	25 (9.7%)
	Absent	20	(7.4%)	19 (7.0%)	18 (7.0%)
	Not Done / Missing	237	(88.1%)	236 (87.4%)	214 (83.3%)
	Air Fluid Level				
	Present	3	(1.1%)	4 (1.5%)	12 (4.7%)
	Absent	29	(10.8%)	30 (11.1%)	30 (11.7%)
	Not Done / Missing	237	(88.1%)	236 (87.4%)	215 (83.7%)
	>=6 mm Mucosal Thickening				
	Present	20	(7.4%)	20 (7.4%)	25 (9.7%)
	Absent	12	(4.5%)	14 (5.2%)	17 (6.6%)
	Not Done / Missing	237	(88.1%)	236 (87.4%)	215 (83.7%)
	Comparison To Baseline				
	Worse Than At Baseline	5	(1.9%)	6 (2.2%)	12 (4.7%)
	Same As Baseline	9	(3.3%)	10 (3.7%)	7 (2.7%)
	Better Than Baseline	15	(5.6%)	12 (4.4%)	20 (7.8%)
	Complete Resolution	3	(1.1%)	3 (1.1%)	3 (1.2%)
	Not Done	237	(88.1%)	239 (88.5%)	215 (83.7%)
End of Study (Visit 4)	Number of Subjects*	265		262	241
	Opacification				
	Present	81	(30.6%)	68 (26.0%)	71 (29.5%)
	Absent	176	(66.4%)	181 (69.1%)	159 (66.0%)
	Not Done / Missing	8	(3.0%)	13 (5.0%)	11 (4.6%)

Table C-18: Radiological Findings – Clinically evaluable Population (cont.)

	Azi 3-Day		Azi 6-Day		Amox/Clav	
Air Fluid Level						
Present	27	(10.2%)	17	(6.5%)	17	(7.1%)
Absent	229	(86.4%)	232	(88.5%)	213	(88.4%)
Not Done / Missing	9	(3.4%)	13	(5.0%)	11	(4.6%)
>=6 mm Mucosal Thickening						
Present	104	(39.2%)	90	(34.4%)	96	(39.8%)
Absent	153	(57.7%)	159	(60.7%)	133	(55.2%)
Not Done / Missing	8	(3.0%)	13	(5.0%)	12	(5.0%)
Comparison To Baseline						
Worse Than At Baseline	13	(4.9%)	10	(3.8%)	14	(5.8%)
Same As Baseline	47	(17.7%)	33	(12.6%)	46	(19.1%)
Better Than Baseline	128	(48.3%)	113	(43.1%)	97	(40.2%)
Complete Resolution	69	(26.0%)	92	(35.1%)	73	(30.3%)
Not Done	8	(3.0%)	14	(5.3%)	11	(4.6%)

***: Totals may not match the clinical response tables due to subjects with unknown responses recoded to failure.**

Medical Officer's Comments:

Subjects in the two azithromycin treatment groups were comparable with subjects in the amoxicillin/clavulanate treatment group regarding their radiological findings at baseline. At EOS, a majority of the subjects across all treatment groups had radiological findings which were better than at baseline (range: 38.1%-46.1%) or completely resolved (range: 25.6%-32.5%).

Applicant's Efficacy Conclusions

Nine hundred twenty subjects (307 azi 3-day; 306 azi 6-day; 307 amox/clav) were included in the MITT analyses and 824 subjects (280 azi 3-day; 281 azi 6-day; 263 amox/clav) were included in the clinically evaluable analyses. The results from the MITT analyses and the clinically evaluable analyses demonstrated that clinical success rates for azithromycin administered for 3 days or 6 days were equivalent to that of amoxicillin/clavulanate administered for 10 days.

For both the MITT and clinically evaluable analyses, in all treatment groups, the success rates at EOT and EOS were comparable for subjects with and without baseline allergic rhinitis.

Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall clinical success rates appeared similar whether azithromycin was administered over 3 or 6 days.

For both the MITT and clinically evaluable analyses, protocol specified signs and symptoms (i.e., post-nasal purulent discharge, facial pain, hyposmia, jaw pain with mastication, headache, halitosis, and nasal congestion) improved throughout the course of the study in all treatment groups.

The incidence of radiological findings (i.e., opacification, air fluid level, and mucosal thickening of 6 mm or greater) decreased throughout the course of the study in all treatment groups for both the MITT and clinically evaluable analyses.

Medical Officer's Comments:

The Medical Officer concurs with the Applicant's conclusions.

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SAFETY EVALUATION

Safety Results

The safety population included all subjects who received at least one dose of study drug after randomization. A total of 936 subjects (312 azi 3-day; 311 azi 6-day; 313 amox/clav) were included in the safety analyses. Five subjects randomized to treatment (4 azi 3-day; 1 amox/clav) did not receive study drug and are not included in the safety evaluable population.

Adverse Events

Discontinuations of Study Drug and Dose Reductions due to Adverse Events

Fifty-five subjects discontinued study drug due to adverse events. There were more subjects who discontinued study drug in the amoxicillin/clavulanate treatment group than in either of the two azithromycin treatment groups. The most frequently occurring adverse events that led to study drug discontinuations are shown in the following table.

Table C-19: The Most Frequently Occurring Adverse Event That led to Study Drug Discontinuations

	Azi 3-Day	Azi 6-Day	Amox/Clav
No. of Subjects Who Discontinued Study Drug due to AEs[#]	10	13	32
No. of Subjects Who Discontinued due to:			
Diarrhea	3	5	14
Nausea	4	5	7
Vomiting	1	3	5
Abdominal Pain	1	3	4

[#]Subjects may have discontinued study drug due to more than one adverse event.

Incidence of Adverse Events

All Causality TEAEs (Treatment-Emergent Adverse Events)

Of the 936 subjects who received study drug, 51.0% (159/312) azi 3-day subjects, 53.7% (167/311) azi 6-day subjects, and 67.1% (210/313) amox/clav subjects reported at least one adverse event during the study or up to 35 days after the last dose of study drug.

TEAE that occurred in ≥1% or more subjects within any treatment group are shown in the following table.

Table C-20: TEAEs (All Causality) That Occurred in ≥1% of Subjects Within any Treatment Group

	Azi 3-Day	Azi 6-Day	Amox/Clav
Abdominal Pain	18 (5.8)	25 (8.0)	20 (6.4)
Chest pain	4 (1.3)	3 (1.0)	0
Diarrhea	50 (16.0)	60 (19.3)	86 (27.5)
Dyspepsia	10 (3.2)	7 (2.3)	11 (3.5)
Flatulence	17 (5.4)	11 (3.5)	8 (2.6)
Headache	12 (3.8)	9 (2.9)	7 (2.2)
Nausea	24 (7.7)	29 (9.3)	40 (12.8)
Pruritis	4 (1.3)	0	6 (1.9)
Rhinitis	13 (4.2)	11 (3.5)	6 (1.9)
Stools (loose)	5 (1.6)	12 (3.9)	21 (6.7)
Vomiting	3 (1.0)	9 (2.9)	13 (4.2)

Subjects may have had more than one adverse event.

Medical Officer's Comments:

Diarrhea was the most frequently occurring adverse event across all treatment groups and was the only TEAE that occurred at a 5% or higher difference in rate between the azithromycin treatment groups and the amoxicillin/clavulanate treatment group. The incidences of both diarrhea and nausea were higher in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups. The majority of the adverse events were mild or moderate in severity.

Treatment-Related TEAEs

A higher percentage of amoxicillin/clavulanate treated subjects (51.1%) experienced treatment-related TEAEs than did azithromycin treated subjects (31.1% azi 3-day; 37.6% azi 6-day).

Treatment-related TEAEs that occurred in ≥1% or more of subjects within any treatment group are shown in the following table.

Table C-21: TEAEs (Treatment-Related) That Occurred in ≥1% of Subjects Within any Treatment Group

	Azi 3-Day	Azi 6-Day	Amox/Clav
Abdominal Pain	18 (5.8)	23 (7.4)	19 (6.1)
Diarrhea	49 (15.7)	56 (18.0)	82 (26.2)
Dyspepsia	9 (2.9)	7 (2.3)	10 (3.2)
Flatulence	17 (5.4)	11 (3.5)	6 (1.9)
Nausea	23 (7.4)	27 (8.7)	38 (12.1)
Pruritis	0	0	4 (1.3)
Stools (loose)	5 (1.6)	10 (3.2)	21 (6.7)
Vomiting	0	7 (2.3)	10 (3.2)

Subjects may have had more than one adverse event.

Medical Officer's Comments:

Diarrhea was the most frequently occurring treatment-related TEAE in all treatment groups. Diarrhea and nausea occurred at a higher rate in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups. The majority of the treatment-related TEAEs were mild or moderate in severity.

Serious Adverse Events

Two subjects in the amoxicillin/clavulanate treatment group experienced a serious adverse event. One patient died (detail summary below). A summary of the other subject with serious ADR follows:

Subject 1034-653: A 39 year-old white female subject was randomized to the amoxicillin/clavulanate treatment group. Amoxicillin/clavulanate was administered orally at a total daily dose of 1500 mg amoxicillin/375 mg clavulanate from 23 July 2001 to 26 July 2001, a total of 4 days. On —, study drug was discontinued because the subject developed conjunctivitis, otitis media, and worsening sinusitis, which were treated with double strength sulfamethoxazole/trimethoprim, methylprednisolone, guaifenesin, and cortisporin ophthalmic drops. On — the subject was diagnosed with worsening depression. On — the subject left a telephone message at the site indicating that she had taken 20 tablets of diazepam on — The site tried calling the subject at home but was told by her husband that she was at work. On —, she was admitted to the psychiatric unit and treated with fluoxetine. Evaluations done on — indicated that her physical examination was essentially negative and benign, electrolytes, T4, T3, liver function tests and CBC counts were within normal limits, a rapid plasma reagin test was nonreactive and a pregnancy test done on — was negative. The intentional drug overdose resolved on —

The subject had a medical history of depression, insomnia, seasonal allergic rhinitis, restless leg syndrome, anxiety, post traumatic stress disorder, decreased libido, and drug allergies. Concomitant medications included trazodone, budesonide, bupropion hydrochloride, cetirizine hydrochloride, and diazepam.

In the investigator's opinion, the intentional drug overdose and worsening depression were not due to amoxicillin/clavulanate but to the subject's history of depression.

Deaths

One subject in the amoxicillin/clavulanate treatment group experienced a cardiac arrest on Day 13 and died. A summary for this subject follows.

Subject 1028-1039: A 71 year-old white male subject was randomized to the amoxicillin/clavulanate treatment group. Amoxicillin/clavulanate was administered orally at a total daily dose of 1500 mg amoxicillin/375 mg clavulanate from 10 January 2002 to 19 January 2002, a total of 10 days. The subject completed treatment and at Visit 3 (1/19/2002) was considered to have been clinically cured. On the subject was prescribed venlafaxine hydrochloride for non-serious symptoms of depression. On the subject was found dead in his bed. An autopsy report noted that the cause of death was cardiac arrest and respiratory arrest.

Clinical Laboratory Test Results

Discontinuations of Study Drug due to Laboratory Test Abnormalities

One azithromycin treated subject (1038-0057) discontinued from the study drug due to laboratory test abnormalities. Results of baseline laboratory tests indicated that this subject had elevated levels of SGOT (96 IU/L; 3xULN) and SGPT (181 IU/L; 5xULN). Baseline levels of LDH were slightly elevated. Although this subject permanently discontinued blinded therapy on Day 6, all three doses of azithromycin had been taken by the subject prior to stopping blinded therapy. Results of laboratory tests performed on Day 8 indicated that SGOT levels had decreased to 51 IU/L (1.4xULN) and SGPT had decreased to 97 IU/L (2.6xULN). LDH levels had returned to normal. The subject remained in the study and on Day 29; SGOT and SGPT levels had decreased further but were still above upper limits of normal. The investigator reported that these lab elevations had resolved by Day 69.

Incidence of Clinical Laboratory Test Abnormalities

Three hundred eight (98.7%) subjects in the azi 3-day group, 300 (96.5%) subjects in the azi 6-day group, and 296 (94.6%) subjects in the amoxicillin/clavulanate group had laboratory data analyzed for safety (i.e., at least one laboratory assessment at baseline and at least one laboratory assessment after baseline). Laboratory abnormalities were summarized without regard to baseline laboratory abnormalities.

Without Regard to Baseline Abnormality: Nine hundred four subjects (308 azi 3-day; 300 azi 6-day; 296 amox/clav) had at least one laboratory assessment at baseline and at least one post-baseline laboratory evaluation. Of these 904 subjects, 48 (16%) azi 3-day subjects, 38 (13%) azi 6-day subjects, and 57 (19%) amox/clav subjects has laboratory test abnormalities when analyzed without regard to the presence or absence of a baseline abnormality. The most commonly observed laboratory test abnormality was blood in urine (measured qualitatively) (11/61 [18%] azi 3-day; 13/46 [28%] azi 6-day; 19/62 [31%] amox/clav). There were no meaningful differences among treatment groups.

Applicant's Safety Conclusions

Nine hundred thirty-six subjects received study drug and were included in the safety analyses. The incidence of adverse events, irrespective of relationship to study drug, was higher in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups (51.0% azi 3-day subjects, 53.7% azi 6-day subjects, and 67.1% amox/clav subjects). The incidences of both diarrhea and nausea were higher in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups. Diarrhea was the most frequently occurring adverse event across all treatment groups and was the only TEAE that occurred at a 5% or higher difference in rate between the azithromycin treatment groups and the amoxicillin/clavulanate treatment group. The incidences of diarrhea, nausea, and abdominal pain were slightly higher in the azithromycin 6-day treatment group compared with the azithromycin 3-day treatment group.

A higher percentage of amoxicillin/clavulanate treated subjects (51.1%) experienced treatment-related TEAEs than did azithromycin treated subjects (31.1% azi 3-day; 37.6% azi 6-day). Diarrhea, abdominal pain, nausea, and flatulence were the only treatment-related TEAEs that occurred in 5% or more of subjects. Diarrhea and nausea occurred at a higher rate in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups. Flatulence occurred at a higher rate in the azithromycin treatment groups than in the amoxicillin/clavulanate treatment group. The majority of the treatment-related TEAEs were mild or moderate in severity. The incidences of diarrhea, nausea, and abdominal pain were slightly higher in the azithromycin 6-day treatment group compared with the azithromycin 3-day treatment group.

Fifty-five subjects discontinued study drug due to adverse events. There were more subjects who discontinued study drug due to adverse events in the amoxicillin/clavulanate treatment group (32 subjects) than in either of the two azithromycin treatment groups (10 subjects in the azi 3-day group and 13 subjects in the azi 6-day group).

Two subjects in the amoxicillin/clavulanate treatment group experienced serious adverse events. The first subject experienced a cardiac arrest on ` and died. The second subject was hospitalized for an intentional drug overdose. The investigator considered both of these adverse events to be unrelated to study drug. There were no serious adverse events in the azithromycin treatment groups.

APPLICANT'S SUMMARY AND CONCLUSIONS

The primary objective of this study was to evaluate the clinical efficacy of oral azithromycin administered at 500 mg/day for 3 days or 6 days compared with oral amoxicillin/clavulanate administered as 500 mg amoxicillin/125 mg clavulanate t.i.d. for 10 days in the treatment of subjects with acute bacterial sinusitis. A secondary objective was to compare the safety and toleration of these regimens.

In this study, 500 mg/day of azithromycin administered for either 3 days or 6 days was as efficacious as 1500 mg amoxicillin/375 mg clavulanate per day administered for 10 days. Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall clinical success rates appeared similar whether azithromycin was administered over 3 or 6 days.

In the azithromycin and amoxicillin/clavulanate treatment groups, signs and symptoms of acute bacterial sinusitis as well as the incidence of radiological findings improved throughout the course of the study.

The overall rate of adverse events and number of subjects who discontinued study drug was higher in the amoxicillin/clavulanate treatment group than in either of the azithromycin treatment groups. Based on the results of this study the following conclusions can be made:

- It was observed that administration of azithromycin at 500 mg/day for 3 days was equivalent in efficacy to amoxicillin/clavulanate administered at 1500 mg amoxicillin/375 mg clavulanate per day for 10 days. This was true at both the EOT and EOS time points for both the MITT and clinically evaluable subgroup analyses.
- Treatment with azithromycin (500 mg/day) for 3 days showed improved toleration compared with 10 days of 1500 mg amoxicillin/375 mg clavulanate per day as indicated by a reduction in the overall rate of adverse events, gastrointestinal-related adverse events, and subject discontinuations due to adverse events.
- Treatment with azithromycin (500 mg/day) for 6 days was also equivalent in efficacy to 10 days of 1500 mg amoxixillin/375 mg clavulanate per day, and better tolerated.
- Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall clinical success rates appeared similar whether azithromycin was administered over 3 or 6 days.

Medical Officer's Comments:

The Medical Officer concurs with the Applicant's conclusions.

b). REVIEW OF STUDY A0661057.

Title of the study: *A multicenter open-label trial evaluating oral therapy with Zithromax® (Azithromycin) 500 mg/day for 3 days, and Zithromax® 500 mg/day for 6 days for the treatment of acute bacterial sinusitis.*

Investigative Sites

Fifty-five sites (38 US; 12 Latin America [Argentina=3; Chile=1; Costa Rica=3; Guatamala=1; Mexico=3; Panama=1]; 5 Finland) were filed to the IND and received study drug. A total of 941 subjects were enrolled. The study was conducted between 24 April 2001 and 13 August 2002.
Sites that randomized subjects to treatment are listed in Table

United States	Jay L. Adler, MD; Angelo S. Agro, MD[a]; Malik N. Baz, MD, FAAP; Robert B. Bettis, MD[b]; Milan L. Brandon, MD, FACA.; Patricia Buchanan, MD; Clinton N. Corder, PhD, MD; David Devorkin, MD; Joseph D. Diaz, MD; James I. Fidelholtz, MD; Raul E. Gaona, MD; Dwight Goddhard, MD; Trevor I. Goldberg, MD; James A. Hadley, MD; Kim C. Hendrick, MD; Dan C. Henry, MD[b]; Michael J. Hickham, MD[a]; Stanley R. Horner, DO; David J. Isaacson, MD; James E. Jarrett, MD; Peter A. Johnson, MD; Edward M. Kerwin, MD; Leslie Stephen Kreisler, MD; Edward M. Lane, MD[b]; Brian Keith Lansford, MD; Brian L. Matthews, MD[b]; Gary L. McCulloch, MD[a,b]; Lothar McMillian, MD; Don Lauchlin McNeil, Jr., MD; Michael L. Merrin, MD; John J. Murray, MD, PhD; Anjuli S. Nayak, MD[a]; Richard W. Nielsen, MD; Randall L. Real, MD; Michael A. Safdi, MD; Martin J. Schear, MD; Kenneth A. Scheinberg, MD; Zafar Sheikh, MD; John Siddoway, MD; Sudeep Singh, MD; William N. Sokol, MD[a]; Richard E. Sterling, MD[b]; James Chiu Fai Yee, MD
Finland	Jorma Juhani Haapaniemi, MD; Riitta Helena Hahtamo-Suuronen, MD; Heikki Juhani Kiukaaiemi, MD; Matti Eero Juhani Pietola, MD; Markus Esko Peter Rautiainen, MD
Latin America	
Argentina	Oscar Enrique Candas, MD; Maria Cristina De Salvo, MD; Guillermo Kaminszczik, MD; Enrique Juan Mansilla, MD; Horacio Rafael Marcello, MD
Chile	Jorge Acuna Cisternas, MD; Paz Emparanza Paiva, MD
Costa Rica	Samuel Flikier-Frajnd, MD; Max Guth Morales, MD; Rolanda Gil Ng, MD
Guatamala	Oscar Terraza Calderon, MD
Mexico	Victor M. Belalcazar, MD; Jose Lopez Sisniega, MD; Guillermo Hernandez Valencia, MD
Panama	Manuel Mock Donato, MD

[a] No subjects were randomized.
[b] Center also participated in Study A0661036.
Note: Only sites that received study drug are included in this table.

Study Objectives

Primary Objective

The primary objective of this study was to evaluate the bacteriologic efficacy of oral Zithromax® (azithromycin) administered as 500 mg/day for 3 days or 500 mg/day for 6 days in the treatment of subjects with acute bacterial sinusitis.

Secondary Objective

The secondary objectives were to compare the clinical efficacy and safety and toleration of Zithromax® (azithromycin) dosed as 500 mg/day for 3 days or 500 mg/day for 6 days.

INVESTIGATIONAL PLAN

Details of the investigational plan, efficacy and safety evaluability criteria can be found in Appendix II.

STUDY PATIENTS

Disposition of Patients

Five hundred thirty-nine subjects were randomized to treatment (284 azi 3-day; 255 azi 6-day). Five hundred thirty-six subjects (281 azi 3-day; 255 azi 6-day) were treated with study drug and were evaluable for safety analyses. Three subjects who were randomized to the azi 3-day treatment group did not receive study treatment and were not included in the efficacy and safety analyses. These subjects did not receive study drug for the following reasons: Subject No. 001093—otolaryngologist refused to perform sinus puncture; Subject No. 001641—had uncontrolled hyperglycemia; Subject No. 001124—sub-investigator disagreed with radiologist's interpretation of baseline sinus radiograph. Of the 536 treated subjects, 273 subjects (97.2%) in the azi 3-day group and 249 subjects (97.6%) in the azi 6-day group completed the study. There were more subjects enrolled in the azithromycin 3-day treatment group than in the azithromycin 6-day treatment group. This was because amendment 2 of the protocol allowed randomization to continue in only one treatment group after the required number of subjects with target pathogens had been reached in the other treatment group.

The populations analyzed for efficacy are shown in the following table.

Table C-22: Efficacy Populations

	Azi 3-Day N (%)	Azi 6-Day N (%)
Clinical MITT	**281 (100.0)**	**254 (99.6)**
Clinical Evaluable		
Visit 3 (EOT)	257 (91.5)	233 (91.4)
Visit 4 (EOS)	254 (90.4)	230 (90.2)
Bacteriological MITT	74 (26.3)	92 (36.1)
Bacteriological Evaluable		
Visit 3 (EOT)	71 (25.3)	88 (34.5)
Visit 4 (EOS)	68 (24.2)	84 (32.9)

There were no notable differences between treatment groups in subject disposition.

Reasons for exclusion from the clinical (MITT and evaluable) and bacteriological (MITT and evaluable) efficacy analyses are presented in the table below:

Table C-23: Reasons for Exclusion* from Analysis - Safety Population

	Azi 3-Day	Azi 6-Day
Excluded From Clinical MITT Population:		
Subject had incomplete diagnostic criteria	0	1
TOTAL NUMBER OF SUBJECTS EXCLUDED FROM MITT POPULATION	0	1
Excluded From Clinical Evaluable Population:		
End of Therapy (Visit 3)		
Subject is not in clinical MITT population	0	1
Subject did not meet all inclusion/exclusion criteria	13	12
Subject received < 80% of required study doses (unless failure)	2	2
No clinical response at visit 3	2	0
Clinical response outside 6-12 days (unless failure)	10	6
Antibiotic taken prior to baseline	0	1
Baseline X-ray negative	1	0
Signs/Symptoms not present at baseline for >7 days	0	1
TOTAL NUMBER OF SUBJECTS EXCLUDED AT VISIT 3	24	22
End of Study (Visit 4)		
Subject is not in clinical MITT population	0	1
Subject did not meet all inclusion/exclusion criteria	13	12
Subject received < 80% of required study doses (unless failure)	2	2
No clinical response at visit 4	5	6
Subject received concomitant systemic antibiotic	1	0
Clinical response outside 22-36 days (unless failure)	6	4
Antibiotic taken prior to baseline	0	1
Baseline X-ray negative	1	0
Signs/Symptoms not present at baseline for >7 days	0	1
X-ray not done and not failure**	7	9
TOTAL NUMBER OF SUBJECTS EXCLUDED AT VISIT 4	27	25

MITT=Modified Intent-to-Treat
* Subjects may be excluded for more than one reason.
** Subject not excluded from clinical evaluable population at visit 4 if x-ray done at visit 3 instead of visit 4 and investigator clinical response was cure at both visits.

Table C-24: Reasons for Exclusion* from Analysis – Safety Population

	Azi 3-Day	Azi6-Day
Excluded From Bacteriological MITT Population:		
No baseline pathogen	207	163
Subject is not in clinical MITT population	0	1
TOTAL NUMBER OF SUBJECTS EXCLUDED FROM BACTERIOLOGICAL MITT POPULATION	207	163
Excluded From Bacteriological Evaluable Population:		
End of Therapy (Visit 3)		
No baseline pathogen	207	163
Not clinical evaluable at visit 3	24	22
TOTAL NUMBER OF SUBJECTS EXCLUDED AT VISIT 3	210	167
End of Study (Visit 4)		
No baseline pathogen	207	163
Not clinical evaluable at visit 4	27	25
TOTAL NUMBER OF SUBJECTS EXCLUDED AT VISIT 4	213	171

MITT = Modified Intent-to-Treat
*Subjects may be excluded for more than one reason.

Demography and Baseline Characteristics

Demography

Sex, age, race, weight, and height are summarized for the total safety evaluable subjects in Table C-25:

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Table C-25: Demography – Safety Population

	Azithromycin 3-Day						Azithromycin 6-Day					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number of Subjects	123		158		281		121		134		255	
Age (years):												
< 18	0		0		0		0		0		0	
18-44	75	(61.0)	92	(58.2)	167	(59.4)	84	(69.4)	88	(65.7)	172	(67.5)
45-64	38	(30.9)	56	(35.4)	94	(33.5)	24	(19.8)	38	(28.4)	62	(24.3)
>= 65	10	(8.1)	10	(6.3)	20	(7.1)	13	(10.7)	8	(6.0)	21	(8.2)
Mean	40.3		41.7		41.1		39.1		40.2		39.7	
SD	15.0		13.8		14.4		15.9		13.6		14.7	
Range	18-79		18-83		18-83		18-84		18-72		18-84	
Race:												
WHITE	85	(69.1)	112	(70.9)	197	(70.1)	87	(71.9)	101	(75.4)	188	(73.7)
BLACK	9	(7.3)	13	(8.2)	22	(7.8)	7	(5.8)	4	(3.0)	11	(4.3)
ASIAN	5	(4.1)	2	(1.3)	7	(2.5)	2	(1.7)	2	(1.5)	4	(1.6)
HISPANIC	22	(17.9)	29	(18.4)	51	(18.1)	20	(16.5)	26	(19.4)	46	(18.0)
OTHER	2	(1.6)	2	(1.3)	4	(1.4)	5	(4.1)	1	(0.7)	6	(2.4)
Weight (kg):												
Mean	85.9		72.5				83.0		72.6			
SD	17.8		19.3				16.0		18.1			
Range	55.0-147.0		38.6-136.1				52.0-149.7		41.0-135.2			
N	123	(100.0)	158	(100.0)			121	(100.0)	134	(100.0)		
Height (cm):												
Mean	175.7		161.5				176.3		163.1			
SD	9.3		8.4				9.6		7.0			
Range	144.0-196.0		120.0-193.0				130.0-201.0		148.0-180.0			
N	123	(100.0)	158	(100.0)			121	(100.0)	133	(99.3)		

Medical Officer's Comments:

For the safety evaluable population, the majority of subjects in both treatment groups were female and white. The mean ages in the azithromycin 3-day and azithromycin 6-day treatment groups were 41.1±14.4 years (range 18-83 years) and 39.7±14.7 years (range 18-84 years), respectively.

Subjects enrolled at centers in the US were slightly older (mean age: azithromycin 3-day= 43.1±14.0 years [range 18-83 years]; azithromycin 6-day= 42.6±14.8 years [range 18-84 years]) than subjects enrolled at non-US centers (mean age: azithromycin 3-day= 38.2±14.4 years [range 18-74 years]; azithromycin 6-day= 35.1±13.4 years [range 18-70 years]). All other demographic characteristics were comparable between subjects enrolled at centers in the US versus those subjects enrolled at non-US centers.

Primary Diagnoses and Durations

The primary diagnoses and duration of present episode since diagnosis are summarized by treatment group in table C-26:

Table C-26: Primary Diagnosis and Duration – Safety Population

	Azithromycin 3-Day	Azithromycin 6-Day
Number of Subjects	281	255
Primary Diagnosis		
ACUTE BACTERIAL SINUSITIS		
Number of Subjects	281	255
Duration Since First Signs/Symptoms (days)		
Mean	13.8	13.9
Range	[	]
Unspecified (N)	0	1

Duration (days) from first signs/symptoms to Day 1 of study

Medical Officer's Comments:

The mean duration of signs and symptoms prior to presentation was 13.8 days (range 4.0-29.0 days) for azithromycin 3-day subjects and 13.9 days (range 4.0-29.0 days) for azithromycin 6-day subjects.

Medical History

The percentage of subjects with past or present diseases/syndromes was similar between the two azithromycin treatment groups. The most common medical diseases/syndromes that occurred in at least 10% of subjects in any treatment group and were present at study entry are shown in the following table.

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Table C-27: Medical Diseases/Syndromes That Occurred in ≥ 10% of Subjects in any Treatment Group and Were Present at Study Entry

	Azi 3-Day N (%)	Azi 6-Day N (%)
Total Number of Subjects	281 (100.0)	255 (100.0)
Number of Subjects With at Least One Disease/Syndrome	175 (62.3)	159 (62.4)
Allergic Rhinitis, cause Unspecified	38	30
Allergic Rhinitis due to Other Allergen	21	28
Allergic Rhinitis due to Pollen	31	25
Asthma, Unspecified	27	30
Unspecified Essential Hypertension	38	36

A subject may have had more than one type of allergic rhinitis.

Prior Drug Treatments

The percentage of subjects who used drug treatments (excluding antibiotics) was 58.7% in the azi 3-day group and 63.1% in the azi 6-day group. Prior drug treatments used by 10% or more subjects are shown in the following table.

Table C-28: Drug Treatments Other Than Antibiotics Used by ≥10% of Subjects in any Treatment Group

	Azi 3-Day N (%)	Azi 6-Day N (%)
Total Number of Subjects	281 (100.0)	255 (100.0)
Drugs Used in Rheumatic Diseases & Gout	51 (18.1)	39 (15.3)
Analgesics	39 (13.9)	30 (11.8)
Antihypertensive Drugs	27 (9.6)	28 (11.0)
Drugs Used for Local Anesthesia	28 (10.0)	25 (9.8)
Contraceptives	21 (7.5)	26 (10.2)

Five subjects (3 [1.1%] azi 3-day; 2 [0.8%] azi 6-day) used antibiotics prior to the start of the study. These antibiotics included cephalosporins, cephamycins and other beta-lactams, penicillins and quinolones. All 5 subjects were considered to be protocol deviators and excluded from the clinically evaluable efficacy analyses.

Concomitant Medications

The incidence of concomitant medication use was 96.8% [272/281] in the azi 3-day group and 98.8% [252/255] in the azi 6-day group. General categories of concomitant medications used by 10% or more subjects in any treatment group are shown in the following table.

Table C-29: Concomitant Medications Other Than Antibiotics Taken by ≥10% of Subjects in any Treatment Group

	Azi 3-Day N (%)	Azi 6-Day N (%)
Drugs Used for Local Anesthesia	230 (81.9)	211 (82.7)
Drugs Used in Rheumatic Diseases & Gout	91 (32.4)	67 (26.3)
Analgesics	64 (22.8)	64 (25.1)
Bronchodilators	58 (20.6)	61 (23.9)
Systemic Treatment of Symptoms of URT Infections	46 (16.4)	33 (12.9)
Antihypertensive Drugs	28 (10.0)	29 (11.4)
Contraceptives	23 (8.2)	27 (10.6)
Drugs Used in Allergic Disorders	28 (10.0)	15 (5.9)

In both treatment groups, the most frequently used concomitant medications other than antibiotics were: drugs used for local anesthesia, drugs used in rheumatic diseases and gout, analgesics, and bronchodilators.
Sixty-one subjects (13.2% [37/281] azithromycin 3-day; 9.4% [24/255] azithromycin 6-day) used concomitant antibiotics during the study. The most frequently used classes of antibiotics were quinolones (16 azi 3-day; 11 azi 6-day), penicillins (14 azi 3-day; 9 azi 6-day), and cephalosporins, cephamycins, and other beta-lactams (7 azi 3-day; 3 azi 6-day). Of the subjects who used concomitant antibiotics, 5 subjects received antibiotics for the treatment of conditions other than sinusitis and were considered to be protocol deviators. All subjects receiving systemically active antibiotics during the study for the treatment of sinusitis, or conditions related to sinusitis received a clinical response of failure.

Drug Administration

The duration of exposure to active treatment is presented in Table C-30:

Table C-30: Duration of Treatment – Safety Population

	Azi 3-Day	Azi 6-Day
Number of Subjects	281	255
Duration Category (Days)		
<=1	3	0
2	0	1
3	278	3
4	0	1
5	0	0
6	0	250
>6	0	0
Median Duration	3.0	6.0
Range	1-3	2-6

NOTE: The duration is defined as the total number of dosing days from first to and including last day of each therapy.

Medical Officer's Comments:

The median duration of exposure was 3 days (range 1-3 days) for azithromycin 3-day subjects and 6 days (range 2-6 days) for azithromycin 6-day subjects.

Study Discontinuations

Discontinuations from study are presented in the table below:

Table C-31: Discontiunations for Study

	Azi 3-Day		Azi 6-Day	
Number (%) of Subjects	281		255	
Discontinuations				
Related to Study Drug	2	(0.7)	2	(0.8)
Adverse event	0		1	(0.4)
Lack of efficacy	2	(0.7)	1	(0.4)
Not Related to Study Drug	6	(2.1)	4	(1.6)
Adverse event	1	(0.4)	0	
Other	1	(0.4)	1	(0.4)
Subject defaulted	4	(1.4)	3	(1.2)
Total	8	(2.8)	6	(2.4)

Subject defaulted includes: Lost to follow-up and withdrawn consent
Other includes: Does not meet entrance criteria, other, and protocol violation.

Medical Officer's Comments:

Fourteen subjects (8 azi 3-day; 6 azi 6-day) discontinued from the study. The most frequent reason for study discontinuation in both treatment groups was "Subject Defaulted" (i.e., lost to follow-up), (4 azi 3-day; 3 azi 6-day).

Two subjects (1 azi 3-day; 1 azi 6-day) discontinued from the study due to adverse events.

There were no subjects who had temporary discontinuations, dose reductions due to adverse events or who discontinued due to abnormal laboratory test results.

Protocol Deviations

One hundred seventy-seven subjects (94 azi 3-day; 83 azi 6-day) deviated from the protocol. The protocol deviations are summarized in the following table.

Table C-32: Summary of Protocol Deviations

	Azi 3-Day N	Azi 6-Day N
No. of Subjects With a Protocol Deviation	94	84
General Categories of Protocol Deviations		
Antibiotic use During Study for Condition Other Than Sinusitis	2	3
Concomitant Antihistamine Use[a]	8	3
Concomitant Corticosteroid Use[a]	10	10
Inclusion/Exclusion Criteria	14	14
Missed or Out-of-Window Visits 3 or 4	25	18
Other Protocol Deviations	20	31
Micro Procedure Not Done	4	8
Informed Consent Deviation	8	2
Investigator Interpretation of X-ray Used	8	6
Received <80% or >120% of Required Active Study Medication Doses	5	2
Required Safety Lab or Test Not Done	27	25
X-ray Not Done and Not a Failure	7	9

Subjects may have had more than one protocol deviation.
[a]Concomitant antihistamine or corticosteroid use in subjects assessed as treatment failures was not considered a protocol deviation.

EFFICACY EVALUATION

Data Sets Analyzed

Two populations were analyzed for efficacy: 1) the MITT population which was further defined as the clinical MITT and the bacteriological MITT populations, and 2) the efficacy evaluable population which was further defined as the clinical evaluable and bacteriological evaluable populations. The following table shows the number of subjects that were included in each efficacy population.

Table C-33: Data Sets Analyzed

	Azi 3-Day N (%)	Azi 6-Day N (%)
Total Number of Subjects Treated	**281 (100.0)**	**255 (100.0)**
MITT Populations		
Clinical MITT Population	281 (100.0)	254 (99.6)
Bacteriological MITT Population	74 (26.3)	92 (36.1)
Efficacy Evaluable Populations		
Clinical Evaluable Population		
Visit 3 (EOT)	257 (91.5)	233 (91.4)
Visit 4 (EOS)	254 (90.4)	230 (90.2)
Bacteriological Evaluable Population		
Visit 3 (EOT)	71 (25.3)	88 (34.5)
Visit 4 (EOS)	68 (24.2)	84 (32.9)

Clinical MITT Population

Of the 536 subjects treated, 1 subject in the azi 6-day treatment group was excluded from the clinical MITT population because the subject had incomplete diagnostic criteria.

Bacteriological MITT Population

Three hundred seventy subjects (207 azi 3-day; 163 azi 6-day) were excluded from the bacteriological MITT population because these subjects had no target pathogens at baseline.

Clinically Evaluable Population

Forty-six subjects (24 azi 3-day; 22 azi 6-day) were excluded from the clinically evaluable population at EOT (Visit 3). Most of these subjects did not meet entry criteria, nor had visits outside of the specified time window.

Fifty-two subjects (27 azi 3-day; 25 azi 6-day) were excluded from the clinically evaluable analyses at EOS (Visit 4). Most of these subjects did not meet entry criteria, had visits outside of the specified time window, radiographs were not done and the clinical outcome was not a failure, or had a missing/unknown clinical response evaluation at Visit 4. One subject in the azi 3-day treatment group was excluded from the analyses because the subject used concomitant systemic antibiotics for treatment of a condition other than sinusitis and he was not a prior failure.

Bacteriologically Evaluable Population

Three hundred seventy-seven subjects (210 azi 3-day; 167 azi 6-day) were excluded from the bacteriologically evaluable population at Visit 3 and 384 subjects (213 azi 3-day; 171 azi 6-day) were excluded at Visit 4. Most of these subjects had no target pathogens at baseline or were not clinically evaluable at the applicable visit.

Measurements of Treatment Compliance

The investigators collected records of the exact doses and dosing regimens in the case report form. At the end of the study, all drug supplies unallocated or unused by the subjects were accounted for by the monitors and returned to the sponsor. With the exception of 8 subjects (3 azi 3-day; 5 azi 6-day), treatment compliance was 100%.

Efficacy Results

Efficacy results are discussed with respect to clinical outcomes and bacteriological outcomes.

Clinical Outcomes

Clinical MITT Analyses

Five hundred thirty-five subjects (281 azi 3-day; 254 azi 6-day) were included in the clinical MITT analyses. Three subjects (2 azi 3-day; 1 azi 6-day) had unknown outcomes at EOT and 11 subjects (5 azi 3-day; 6 azi 6-day) had unknown outcomes at

EOS. In these analyses, subjects with a unknown clinical outcome were not included in the calculation of success rates. The clinical success rates at the EOT and EOS time points are shown in the following table.

Table C-34: Clinical Response – Clinical MITT Subjects

	Azi 3-Day	Azi 6-Day
EOT—Visit 3; N (% Success)	248 (88.9%)	240 (94.9%)
EOS—Visit 4; N (% Cure)	214 (77.5%)	210 (84.7%)

EOT Success = Cure + Improvement
EOS Success = Cure

Medical Officer's Comments:

The clinical success rate was slightly higher for subjects in the azithromycin 6-day treatment group than for subjects in the azithromycin 3-day treatment group.
With the exception of the success rate at EOT for subjects in the azithromycin 6-day treatment group, the success rates at the EOT and EOS time points were slightly lower for subjects enrolled at US centers than for subjects enrolled at non-US centers (EOT= 86.2% US vs. 92.9% non-US for azi 3-day; 94.7% US vs. 95% non-US for azi 6-day; EOS= 73.1% US vs. 84.4% non-US for azi 3-day; 81.2% US vs. 89.9% non-US for azi 6-day).

Table C-35: Clinical Response Rates (MITT Subjects Classified as Unknowns are Excluded)

Analysis Population	Time	N (%)	
		Azi 3-Day	Azi 6-Day
MITT			
	EOT	248/279 (88.9)	240/253 (94.9)
	EOS	214/276 (77.5)	210/248 (84.7)

EOT Success = Cure + Improvement; EOS Success = Cure

The above table was submitted by the sponsor. Subjects who are unknowns were excluded from the calculation of response rates for that visit rather than including them as failures. The sponsor has submitted sensitivity analyses where unknowns were classified as failures. The effect of this change does not substantially change the results of the analyses. These sensitivity analyses were performed by the statistician, Dr. Scott Komo. The revised results are presented in table C-36:

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Table C-36: Clinical Response Rates for the MITT Population with Unknowns Classified as Failures

Time	#Unknowns		N (%)		95 % CI (%)
	Azi 3-Day	Azi 6-Day	Azi 3-Day	Azi 6-Day	Azi 6-Day – Azi 3-Day
EOT	2	1	248/281 (88.3)	240/254 (94.5)	(1.5, 11.1)
EOS	5	6	214/281 (76.2)	210/254 (82.7)	(-0.4, 13.3)

EOT Success = Cure + Improvement; EOS Success = Cure

Clinical Response Stratified by Presence or Absence of Allergic Rhinitis at Baseline (Clinical MITT Population)

Clinical response at EOT (Visit 3) and EOS (Visit 4) stratified by baseline allergic rhinitis. For both treatment regimens, the success rates at EOT were comparable for subjects with and without baseline allergic rhinitis. At EOS, the success rates were slightly higher for subjects without baseline allergic rhinitis (79.6% azi 3-day; 86.9% azi 6-day) than for subjects with baseline allergic rhinitis (72.5% azi 3-day; 78.5% azi 6-day).

Clinical Response by Baseline Pathogen (Bacteriological MITT Population)

The clinical success rates at EOT and EOS for the different pathogens are shown in the following table.

Table C-37: Clinical Response by Baseline Pathogen—Bacteriological MITT Subjects

	Azi 3-Day		Azi 6-Day	
EOT; n/N (% Success)				
H. influenzae	28/32	(87.5)	27/28	(96.4)
S. pneumoniae	23/26	(88.5)	39/42	(92.9)
M. catarrhalis	14/15	(93.3)	19/19	(100.0)
S. aureus	2/2	(100.0)	6/6	(100.0)
EOS; n/N (% Cure)				
H. influenzae	24/32	(75.0)	24/28	(85.7)
S. pneumoniae	21/25	(84.0)	34/42	(81.0)
M. catarrhalis	13/15	(92.9)	15/19	(78.9)
S. aureus	2/2	(100.0)	6/6	(100.0)

EOT Success = Cure + Improvement, EOS Success = Cure.
n/N = number of subjects with clinical success/number of subjects evaluable at that time point.

Medical Officer's Comments:

The clinical success rates for all baseline pathogens ranged from 75% to 100% at EOS.

Clinical Evaluable Analyses

Four hundred ninety subjects (257 azi 3-day; 233 azi 6-day) were included in the EOT analysis and 484 subjects (254 azi 3-day; 230 azi 6-day) were included in the EOS

analysis. The clinical success rates at the EOT and EOS time points are shown in the following table.

Table C-38: Clinical Response – Clinical Evaluable Subjects

	Azi 3-Day	Azi 6-Day
EOT—Visit 3; N (% Success)	228 (88.7%)	220 (94.4%)
EOS—Visit 4; N (% Cure)	195 (76.8%)	193 (83.9%)

EOT Success = Cure + Improvement
EOS Success = Cure.

Medical Officer's Comments:

With the exception of the azithromycin 6-day treatment group at EOT, the success rates at the EOT and EOS time points were slightly lower for subjects enrolled at US centers than for subjects enrolled at non-US centers. These results are similar to those described previously for the clinical MITT population.
Overall, the results from the clinical evaluable analyses and clinical MITT analyses were consistent.

Clinical Response Stratified by Presence or Absence of Allergic Rhinitis at Baseline (Clinically Evaluable Population)

Similar to the clinical MITT population, the success rates at EOT were comparable for subjects with and without baseline allergic rhinitis. At EOS, the success rates were slightly higher for subjects without baseline allergic rhinitis (77.9% azi 3-day; 86.0% azi 6-day) than for subjects with baseline allergic rhinitis (74.0% azi 3-day; 78.0% azi 6-day).

Clinical Response by Baseline Pathogen (Bacteriologically Evaluable Population)

The clinical success rates at the EOT and EOS time points are shown in the following table.

Table C-39: Clinical Response by Baseline Pathogen—Bacteriological Evaluable Subjects

	Azi 3-Day	Azi 6-Day
EOT; n/N (% Success)		
H. influenzae	27/31 (87.1)	25/26 (96.2)
S. pneumoniae	23/26 (88.5)	38/41 (92.7)
M. catarrhalis	13/14 (92.9)	18/18 (100.0)
S. aureus	1/1 (100.0)	6/6 (100.0)
EOS; n/N (% Cure)		
H. influenzae	22/30 (73.3)	20/24 (83.3)
S. pneumoniae	21/25 (84.0)	32/40 (80.0)
M. catarrhalis	12/13 (92.3)	13/17 (76.5)
S. aureus	1/1 (100.0)	6/6 (100.0)

EOT Success = Cure + Improvement, EOS Success = Cure.
n/N = number of subjects with clinical success/number of subjects evaluable at that time point.

Medical Officer's Comments:

The clinical success rates by baseline pathogen for the bacteriological MITT and bacteriological-evaluable populations were consistent.

Findings in Special Subgroups:

Gender, Age and Race:

The sponsor did not submit any analyses that examined any gender, race or age differences in the primary endpoint. The statistical reviewer, Dr. Scott Komo, has calculated the following results based on the sponsor's MITT population.
In the bacteriologic MITT for the EOS assessment, bacteriologic response did not differ much for the three treatment groups for gender. Similarly, for age, for the clinical response rates did not differ much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few subjects in this group. Finally, because most of the subjects were Caucasian, it was not possible to determine if the clinical response rates varied by ethnic group.

Table C-40: Subgroup analyses of the Overall Bacteriologic Response in the Bacteriologic MITT Population (Unknowns classified as Failures)

Subgroup	n/N (%)	
	Azi 3-Day	Azi 6-Day
Gender		
Female	34/40 (85.0)	48/56 (85.7)
Male	26/34 (76.5)	29/36 (80.6)
Age		
18-44	40/48 (83.3)	53/61 (86.9)
45-64	16/21 (76.2)	17/23 (73.9)
>=65	4/5 (80.0)	7/8 (87.5)
Race		
Asian	0/0 (0.0)	1/1 (100.0)
Black	4/5 (80.0)	0/0 (0.0)
Hispanic	10/15 (66.7)	21/23 (91.3)
Other	0/0 (0.0)	1/2 (50.0)
White	46/54 (85.2)	54/66 (81.8)

Signs and Symptoms

The signs and symptoms present at baseline were consistent with acute bacterial sinusitis and comparable between the azithromycin treatment groups. At baseline, a majority of the clinical MITT subjects had moderate or severe post-nasal purulent discharge (azi 3-day: 77.2%; azi 6-day: 82.7%), facial pain (azi 3-day: 68.7%; azi 6-day: 75.2%), headache (azi 3-day: 68.0%; azi 6-day: 72.8%), and nasal discharge (azi 3-day: 87.9%; azi 6-day: 87.8%). The results were similar for the clinically evaluable population. In both the clinical MITT and clinically evaluable populations, of the

signs and symptoms present at baseline, post-nasal purulent discharge, facial pain, and headache were predominantly moderate in intensity across both treatment groups. Nasal congestion was predominantly severe in intensity in the azithromycin 6-day group and moderate in intensity in the azithromycin 3-day group. At EOT (Visit 3), these signs and symptoms (along with hyposmia, jaw pain with mastication, and halitosis) improved and with the exception of nasal congestion were not present in the majority of subjects in both treatment groups. At EOS (Visit 4), all the signs and symptoms continued to improve and individual signs and symptoms were not present in 61.7% to 98.8% of subjects.

Radiological Findings

Subjects in the two azithromycin treatment groups were comparable with respect to their radiological findings at baseline (air fluid level: 28.1% azi 3-day; 29.1% azi 6-day; opacification: 57.3% azi 3-day; 58.7% azi 6-day; ≥6 mm mucosal thickening: 57.3% azi 3-day; 53.5% azi 6-day). Baseline radiological findings were consistent with a diagnosis of acute bacterial sinusitis. At EOS, a majority of the subjects in both treatment groups had radiological findings that were better than at baseline (range: 38.6%-41.0%) or completely resolved (range: 36.6%-38.2%). Radiological findings for the clinically evaluable population were consistent with those for the clinical MITT population.

Bacteriological Outcomes

Bacteriological MITT Analyses

One hundred sixty-six subjects (74 azi 3-day; 92 azi 6-day) were included in the bacteriological MITT analyses. The bacteriological success rates at EOT and EOS are shown in the following table.

Table C-41: Overall Bacteriological Response—MITT Subjects

	Azi 3-Day	Azi 6-Day
EOT—Visit 3; N (% Success)	66 (89.2%)	88 (95.7%)
EOS—Visit 4; N (% Success)	60 (83.3%)	77 (83.7%)

Success = Documented Eradication + Presumed Eradication.

Medical Officer's Comments:

The overall bacteriological outcomes in the bacteriological MITT population were similar to clinical success rates in the clinical MITT population. Thus, overall response rates were similar in the subset of subjects with baseline target pathogens (bacteriological MITT population) and subjects with a clinical diagnosis of sinusitis (clinical MITT population).

For both azithromycin treatment groups, the success rates at EOS were slightly higher for subjects at non-US centers (84.2% azi 3-day; 92.2% azi 6-day) than for subjects at US centers (82.4% azi 3-day; 73.2% azi 6-day).

Bacteriologically Evaluable Analyses

One hundred fifty-nine subjects (71 azi 3-day; 88 azi 6-day) were included in the EOT analysis and 152 subjects (68 azi 3-day; 84 azi 6-day) were included in the EOS analysis. The success rates for the bacteriologically evaluable subjects were consistent with those for the bacteriological MITT subjects and were consistent with clinical response rates in clinical MITT subjects.

Similar to the bacteriological MITT analysis subdivided by geographical area, the success rates at EOS were slightly higher for subjects at non-US centers (83.3% azi 3-day; 91.3% azi 6-day) than for subjects at US centers (81.3% azi 3-day; 71.1% azi 6 day).

Bacteriological Response by Baseline Pathogen

The success rates at EOT and EOS by baseline pathogen for the bacteriological MITT subjects are shown in the following table.

Table C-42: Bacteriological Response by Baseline Pathogen – Bacteriological MITT Population

	Azi 3-Day		Azi 6-Day	
EOT; n/N (% Success)				
H. influenzae	28/32	(87.5)	27/28	(96.4)
S. pneumoniae	23/26	(88.5)	39/42	(92.9)
M. catarrhalis	14/15	(93.3)	19/19	(100.0)
S. aureus	2/2	(100.0)	6/6	(100.0)
EOS; n/N (% Success)				
H. influenzae	25/32	(78.1)	24/28	(85.7)
S. pneumoniae	21/25	(84.0)	34/42	(81.0)
M. catarrhalis	13/15	(92.9)	15/19	(78.9)
S. aureus	2/2	(100.0)	6/6	(100.0)

Success = Documented Eradication + Presumed Eradication.
n/N = number of subjects with bacteriological success/number of subjects evaluable at that time point.

Medical Officer's Comments:

As would be expected based on the small number of post-baseline cultures obtained during the study, bacteriological outcome by baseline pathogen was consistent with clinical outcome by pathogen for both azithromycin 3-day and azithromycin 6-day treatment groups.

The success rates at EOT and EOS by baseline pathogen for the bacteriologically evaluable subjects are shown in the following table.

Table C-43: Bacteriological Response by Baseline Pathogen – Bacteriologically Evaluable Population

	Azi 3-Day		Azi 6-Day	
EOT; n/N (% Success)				
H. influenzae	27/31	(87.1)	25/26	(96.2)
S. pneumoniae	23/26	(88.5)	38/41	(92.7)
M. catarrhalis	13/14	(92.9)	18/18	(100.0)
S. aureus	1/1	(100.0)	6/6	(100.0)
EOS; n/N (% Success)				
H. influenzae	23/30	(76.7)	20/24	(83.3)
S. pneumoniae	21/25	(84.0)	32/40	(80.0)
M. catarrhalis	12/13	(92.3)	13/17	(76.5)
S. aureus	1/1	(100.0)	6/6	(100.0)

Success = Documented Eradication + Presumed Eradication.
n/N = number of subjects with bacteriological success/number of subjects evaluable at that time point.

The results were consistent with those for the bacteriological MITT subjects.

Cross Tabulation of Clinical and Pathogen Outcome

For the bacteriological MITT subjects, 74 azi 3-day subjects and 92 azi 6-day subjects were determined to be bacteriologically evaluable at EOT and EOS. The relationships of clinical failures to pathogen outcomes for the bacteriological MITT subjects are summarized in the following table.

Table C-44: Clinical Outcome Failures and Pathogen Response –Bacteriological MITT Subjects

	Azi 3-Day		Azi 6-Day	
	Clinical Failures	**Pathogen Response**	**Clinical Failures**	**Pathogen Response**
H. influenzae				
EOT	4	4 PP	1	1 PP
EOS	8	1 DE; 7 PP	4	3 PP; 1 DP
S. pneumoniae				
EOT	3	3 PP	3	2 PP; 1 DP
EOS	4	4 PP	8	8 PP
M. catarrhalis				
EOT	1	1 PP	0	N/A
EOS	1	1 PP	4	4 PP
S. aureus				
EOT	0	N/A	0	N/A
EOS	0	N/A	0	N/A

DE=Documented Eradication; DP=Documented Persistence; PP=Presumed Persistence; PE=Presumed Eradication; NA=not applicable

Two cases of documented persistence were noted in the azithromycin 6-day treatment group. The first subject (Subject No. 000438) had *H. influenzae* isolates cultured at baseline and at EOS which were sensitive to azithromycin (MIC=2 mcg/mL at both baseline and EOS). The second subject (Subject No. 000446) had *S. pneumoniae*

isolates cultured at baseline and at EOT which were resistant to azithromycin (MIC=16 mcg/mL at both baseline and EOT).

One case of documented eradication was noted in the azithromycin 3-day treatment group. Subject No. 000439 had *H. influenzae* cultured at baseline that were susceptible to azithromycin (MIC=2 mcg/mL). An antral puncture performed at EOS did not yield any pathogens. However, the subject had mild to moderate signs and symptoms of sinusitis (hyposmia, jaw pain with mastication, and halitosis were absent) and results from a sinus radiograph showed no change from baseline.

Baseline Susceptibility to Azithromycin

Overall, 57 isolates of *H. influenzae*, 66 of *S. pneumoniae*, 34 of *M. catarrhalis*, and 8 of *S. aureus* were evaluated for susceptibility. The majority of isolates were considered to be susceptible to azithromycin with the exception of 11/66 (17%) isolates of *S. pneumoniae* and 2/8 (25%) isolates of *S. aureus* that were categorized as resistant.

In the US, 24 isolates of *H. influenzae*, 31 of *S. pneumoniae*, 11 of *M. catarrhalis*, and 6 of *S. aureus* were evaluated for susceptibility. With the exception of 4/31 (13%) *S. pneumoniae* isolates and 1/6 (17%) S. aureus isolate, all isolates were considered susceptible to azithromycin. At non-US sites, 33 isolates of *H. influenzae*, 35 of *S. pneumoniae*, 23 of *M. catarrhalis*, and 2 of *S. aureus* were evaluated for susceptibility. With the exception of 7/35 (20%) *S. pneumoniae* isolates and 1/2 (50%) *S. aureus* isolate, all isolates were considered susceptible to azithromycin.

Twenty-seven subjects (12 azi 3-day; 15 azi 6-day) were bacteriological failures at the EOS time point. All 12 of the azi 3-day subjects had isolates that were susceptible to azithromycin. Among the 15 azi 6-day subjects, 2 subjects had *S. pneumoniae* isolates that were resistant to azithromycin. Subject 000446 had *S. pneumoniae* isolates at both baseline and EOT (Day 8) that were resistant to azithromycin.

Applicant's Efficacy Conclusions

Five hundred thirty-five subjects (281 azi 3-day; 254 azi 6-day) were included in the clinical MITT analyses. For the clinically evaluable analyses, 490 subjects (257 azi 3-day; 233 azi 6-day) were included in the EOT analysis and 484 subjects (254 azi 3-day; 230 azi 6-day) were included in the EOS analysis. The results from the clinical MITT and the clinically evaluable analyses demonstrated that the overall clinical success rates appeared similar whether azithromycin was administered over 3 or 6 days.
One hundred sixty-six subjects (74 azi 3-day; 92 azi 6-day) were included in the bacteriological MITT analyses. For the bacteriologically evaluable analysis, 159 subjects (71 azi 3-day; 88 azi 6-day) were included in the EOT analysis and 152 subjects (68 azi 3-day; 84 azi 6-day) were included in the EOS analysis. Similar to the clinical MITT and clinically evaluable analyses, the results from the bacteriological MITT and bacteriologically evaluable analyses demonstrated that the overall bacteriological success rates appeared similar whether azithromycin was administered over 3 or 6 days.

For subjects with baseline isolates, the clinical and bacteriological success rates were high (azi 3-day: 87%-93% at EOT and 73-100% at EOS; azi 6-day: 93%-100% at EOT

and 77%-100% at EOS) irrespective of the pathogen. Although no statistical comparisons were conducted between the two azithromycin treatment groups, the clinical and bacteriological success rates in subjects with *H. influenzae* appeared slightly higher when azithromycin was administered for 6 days.

For both the clinical MITT and clinically evaluable analyses, in both treatment groups, the success rates at EOT were comparable for subjects with and without baseline allergic rhinitis. At EOS, the success rates were slightly higher for subjects without baseline allergic rhinitis than for subjects with baseline allergic rhinitis.

For both the clinical MITT and clinically evaluable analyses, protocol specified signs and symptoms (i.e., post-nasal purulent discharge, facial pain, hyposmia, jaw pain with mastication, headache, halitosis, and nasal congestion) improved throughout the course of the study in both treatment groups.

The incidence of radiological findings (i.e., opacification, air fluid level, and mucosal thickening of 6 mm or greater) decreased throughout the course of the study in both treatment groups for both the clinical MITT and clinically evaluable analyses.

Medical Officer's Comments:
The Medical reviewer concurs with the Applicant's conclusions.

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SAFETY EVALUATION

Safety Results

The safety population included all subjects who received at least one dose of study drug after randomization. A total of 536 subjects (281 azi 3-day; 255 azi 6-day) were included in the safety analyses. Three subjects randomized to the azi 3-day treatment group did not receive study drug and are not included in the safety evaluable population.

Adverse Events

Discontinuations of Study Drug and Dose Reductions due to Adverse Events

Five subjects (2 azi 3-day; 3 azi 6-day) discontinued study drug due to adverse events; 4 of these 5 subjects went on to complete the study. One subject in the azithromycin 3-day group completed treatment but discontinued from the study due to adverse events during the post-treatment follow-up period. A listing summarizing the discontinuations due to adverse events for these 6 subjects is provided in the following table.

Table C-45: Listing of Subjects who Discontinued due to Adverse Events

Treatment Group **Subject Number**	**Study Drug**	**Duration of Treatment**	**Study**	**Adverse Event**
Azi 3-Day				
000264	Discontinued	1 Day	Completed	Urticaria (Hives on Body)
000569	Completed	3 Days	Discontinued	Worsening of Sinusitis
001707	Discontinued	1 Day	Completed	Asthma, Fever, and Generalized Myalgia
Azi 6-Day				
000135	Discontinued	3 Days	Discontinued	Diarrhea and Nausea
000942	Discontinued	4 Days	Completed	Bilirubinemia (Gilbert's Disease)
001092	Discontinued	2 Days	Completed	Angioedema (Idiopathic Angioedema)

With the exception of "Worsening Sinusitis" and "Bilirubinemia", all the adverse events that led to discontinuations were considered by the investigator to be related to study drug.

Of note are two subjects (Subject Nos. 000942 and 001092) in the azithromycin 6-day treatment group who discontinued study drug due to bilirubinemia and angioedema, respectively. Further information for these 2 subjects is provided below.

Subject No. 000942: An 18-year old Hispanic male with no significant medical history was randomized to the azithromycin 6-day group. The subject received 4 days of

azithromycin therapy and was discontinued from study drug on Day 5 due to bilirubinemia. Baseline laboratory tests results indicated a total bilirubin level of 4.3 mg/dL (normal range=0.2-1.2 mg/dL). No other action was taken. The subject remained in the study for further safety evaluations and completed all study visits. Follow up laboratory tests performed on Days 7 and 28 revealed total bilirubin levels of 4.7 mg/dL and 4.3 mg/dL, respectively. There were no other clinically significant laboratory abnormalities noted at baseline or at the post-baseline laboratory evaluations. The investigator considered the adverse event of bilirubinemia (Gilbert's Disease) to be of mild severity.

Subject 001092: A 22 year-old white female subject was randomized to the azithromycin 6-day group. The subject received 2 days of azithromycin therapy and was discontinued from study drug on Day 3 due to severe angioedema (Idiopathic Angioedema). The angioedema started on Day 2 and resolved on Day 8. In addition to discontinuation of study drug, other treatments included cetirizine, prednisone, and diphenhydramine for the angioedema and levofloxacin for sinusitis. The subject also reported an adverse event of moderate worsening of facial pain, which started on Day 1 and resolved on Day 5. The angioedema was considered by the investigator to be related to study drug and the worsening of facial pain was considered to be related to concomitant treatment, i.e., the antral puncture. The subject completed the study with no further adverse events recorded. No clinically significant laboratory abnormalities were noted at baseline or at the post-baseline visits.

Incidence of Adverse Events

All Causality TEAEs

Of the 536 subjects who received study drug, 38.8% (109/281) azi 3-day subjects and 38.4% (98/255) azi 6-day subjects reported at least one adverse event during study therapy or up to 35 days after the last dose of study drug. Body system categories that had the most frequently reported adverse events were the "Digestive", "Body as a Whole", and "Respiratory" systems.

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Table C-46: Treatment-Emergent Adverse Events by Body System (All Causalities)

	Azi 3-Day		Azi 6-Day	
	N	(%)	N	(%)
Number (%) of Subjects:				
Evaluable for adverse events	281		255	
With adverse events	109	(38.8)	98	(38.4)
Discontinued due to adverse events	3	(1.1)	3	(1.2)
Number of Subjects with Adverse Events by Body System:				
BODY AS A WHOLE	45	(16.0)	38	(14.9)
CARDIOVASCULAR	5	(1.8)	5	(2.0)
DIGESTIVE	49	(17.4)	41	(16.1)
HEMIC AND LYMPHATIC	2	(0.7)	3	(1.2)
METABOLIC AND NUTRITIONAL	3	(1.1)	5	(2.0)
MUSCULOSKELETAL	2	(0.7)	3	(1.2)
NERVOUS	8	(2.8)	6	(2.4)
RESPIRATORY	29	(10.3)	26	(10.2)
SKIN AND APPENDAGES	7	(2.5)	8	(3.1)
SPECIAL SENSES	7	(2.5)	3	(1.2)
UROGENITAL	3	(1.1)	5	(2.0)

Subjects are only counted once per treatment for each row.
Includes data up to 35 days after last dose of study drug.

TEAEs that occurred in ≥1% or more subjects within any treatment group are shown in the following table.

Table C-46A: TEAEs (All Causality) That Occurred in ≥1% of Subjects Within any Treatment Group

	Azi 3-Day	**Azi 6-Day**
Abdominal Pain	11 (3.9)	18 (7.1)
Colitis	3 (1.1)	0
Diarrhea	28 (10.0)	26 (10.2)
Dyspepsia	3 (1.1)	4 (1.6)
Face Edema	7 (2.5)	4 (1.6)
Headache	10 (3.6)	10 (3.9)
Nausea	11 (3.9)	11 (4.3)
Pain	13 (4.6)	6 (2.4)
Rhinitis	5 (1.8)	8 (3.1)
Vomiting	4 (1.4)	0

Subjects may have had more than one adverse event.

Medical Officer's Comments:

Diarrhea and abdominal pain were the most frequently reported adverse events in both treatment groups.
The incidence of diarrhea was 10.0% (28/281) in the azi 3-day group and 10.2% (26/255) in the azi 6-day group. Abdominal pain was reported at a higher rate in the azi 6-day group (7.1% [18/255]) than in the azi 3-day group (3.9% [11/281]). The majority of the adverse events were mild or moderate in severity.

Treatment-Related TEAEs

The incidence of treatment-related TEAEs was 20.6% (58/281) in the azi 3-day group and 17.6% (45/255) in the azi 6-day group. Body system categories that had the most frequently reported treatment-related adverse events were the "Digestive", and "Body as a Whole" systems.

Table C-47: Treatment-emergent Adverse Events by Body System (Treatment-Related)

	Azi 3-Day		Azi 6-Day	
	n	(%)	n	(%)
Number (%) of Subjects:				
Evaluable for adverse events	281		255	
With adverse events	58	(20.6)	45	(17.6)
Discontinued due to adverse events	2	(0.7)	2	(0.8)
Number of Subjects with Adverse Events by Body System:				
BODY AS A WHOLE	16	(5.7)	17	(6.7)
CARDIOVASCULAR	1	(0.4)	1	(0.4)
DIGESTIVE	38	(13.5)	30	(11.8)
HEMIC AND LYMPHATIC	1	(0.4)	0	
METABOLIC AND NUTRITIONAL	1	(0.4)	0	
MUSCULOSKELETAL	1	(0.4)	0	
NERVOUS	2	(0.7)	1	(0.4)
RESPIRATORY	1	(0.4)	1	(0.4)
SKIN AND APPENDAGES	6	(2.1)	3	(1.2)
SPECIAL SENSES	1	(0.4)	2	(0.8)
UROGENITAL	1	(0.4)	1	(0.4)

Subjects are only counted once per treatment for each row.
Includes data up to 35 days after last dose of study drug.

TEAE that occurred in ≥1% or more subjects within any treatment group are shown in the following table.

Table C-47A: TEAE (Treatment-Related) That Occurred in ≥1% of Subjects Within any Treatment Group

	Azi 3-Day	Azi 6-Day
Abdominal Pain	11 (3.9)	14 (5.5)
Diarrhea	26 (9.3)	22 (8.6)
Headache	0	3 (1.2)
Nausea	9 (3.2)	8 (3.1)

Subjects may have had more than one adverse event.

Medical Officer's Comments:

Diarrhea (9.3% [26/281] azi 3-day; 8.6% [22/255] azi 6-day), abdominal pain (3.9% [11/281] azi 3-day; 5.5% [14/255] azi 6-day), and nausea (3.2% [9/281] azi 3-day; 3.1% [8/255] azi 6-day) were the most frequently reported treatment-related TEAEs in both treatment groups. The majority of the treatment-related TEAEs were mild or moderate in severity.

Deaths

There were no deaths reported during this study.

Serious Adverse Events

Serious adverse events were reported in 2 subjects. The first subject (Subject No. 000082) in the azi 3-day group was hospitalized for suicidal ideation on Day 6. The second subject (Subject No. 001187) in the azi 6-day group was hospitalized for septicemia on Day 26. Both these events resolved and were considered by the investigator to be not related to study drug. A summary for both these subjects follows.

Subject No. 000082: A 27 year-old white female subject was randomized to the azithromycin 3-day treatment group. Azithromycin was administered orally at a total daily dose of 500 mg from 31 July 2001 to 02 August 2001, a total of 3 days. The subject completed treatment and was considered a clinical failure at EOT (Visit 3) and EOS (Visit 4). On —— the subject had an episode of depression that was considered by the investigator not to be a serious adverse event. On —— the subject was hospitalized for suicidal ideation and treated with an increased dose of quetiapine fumarate. The suicidal ideation resolved on —— and the subject was discharged from the hospital on the same day.

The subject had a medical history of bipolar disorder and hypothyroidism. Concomitant medications included quetiapine fumarate, oxcarbazepine, lorazepam and alprazolam.

In the investigator's opinion, the suicidal ideation was not due to azithromycin but to the subject's loss of a close friend.

Subject No. 001187: A 75 year-old white male subject was randomized to the azithromycin 6-day treatment group. Azithromycin was administered orally at a total daily dose of 500 mg from 09 May 2002 (Baseline) to 14 May 2002, a total of 6 days. Signs and symptoms of sinusitis at baseline included severe post-nasal purulent discharge, severe hyposmia, severe nasal congestion, severe cough, mild facial pain, and mild headache. Jaw pain with mastication and halitosis were absent. A transantral puncture and aspiration performed at baseline isolated penicillin-susceptible *S. pneumoniae* which was also susceptible to azithromycin (MIC=0.25 mcg/mL). A sinus radiograph performed at baseline revealed opacification of the maxillary sinuses. The subject completed treatment and was considered clinically improved at EOT (Visit 3; 17 May 2002). However the subject received additional treatment for sinusitis with azithromycin for 5 days from 29 May 2002 to 02 June 2002. On — the subject developed a fever and was taken to the emergency room. He was admitted to the hospital with a diagnosis of septicemia. A blood culture performed on — isolated *S. pneumoniae*, which was susceptible to several antibiotics including azithromcyin. A computed tomography scan of the sinuses performed on — revealed residual opacification of the left maxillary sinus, sphenoid, and ethmoid sinuses. These findings were an improvement compared with the findings from an initial radiograph taken on — The subject was treated with levofloxacin from — The septicemia was considered resolved on — subject was seen by the investigator for the EOS visit on 17 June 2002 and was considered a clinical failure due to the use of additional antibiotics during the study to treat the sinusitis. Signs and symptoms of sinusitis at the EOS visit were absent.

The subject had a medical history of actinic keratoses, chronic lymphocytic leukemia, interstitial lung disease (since — basal cell carcinoma (biopsy in 1990), and prostate cancer (surgery in 1995). Concomitant medications at baseline included topical fluorouracil.

In the investigator's opinion, the septicemia was unrelated to the study drug.

Clinical Laboratory Test Results

Discontinuations of Study Drug due to Laboratory Test Abnormalities

No subject discontinued study drug due to laboratory test abnormalities.

Incidence of Clinical Laboratory Test Abnormalities

Two hundred eighty-one (100%) subjects in the azi 3-day group and 255 (100%) subjects in the azi 6-day group had laboratory data analyzable for safety (i.e., at least one laboratory assessment at baseline and at least one laboratory assessment post-baseline). Urine samples were initially tested via dipstick at the site. If a clinically significant abnormality was detected at the site, the urine sample was sent to the central laboratory for further testing and culture.

Laboratory abnormalities were summarized without regard to baseline laboratory abnormalities.

Without Regard to Baseline Abnormality: Five hundred twenty-six subjects (278 azi 3-day; 248 azi 6-day) had at least one laboratory assessment at baseline and at least one post-baseline laboratory evaluation. Of these 526 subjects, 39 (14%) azi 3-day subjects and 44 (18%) azi 6-day subjects had laboratory test abnormalities when analyzed without regard to the presence or absence of a baseline laboratory abnormality. The most commonly observed laboratory test abnormality was blood in urine (measured qualitatively) (11/46 [24%] azi 3-day; 13/58 [22%] azi 6-day). These results are consistent with those observed for subjects with normal or abnormal laboratory values at baseline.

Applicant's Safety Conclusions

Five hundred thirty-six subjects received study drug and were included in the safety analyses. The incidence of adverse events, irrespective of relationship to study drug, was 38.8% in the azithromycin 3-day group and 38.4% in the azithromycin 6-day group. Diarrhea and abdominal pain were the most frequently reported adverse events in both treatment groups. The incidence of abdominal pain was slightly higher in the azithromycin 6-day treatment group than in the azithromycin 3-day treatment group. The majority of TEAEs were mild or moderate in severity.

The incidence of treatment-related TEAEs was 20.6% in the azithromycin 3-day group and 17.6% in the azithromycin 6-day group. Diarrhea, abdominal pain, and nausea were the most frequently reported treatment-related TEAEs. The majority of the treatment-related TEAEs were mild or moderate in severity.

Five subjects (2 azi 3-day; 3 azi 6-day) discontinued study drug due to adverse events; 4 of these 5 subjects went on to complete the study.

Two subjects (one subject in each treatment group) experienced serious adverse events. The first subject (azi 3-day) was hospitalized for suicidal ideation on Day 6. The second subject (azi 6-day) was hospitalized for septicemia on day 26. Both these events resolved and the investigators considered these events to be unrelated to study drug.

APPLICANT'S SUMMARY AND CONCLUSIONS

The primary objective of this study was to evaluate the bacteriologic efficacy of oral azithromycin administered as 500 mg/day for 3 days or 500 mg/day for 6 days in the treatment of subjects with acute bacterial sinusitis. The secondary objectives of this study were to evaluate the clinical efficacy and the safety and toleration of azithromycin dosed as 500 mg/day for 3 days and 500 mg/day for 6 days.

In this study, 500 mg/day of azithromycin administered for either 3 days or 6 days was efficacious in the treatment of subjects with clinically and radiologically documented acute bacterial sinusitis. Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall clinical and bacteriological success rates appeared similar whether azithromycin was administered over 3 or 6 days.

In the azithromycin 3-day and 6-day treatment groups, signs and symptoms of acute bacterial sinusitis as well as the incidence of radiological findings at baseline were consistent with a diagnosis of acute bacterial sinusitis and improved throughout the course of the study.

The overall rate of adverse events and number of subjects who discontinued study drug was similar between the two azithromycin treatment groups. Based on the results of this study the following conclusions can be made:

- The efficacy of azithromycin at 500 mg/day administered for either 3 or 6 days was demonstrated in subjects with documented infections caused by *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.
- In subjects with *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* isolated at baseline, the clinical and bacteriological success rates were generally high (azi 3-day: 87%-93% at EOT and 73-93% at EOS; azi 6-day: 93%-100% at EOT and 77%-86% at EOS). Although no statistical comparisons were conducted between the two azithromycin treatment groups, the clinical and bacteriological success rates in subjects with *H. influenzae* appeared slightly higher when azithromycin was administered for 6 days. Overall success rates in subjects with baseline pathogens appeared similar whether azithromycin was administered over 3 or 6 days.
- In all subjects, those with or without documented baseline pathogens, the clinical success rates were also high (azi 3-day: 89% at EOT and 77-78% at EOS; azi 6-day: 94%-95% at EOT and 84%-85% at EOS). Although no statistical comparisons were conducted between the two azithromycin treatment groups, overall success rates appeared to be slightly higher when azithromycin was administered over 6 days as compared with 3 days.

Medical Officer's Comments:

The Medical Reviewer concurs with the Applicant's conclusions.

Medical Officer's Recommendations:

In sNDA 50-784 (S-004), the Applicant submitted two studies to assess the administration of azithromycin 500 mg/day for 3 days for patients with acute maxillary sinusitis, a total dose of 1.5 gm.
The efficacy and safety data in this supplemental NDA provides satisfactory evidence of efficacy and safety of azithromycin at 500 mg/day for 3 days for patients with acute maxillary sinusitis.
The reviewing Medical Officer recommends an action of Approval for sNDA 50-784/s-004 for the use of azithromycin at 500 mg/day for 3 days for patients with acute maxillary sinusitis.
Azithromycin at 500 mg/day for 3 days achieved the goal of noninferiority to the comparator and there were no new safety issues identified to alter the risk benefit profile for Azithromycin®.

The draft labeling for this supplement is reviewed separately.

The above recommendations should be conveyed to the sponsor of this sNDA.

/S/

Nasim Moledina, M.D.
Medical Officer, DAIDP

Concurrence only:
HFD-520/DivDir/JSoreth

cc: ***NDA 50-784/S-004***

HFD-520
HFD-520/MO/NMoledina
HFD-520/PM/JMilstein
HFD-520/MTL/JAlexander
HFD-520/Pharm/AEllis
HFD-520/Micro/HSilver
HFD-520/Chem/AYu
nm/12/03/2003;rev01/14/2004.

APPENDICES

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APPENDIX I

STUDY A0661036

INVESTIGATIONAL PLAN

Study Design and Plan

Male or female subjects, 18 years of age and older with clinically documented acute bacterial infection of the maxillary sinuses entered this randomized, double-blind, comparative, multicenter study. They received one of three treatments: azithromycin (azith) 500 mg/day or placebo administered as one tablet each day for 3 days, azith 500 mg/day or placebo administered as one tablet each day for 6 days, or 1500 mg amoxicillin/375 mg clavulanate (amox/clav) per day administered in 10 mL doses (2 teaspoons) TID for 10 days. Subjects were followed for 28±4 days.

At baseline, all subjects had a physical examination and provided a medical history. Subjects were enrolled in the study after satisfying the inclusion/exclusion criteria, including provision of the appropriate informed consent. A sinus radiograph was obtained at the baseline visit, unless one had been performed within the previous 48 hours.

Follow-up included a telephone contact on Day 4±1 (designated Visit 2), and visits to the site on Day 10±2, (designated Visit 3; End of Therapy [EOT]) and Day 28±4 (designated Visit 4, End of Study [EOS]). The clinical outcome at EOS, which was based on the investigator assessment, was the primary endpoint.

There were two amendments to the protocol, 11 November 2000, and 24 July 2001. The amendments did not affect informed consent or efficacy and safety procedures performed on those subjects enrolled in the study prior to the amendments.

In addition to administration changes to the protocol, the two amendments included the following changes:

- Fiberoptic endoscopy of maxillary sinus was removed from the protocol. Fiberoptic endoscopy had been included as an exploratory procedure in the original protocol but was subsequently removed.
- Clarification of allowable concomitant medications, e.g., theophylline, warfarin, antacids, and pseudoephedrine. Revisions to these concomitant medications were made in order to be consistent with the US product label, and to clarify pseudoephedrine use during the study.
- Clarification of Visit 2 requirements (i.e., the subject's response to therapy was to be assessed via the telephone contact and did not include assessment of clinical signs and symptoms.)
- The total number of subjects enrolled was increased from 390 to 912. This was based on feedback received from the FDA during an End of Phase 2 meeting on May 21, 2001.

- Follow-up requirement for SAEs was changed to 35 days after the last administration of study drug. This was revised in order to be consistent with current Pfizer policies for azithromycin.
- Clarification of the requirements for adverse events related to abnormal laboratory values and physical examination findings. These revisions were made in order to be consistent with Pfizer policies.

Study Population

Inclusion Criteria

Subjects who met the following criteria were considered for enrollment into the study and could receive study drug, if eligible.

1. Outpatient males and females 18 years of age and over.
2. Women of childbearing potential, who used adequate contraception, defined as hormonal contraception, intrauterine device, or barrier methods (condom or vaginal diaphragm) with spermicide, throughout the study and for four weeks after completion of the study. The pre-study pregnancy test (urine or serum gonadotropin) must have been negative. Women who had been surgically sterilized or were at least two years postmenopausal could be enrolled and did not need to use birth control. Women whose method of birth control was hormonal were required to use an additional barrier method during the study and for one month following the completion of the study.
3. Subjects must have had clinically documented acute bacterial infection of the maxillary sinuses including one or both of the following signs and symptoms lasting longer than 7 days but less than 28 days:

   —Purulent nasal discharge

   —Facial pain/pressure/tightness typically over the maxillary sinuses, or pain that worsens with movement or percussion

   Subjects may also have had other diagnostic symptoms, including hyposmia, jaw pain with mastication, nasal congestion, headache, halitosis, and a history of recent upper respiratory infection.
4. Subjects who had a positive sinus X-ray (i.e., opacification of the affected sinuses, an air-fluid level, or ≥ 6 mm mucosal thickening).
5. Subjects must have given written informed consent by signing and dating an informed consent form prior to study entry.

Exclusion Criteria

Subjects with any of the following conditions could not be enrolled in this study.

1. Pregnant or lactating women.

2. Subjects with an allergy, hypersensitivity, or other contraindications to any penicillin or macrolide antibiotic.
3. Subjects who were currently hospitalized for any reason.
4. Subjects who were treated with any other systemic antibiotic for 24 hours or longer within 2 weeks prior to the baseline visit.
5. Subjects with infections that may have required treatment with an antibiotic other than the study drugs.
6. Subjects with a history of chronic sinusitis (3 or more episodes of sinusitis in the last 6 months).
7. Subjects who had a history of sinus surgery other than for a diagnostic procedure.
8. Subjects with significant gastrointestinal or other conditions that could affect study drug absorption.
9. Subjects with evidence or history of significant hematological, renal or cardiovascular disease or immunologic compromise (i.e., neutropenia, ARC/AIDS, non-skin cancers or malignant melanoma).
10. Subjects who had received any investigational drug during the previous 30 days or five times the plasma half-life (if known), whichever was longer, or who previously participated in this trial.
11. Subjects who were abusers of alcohol and/or other drugs.
12. Subjects in whom concurrent use of certain medications with study drug may have interfered with the evaluation of the study drug.
13. Subjects with any condition that, in the opinion of the investigator, could have affected subject safety, precluded evaluation of response, or made it unlikely that the contemplated course of therapy and follow-up could have been completed, including any subject who was unable/unlikely to follow the study protocol.
14. Subjects who intended to donate blood or blood products during the study or within one month following the completion of the study.

Removal of Subjects from Treatment or Assessment

A discontinuation occurred when an enrolled subject ceased participation in the study, regardless of the circumstances, prior to completion of the protocol. Subjects could discontinue from study treatment and still complete the study by returning for scheduled visits and being evaluated for safety. The investigator was required to determine the primary reason for discontinuation. The final evaluation required by the protocol was performed at the time of study discontinuation. The investigator was required to record the reason for study discontinuation in the CRF, and to provide or arrange for appropriate follow-up (if required) for such subjects and document the course of the subject's condition. Subjects with marked liver function abnormalities were to

discontinue their study drug immediately, and the Pfizer appointed monitor was to be notified. The abnormal tests should have been repeated within 48 hours, and then at 3 to 7 day intervals until they resolved.

Blinding

All medication was blinded using a double-dummy technique. Azithromycin was presented in the form of tablets (500 mg) or matching placebo. Amoxicillin/clavulanate or matching placebo was provided in bottles as powder for oral suspension. At the time of randomization, the investigator or approved representative constituted the powder according to label instructions to obtain a final suspension containing 250 mg amoxicillin and 62.5 mg clavulanic acid per 5 mL.

Each subject received a study medication kit that included a blister pack containing 6 blinded tablets of azithromycin or matching placebo, plus 3 bottles of amoxicillin/clavulanate oral suspension or matching placebo (depending on the randomization arm). Subjects were to take medications in the following manner:

			Treatment Groups	
Study Days	Study Drugs	Azith 3-Day	Azith 6-Day	Amox/Clav
Days 1–3	Azith	Azith	Azith	Placebo
	Amox/Clav	Placebo	Placebo	Amox/Clav
Days 4–6	Azith	Placebo	Azith	Placebo
	Amox/Clav	Placebo	Placebo	Amox/Clav
Days 7–10	Amox/Clav	Placebo	Placebo	Amox/Clav

Azith= azithromycin; Amox/Clav=amoxicillin/clavulanate

Subjects were instructed that study medication (azithromycin oral tablets and amoxicillin/clavulanate oral suspension) might be taken without regard to food. However, to minimize the potential for gastrointestinal intolerance, amoxicillin/clavulanate or matching placebo suspensions were to be taken at the start of a meal. A measuring cup was provided for dispensing the correct dose of amoxicillin/clavulanate or matching placebo suspensions.

Efficacy Assessments

Clinical

Visit 1 (Baseline)

The baseline visit (Visit 1) assessment included collection of demographic information, past medical history and allergy history, concurrent diseases, antibiotic therapy within the last 14 days, concomitant medications, vital signs, laboratory assessments, and a targeted physical examination. A Sinus radiograph (Waters' view – Caldwell's and lateral views only if Waters' was inconclusive) was obtained (unless one had been performed within 48 hours of the baseline visit) and read by a qualified radiologist.

Assessment of current signs and symptoms of acute bacterial sinusitis included documentation of at least one of the following: post-nasal purulent discharge, facial pain over the affected sinus that worsened with movement or percussion. In addition, subjects were assessed for the presence of hyposmia, jaw pain with mastication, headache, halitosis and nasal congestion. These signs and symptoms were graded as 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

Visit 2 (Telephone Contact)

Visit 2 (Telephone Contact) was designated to occur on study Day 4±1. Through telephone contact, the subject's response to therapy was determined as provided by the subject. Information on how the subject felt since the previous visit (improved, same or worse) was recorded, and use of concomitant medications and occurrence of adverse events since the previous visit was assessed. Additionally, compliance was confirmed.

At the discretion of the investigator, the subject was encouraged to return for an unscheduled visit if he or she reported feeling the same as at the previous visit. If the subject felt worse than at the previous visit, he or she was encouraged to return for an unscheduled visit as soon as possible. The investigator assessed the subject's response to therapy at this unscheduled visit. If necessary, study drug was discontinued and appropriate non-study antimicrobial therapy was initiated. Subjects who discontinued study drug were directed to return for final clinical assessments.

Visit 3 (End of Therapy Visit) and Visit 4 (End of Study Visit)

Visit 3 (End of Therapy Visit, EOT) was designated to occur on study Day 10±2. Visit 4 (End of Study Visit, EOS) was designated to occur on study Day 28±4. The primary efficacy outcome time point for the study was EOS.

All signs and symptoms of sinusitis that were identified at baseline (Visit 1) were assessed and numerically graded as had been done previously. Vital signs, adverse events and concomitant drug and non-drug treatments were recorded. Clinical laboratory tests were performed at Visit 3. Clinical laboratory tests were performed at Visit 4 if a clinically significant abnormality was present or if the subject experienced a clinically significant adverse event.

At Visits 3 and 4, the investigator also determined the overall clinical outcomes based on predefined criteria: cure, improvement, failure, or unknown at Visit 3 and cure, failure, or unknown at Visit 4. The overall clinical success rate was defined by the sponsor as cure plus improvement at EOT (Visit 3, Day 10±2) and cure at EOS (Visit 4, Day 28±4). A sinus radiograph was repeated at Visit 3 only if the subject failed to respond clinically. A sinus radiograph was obtained for all subjects at Visit 4. The same radiographic view was obtained and read by the same radiologist as at Visit 1, whenever possible.

Study medications were returned to the investigator and study drug accountability was performed at Visit 3 and Visit 4.

Bacteriologic

Because of the invasive nature of the transantral puncture (TAP) and aspiration of the maxillary sinus, this procedure was not required for the study. However, investigators were strongly encouraged to have any subject who had been assessed as a clinical failure at Visits 3 or 4 undergo a TAP and aspiration for culture. The isolates obtained were to be sent to a central laboratory for susceptibility testing and storage. At the time of study completion, the central laboratory was to perform susceptibility testing for all isolates obtained during the study.

Safety Assessments

Adverse Events

All adverse events, either reported by the subject or observed by the investigator, were recorded at each visit or phone contact on the adverse event page of the CRF with information on their severity (mild, moderate, severe), date of onset, duration, withdrawal from treatment and/or study, treatment required, seriousness, and the investigator's assessment of relationship to study drug. Adverse events included adverse drug reactions, illnesses with an onset during the study, or exacerbation of preexisting illnesses (including the disease under study). Insufficient or lack of clinical response, benefit, efficacy, or therapeutic effect was not considered an adverse event. Thus the investigator had to distinguish between an exacerbation of disease under study (pre-existing illness) and lack of efficacy. Objective test findings (e.g., abnormal laboratory test results) specified in the protocol which resulted in a change in study drug dosage, treatment discontinuation, or intervention/diagnostic evaluation to assess risk were also recorded as adverse events, as were clinically significant changes in physical examination findings. Subjects were to be followed until adverse events (or their sequelae) resolved or stabilized.

Serious Adverse Events

A serious adverse event (SAE) included any adverse drug experience occurring at any dose that:

- resulted in death
- was life-threatening, resulted in inpatient hospitalization, or prolonged an existing hospitalization
- resulted in persistent or significant disability/incapacity
- resulted in congenital anomaly/birth defect

Clinical Laboratory Tests

All clinically important abnormal laboratory tests that occurred during the study were repeated at appropriate intervals until they returned either to baseline or to a level deemed acceptable by the investigator and Pfizer clinical monitor (or his/her designated representative), or until a diagnosis that explained them was made. An abnormal

laboratory test result was to be recorded as an adverse event if any one of the following criteria was met:

- the test result was associated with accompanying symptoms
- the test result required additional diagnostic testing or medical/surgical intervention
- the test result led to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy
- the test result led to any of the outcomes included in the definition of a serious adverse event
- the test result was considered to be an adverse event by the investigator of sponsor

The following laboratory tests were performed at Baseline (Visit 1, Day1), at EOT (Visit 3, Day 10), or at the time of discontinuation for an adverse event.

Hematology	**Clinical Chemistry**	**Urinalysis (by Dipstick)**
Hemoglobin	SGOT/AST	Protein
Hematocrit	SGPT/ALT	Glucose
Red blood cells	Total bilirubin	Ketones
Platelet count	LDH	Bilirubin
WBC count with differential	Alkaline phosphatase	pH
	Urea (BUN)	Urobilinogen
	Creatinine	Blood
	Total protein	Nitrite
	Albumin	
	Sodium	
	Potassium	
	Bicarbonate	
	Chloride	
	Random blood glucose	

In addition, at baseline (Visit 1) a pregnancy test (blood or urine gonadotropin) was performed on female subjects of child-bearing potential.

Clinical laboratory tests, including blood chemistry, hematology and dipstick urinalysis, were obtained at Visit 4 (EOS, Day 28±4) only if clinically significant abnormalities were present at Visit 3, or if the subject was experiencing a clinically significant adverse event.

Moderate and marked liver function abnormalities were defined as follows:

	SGOT/SGPT	Alkaline Phosphatase	Total Bilirubin
Moderate	>1.5 x ULN	>1.2 x ULN	>1.5 x ULN
Marked	>3 x ULN	>1.5 x ULN	>2.0 x ULN

where ULN was defined as the upper limit of normal, if the pretreatment baseline was normal or the pretreatment baseline if it was abnormal.

Moderately abnormal liver function tests were repeated within three to seven days. If confirmed, liver function tests were repeated at weekly intervals until they resolved. Subjects with marked liver function abnormalities discontinued treatment immediately, and the Pfizer appointed clinical monitor was notified. The abnormal tests were repeated within 48 hours, and then at three to seven day intervals until they resolved. After discussion with the Pfizer appointed clinical monitor, additional evaluation of subjects with marked abnormalities that persisted after study drug treatment was discontinued was arranged. The additional evaluation may have included GI consultation and additional laboratory tests (e.g., HBV, HAV, or CMV serology, CPK, reticulocyte count). Subjects with moderate and marked abnormal liver function tests were to be followed until the abnormalities resolved or the Pfizer appointed clinician agreed that the abnormal findings stabilized and additional testing would be of no value in clarifying the findings.

In addition, any of the following marked laboratory abnormalities lead to automatic additional local laboratory testing on stored samples.

Bilirubin increase from Baseline	≥1.0 mg/dL or ≥17 μmol/L
Creatinine increase from Baseline	≥0.8 mg/dL or ≥73 μmol/L
Hemoglobin decrease from baseline	≥2 g/dL or ≥1.24 mmol/L

These data were reviewed by a Pfizer clinician, and in consultation with the investigator, additional laboratory evaluation may have been performed.

Statistical Methods

Sample Size

The objective of this study was to demonstrate that azithromycin administered as either 1.5 grams (500 mg/day) over 3 days or as 3.0 grams (500 mg/day) over 6 days, is as effective as standard therapy with 500 mg amoxicillin/125 mg clavulanate administered TID for 10 days. Azithromycin was to be considered as effective as amoxicillin/clavulanate if the lower bound of the 97.5% confidence interval on the difference between the two treatments in response rates was greater than or equal to -10%.

Because this was a three-arm study with construction of confidence intervals for each of the azithromycin arms compared to amoxicillin/clavulanate, the significance level was adjusted using a Bonferroni approach to insure that the overall Type I error rate did not exceed 0.05. Thus, because there were two planned comparisons, each was performed on a 0.05/2 significance level. Assuming the clinical success rate of amoxicillin/clavulanate at the end of the study was 85%, the number of subjects in each treatment group required to insure with 80% probability that the lower bound of the 97.5% confidence interval for the true difference in efficacy was not less than –10% was 243 subjects per treatment group. If about 20% of the subjects were expected to be non-evaluable, then 304 subjects per group were required to protect the power of the study.

Hence, based on these assumptions, the planned enrollment of 912 subjects was determined to be statistically adequate.

Statistical and Analytical Plans

The analyses of efficacy were based on the pooled data from 46 centers. Subjects enrolled at Center 1007 were excluded from the efficacy analyses because this site was subsequently considered ineligible by the FDA. The analyses of safety were based on the pooled data from 47 sites and included subjects enrolled at Center 1007.

Study Populations Analyzed

There were three analysis populations:

1. The safety population included all treated subjects.

2. The modified intent-to-treat population (MITT), included all randomized subjects who had clinically documented acute bacterial infection of the maxillary sinuses at baseline, and received at least one dose of study drug.

3. The clinically evaluable population, included all subjects in the MITT population, unless any one or more of the following criteria applied:

   a) did not meet all inclusion and exclusion criteria, b) received less than 80% of required active study medication doses except if failed and discontinued, c) received more than 120% of required active study medication doses.

   In addition, subjects who met the following criteria were excluded from the clinical evaluable analyses at the relevant visit(s):

   a) received concomitant systemic antibiotic for intercurrent illness prior to the evaluation point, b) had no visit at an evaluation point unless the subject was previously designated as a treatment failure, c) had a visit date outside the visit window, unless the subject was previously designated as a treatment failure, d) had no radiology data at Visit 4 unless: 1) the subject was considered a clinical failure prior to Visit 4, or 2) the subject had an x-ray at Visit 3 and was a cure at both Visits 3 and 4.

Efficacy Parameters and Analyses

Two populations, the MITT and clinically evaluable populations were analyzed for efficacy in this study.

Primary Efficacy Endpoint:

The primary efficacy endpoint was the clinical response based on the investigators' assessment of the clinical outcome (cure, failure, or unknown) at the EOS visit (Visit 4).

Secondary Efficacy Endpoint:

The clinical response (cure, improvement, failure, or unknown) at the EOT visit (Visit 3) was the secondary endpoint.

Clinical Response:

Clinical response was determined by the investigator at Visits 3 and 4 and was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. The investigator classified the clinical presentation of the subject at the evaluation time point using the criteria listed below. At Visit 3 the clinical response was cure, improvement, failure, or unknown, with success defined as cure or improvement and the success rate defined as (cure + improvement) / (cure + improvement + failure). At Visit 4 the clinical response was cure, failure, or unknown, with success defined as cure and the success rate defined as cure / (cure + failure).

Cure: Resolution of signs and symptoms of acute sinusitis to the level that existed prior to the occurrence of the acute illness. No worsening in the radiographic appearance of the sinuses noted (applicable to Visit 4 or where radiographic information is available). No antibiotics (other than study drug) were given.

Improvement: Improvement but incomplete resolution of the signs and symptoms of acute sinusitis and no requirement for additional antibiotic.

Failure: Persistence of one or more signs or symptoms of sinusitis or appearance of new signs or symptoms. Need for additional antimicrobials or change in antimicrobial therapy.

Unknown: Subject response could not be assessed due to missed visit or failure to record clinical outcome.
The occurrence of any of the following conditions superseded the evaluation of response as cure, improvement, failure or unknown, and resulted in the reassignment of outcome by the sponsor as follows:

1. For subjects who were previously assessed as failures, the outcome was always failure at subsequent time points.

2. For subjects who were given a concomitant antibiotic prior to the evaluation time point, response was classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.

All reassignments of outcome by the sponsor were completed prior to breaking the blind.

Statistical Methods:

For clinical efficacy, 97.5% confidence intervals were computed, comparing the proportion of subjects with a clinical response of "success" for each of the two azithromycin treatment groups with the amoxicillin/clavulanate group. The confidence intervals on the differences in proportions were computed using the Normal approximation to the binomial distribution. All variables were summarized by treatment and visit. Continuous variables were summarized by presenting n, mean, standard deviation, median and range. Categorical variables were summarized by presenting the frequency and percentage of subjects in each category. All safety parameters were summarized based on the specifications in Pfizer Worldwide Safety Standards (WSS)

3.0. The baseline value for each variable was computed as the latest value prior to the administration of study medication (value at Visit 1). The day of first treatment with study medication was considered Study Day 1. For the purpose of analysis only, if the day was missing from a date, the day was imputed as the first day of the month. If both the month and day were missing from a date, the month and day were imputed as January 1st. Duration was calculated by subtracting the onset date from the stop date plus one. When converting days to years or months, the following convention was followed: one year = 365 days, one month = 30.44 days.

Efficacy Analyses:

The clinical response at EOT (Visit 3) and at EOS (Visit 4) were summarized and analyzed for both the clinically evaluable subjects and the MITT subjects.

The primary efficacy analysis was the 97.5% confidence interval of the difference in clinical response between each of the azithromycin treatment groups and the amoxicillin/clavulanate group (i.e., azithromycin – amoxicillin/clavulanate) at the end of study (Visit 4) for the clinically evaluable population. The treatments were deemed equivalent if the lower limit of the 97.5% confidence interval of the difference in the success rate between the two treatment groups was greater than or equal to –10%.

Secondary efficacy analyses included computation of the 97.5% confidence intervals on the difference in the proportion of subjects with a successful clinical response for the MITT population at the end of study (Visit 4) and for the MITT and clinically evaluable populations at the end of treatment (Visit 3).

In the previous analyses of clinical response, subjects with unknown clinical outcome were not included in the calculation of the success rate. As a result, two further analyses of clinical response were performed for the MITT population. In the first analysis, subjects with missing/unknown observations were set to failure, and in the second analysis, subjects with missing/unknown observations were set to cure.

The distribution of clinical response by treatment group was also presented by strata defined as the presence or absence of allergic rhinitis at baseline. Allergic rhinitis status was determined from the information contained on the medical history CRF. Subjects were considered to have allergic rhinitis if at least one of their medical history entities coded to the following: allergic rhinitis due to pollen, allergic rhinitis due to other allergen or allergic rhinitis due to unspecified cause. These distributions were displayed at Visit 3 and Visit 4 for both the MITT and the clinically evaluable populations.

Signs and symptoms of acute sinusitis were summarized by visit and treatment. The number and percent of subjects with absent, mild, moderate and severe responses were presented for each sign and symptom.

The number and percent of subjects with each sinus radiograph criteria present or absent were presented by treatment group at each visit for which radiographs were required. In addition, the distribution of the comparison between baseline and follow-up radiograph were presented by treatment group at Visits 3 and 4.

No antral punctures were performed and no bacteriological data were collected.

Day 1 (Baseline) was the first day of treatment. For analysis purposes, the windows for evaluability were defined as follows:

Visit	Day Range
Baseline (Day 1)	N/A
Visit 2	3 to 5
EOT (Visit 3)	8 to 15
EOS (Visit 4)	22 to 36

Safety Parameters and Analyses

Safety parameters included adverse events, concomitant medications, laboratory data, physical examination, vital signs and discontinuations. Safety parameters were summarized for the safety population as defined in Pfizer Worldwide Safety Standards.

Adverse Events:

All treatment-emergent adverse events (TEAE), regardless of suspected causality to study drug, were summarized. The number and percentage of subjects reporting TEAE were summarized within each WHO body system, preferred term and treatment. All adverse events were also summarized by severity. Similar summaries were generated for all TEAE.

Serious Adverse Events:

Serious adverse events were summarized from data collected from the Pfizer Adverse Events Monitoring database of all subjects who reported a serious adverse event during the course of the study.

Concomitant Medications and Non-drug Treatments:

Medications and non-drug treatment were summarized separately at both entry to the study and during the study. These tables were summarized by treatment assignment.

Laboratory Data:

The incidence of clinically significant laboratory abnormalities for each laboratory parameter and the median change in laboratory test results from baseline to last observation on treatment were summarized by treatment group.

Vital Signs:

Median changes from baseline to the last observation for each vital sign was summarized by treatment group.

Changes in the Conduct of the Study or Planned Analyses

During the conduct of this study the sponsor was advised that one investigational site (Site No. 1007) was considered by the FDA to be ineligible to conduct investigational studies due to previous findings of fraudulent study conduct. At the time that Pfizer, Inc. received this information, 16 subjects at Site No. 1007 had been randomized. This site was immediately closed to further enrollment. In the analyses performed for this

report, the sponsor has excluded all 16 subjects from the MITT and clinically evaluable populations, but has included them in the safety evaluable population. Additional subjects were enrolled at other centers to compensate for the exclusion of these subjects.

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APPENDIX II

STUDY A0661057

INVESTIGATIONAL PLAN

Study Design and Plan

Male or female subjects, 18 years of age and older who met rigorous clinical and radiological entrance criteria for acute bacterial infection of the maxillary sinuses entered this randomized, open-label, multicenter study. Subjects were randomly assigned to receive one of two treatments: Zithromax® (azithromycin) 500 mg/day for 3 days or Zithromax® (azithromycin) 500 mg/day for 6 days. Subjects were followed for 28±4 days.

Subjects were enrolled in the study after satisfying the inclusion/exclusion criteria, including provision of the appropriate informed consent. At baseline, all subjects had a targeted physical examination, clinical laboratory assessments, a sinus transantral puncture (TAP) and aspiration, and provided a medical history. A sinus radiograph was obtained at the baseline visit, unless one had been performed within the previous 48 hours.

Subjects were assigned screening identification numbers sequentially at the time that written informed consent was obtained.

There were two amendments to the protocol, 11 July 2001, and 18 April 2002. The amendments did not affect efficacy or safety procedures performed on those subjects enrolled in the study prior to the implementation of the amendments. The informed consent form was revised in accordance with amendment 2 and changes were communicated to the sites through the monitoring CRO or the internal country offices wherever implemented.

In addition to administrative changes to the protocol, the first amendment included the following changes:

- Inclusion of centers in Latin America (Argentina, Chile, Costa Rica, Guatemala, Panama, and Mexico) and Europe.
- Clarification of allowable concomitant medications, e.g., theophylline, antihistamines, and warfarin. Revisions to these concomitant medications were made in order to be consistent with the US product label.
- Clarification of TAP culture guidelines, which included the requirement of local laboratories to examine the specimen by Gram stain, quantitative aerobic culture, and identification of pathogens. Endoscopically guided cultures in the absence of sinus puncture were not acceptable.
- Inclusion of microbiological methods.
- Follow-up requirement for SAEs was changed to 35 days after the last administration of study drug. This was revised in order to be consistent with current Pfizer, Inc. policies for azithromycin.

- Clarification of the requirements for adverse events related to abnormal laboratory values and physical examination findings. These revisions were made in order to be consistent with Pfizer, Inc. policies.

The second amendment included the following changes to the protocol:

- Randomization was allowed to continue in only one treatment group after the required number of subjects with target pathogens had been reached in the other treatment group.
- The sample size was increased from 300 subjects to approximately 500 subjects to ensure that there would be an adequate number of subjects with each of the target pathogens within each treatment group. This was necessary because 1) the number of subjects with *S. pneumoniae* at baseline was unevenly distributed across the two treatment groups, and 2) the number of subjects with targeted pathogens was slightly lower than anticipated.
- Sites were allowed to send the sinus aspirate directly to the central laboratory in cases where a qualified local laboratory was not available.

Study Population

Inclusion Criteria

Subjects who met the following criteria were considered for enrollment into the study and could receive study drug, if eligible.

1. Outpatient males and females 18 years of age and over.
2. Women of childbearing potential who used adequate contraception, defined as hormonal contraception, intrauterine device, or barrier methods (condom or vaginal diaphragm) with spermicide, throughout the study and for four weeks after completion of the study. The pre-study pregnancy test (urine or serum gonadotropin) must have been negative. Women who had been surgically sterilized or were at least two years postmenopausal could be enrolled and did not need to use birth control. Women whose method of birth control was hormonal were required to use an additional barrier method during the study and for one month following the completion of the study.
3. Subjects must have had clinically documented acute bacterial infection of the maxillary sinuses including one or both of the following signs and symptoms lasting longer than 7 days but less than 28 days:

—Purulent nasal discharge

—Facial pain/pressure/tightness typically over the maxillary sinuses, or pain that worsens with movement or percussion

Subjects may also have had other diagnostic symptoms, including hyposmia, jaw pain with mastication, nasal congestion, headache, halitosis, and a history of recent upper respiratory infection.

4. Subjects who had a positive sinus X-ray (i.e., opacification of the affected sinuses, an air-fluid level, or ≥ 6 mm mucosal thickening).

5. Subjects willing to undergo direct aspiration of the sinus cavity.
6. Subjects must have given written informed consent by signing and dating an informed consent form prior to study entry.

Exclusion Criteria

Subjects with any of the following conditions could not be enrolled in this study.

1. Pregnant or lactating women.
2. Subjects with an allergy, hypersensitivity, or other contraindications to any macrolide antibiotic.
3. Subjects who were currently hospitalized for any reason.
4. Subjects who were treated with any other systemic antibiotic for 24 hours or longer within 2 weeks prior to the baseline visit.
5. Subjects with infections that may have required treatment with an antibiotic other than the study drug.
6. Subjects with a recent history of chronic sinusitis including but not limited to those subjects with 3 or more episodes of sinusitis in the last 6 months.
7. Subjects who have had a history of sinus surgery other than for a diagnostic procedure within a year prior to the baseline visit.
8. Subjects with significant gastrointestinal or other conditions that could affect study drug absorption.
9. Subjects with evidence or history of significant hematological, renal or cardiovascular disease or immunologic compromise (i.e., neutropenia, ARC [AIDS-related complex]/AIDS [acquired immunodeficiency syndrome], non-skin cancers or malignant melanoma).
10. Subjects who had received any investigational drug during the previous 30 days or five times the plasma half-life (if known), whichever was longer, or who previously participated in this trial.
11. Subjects who were abusers of alcohol and/or other drugs.
12. Subjects in whom concurrent use of certain medications with study drug may have interfered with the evaluation of the study drug.
13. Subjects with any condition that, in the opinion of the investigator, could have affected subject safety, precluded evaluation of response, or made it unlikely that the contemplated course of therapy and follow-up could have been completed, or who were unable/unlikely to follow the study protocol.
14. Subjects who intended to donate blood or blood products during the study or within one month following the completion of the study.

Removal of Subjects from Treatment or Assessment

A discontinuation occurred when an enrolled subject ceased participation in the study, regardless of the circumstances, prior to completion of the protocol. Subjects could discontinue from study treatment and still complete the study by returning for scheduled visits and being evaluated for safety. The investigator was required to determine the primary reason for discontinuation. The final evaluation required by the protocol was

performed at the time of study discontinuation. The investigator was required to record the reason for study discontinuation in the CRF, and to provide or arrange for appropriate follow-up (if required) for such subjects and document the course of the subject's condition.
Subjects with marked liver function abnormalities (SGOT/SGPT >3xULN; alkaline phosphatase >1.5xULN; total bilirubin >2.0xULN) were to discontinue their study drug immediately, and the Pfizer Inc appointed monitor was to be notified. The abnormal tests should have been repeated within 48 hours, and then at 3 to 7 day intervals until they resolved.

Treatments

Investigational Products

Pfizer, Inc. provided the study medication. All study medication was to be provided in bottles packed in boxes. Each bottle was to have 3 tablets. For each subject, a total of 1 or 2 labeled bottles was to be supplied depending on the randomization assignment at Visit 1 (Day 1). Subjects were to take the first dose of study medication irrespective of the time of day. It was recommended that this dose be taken during Visit 1. Subsequent doses should have been taken in the morning, preferably at the same time of day. Study medication may have been taken without regard to meals.

At all sites the following lot numbers and FID number were used.

Lot Nos./FID No.	N0118-G1; N0118-G2; N0118-G3/QC2468
Dosage Form	500 mg tablets
Dosing	One 500 mg tablet per day
Duration	Active treatment for 3 days or 6 days. Follow-up until at least 24 to 32 days.

Method of Assigning Subjects to Treatment Groups

The investigator was provided with a randomization schedule consisting of a list of numbers to which the study drug had been randomly allocated (1:1 ratio). Following implementation of the second amendment, investigators were provided with a randomization schedule for the remaining treatment arm. The investigator assigned study numbers sequentially to the subjects as they were determined to be eligible for treatment. The randomization number was entered onto the subject's case report form and the subject received the study medication assigned to the corresponding number.

Blinding

This was an open-label study.

Prior and Concomitant Therapy

To be eligible for entry into the study, subjects were not to have received systemic antibiotics for 24 hours or longer within the prior two weeks. During the study, if treatment with another systemic antibiotic was deemed necessary, the appropriate alternate/additional therapy was initiated. Subjects who received additional systemic

antibiotic therapy for treatment of sinusitis were classified as treatment failures and discontinued from treatment but were to return for subsequent study visits to continue safety evaluations. If the antibiotic was taken for treatment of an infection other than sinusitis, a final efficacy assessment was to be undertaken prior to starting the new antibiotic.

Treatment Compliance

The investigator or their designee described the dosing instructions and emphasized the importance of following the instructions. Treatment compliance was assessed at the first follow-up visit, Visit 3 (Day 7±2). Subjects were instructed to return all unused medication at the end of treatment.

Efficacy Assessments

After written informed consent was obtained, the protocol specified efficacy assessments specific to the scheduled visit were performed.

Clinical

Visit 1 (Baseline)

The baseline visit (Visit 1) assessment included collection of demographic information, past medical history and allergy history, concurrent diseases, pregnancy test for women of child-bearing potential, antibiotic therapy within the last 14 days, concomitant drug and non-drug treatments, vital signs, laboratory assessments, and a targeted physical examination. A sinus radiograph (Waters' view – Caldwell's and lateral views only if Waters' was inconclusive) was obtained (unless one had been performed within 48 hours of the baseline visit) and read by a qualified radiologist. A sinus TAP, aspiration and culture was performed.

Assessment of current signs and symptoms of acute bacterial sinusitis included documentation of at least one of the following: post-nasal purulent discharge, facial pain over the affected sinus that worsened with movement or percussion. In addition, subjects were assessed for the presence of hyposmia, jaw pain with mastication, headache, halitosis and nasal congestion. These signs and symptoms were graded as 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

Visit 2 (Telephone Contact)

Visit 2 (Telephone Contact) was designated to occur on study Day 4±1. Through telephone contact, the subject's response to therapy was determined as provided by the subject. Information on how the subject felt since the previous visit (improved, same or worse) and the use of concomitant drug and non-drug treatments were recorded, and occurrence of adverse events since the previous visit was assessed. Additionally, compliance was confirmed.

At the discretion of the investigator, the subject was encouraged to return for an unscheduled visit if he or she reported feeling the same as at the previous visit. If the subject felt worse than at the previous visit, he or she was encouraged to return for an

unscheduled visit as soon as possible. The investigator assessed the subject's response to therapy at this unscheduled visit. If necessary, study drug was discontinued and appropriate non-study antimicrobial therapy was initiated. Subjects who discontinued study drug were directed to return for final clinical assessments.

Visit 3 (End of Therapy Visit) and Visit 4 (End of Study Visit)

Visit 3 (End of Therapy Visit, EOT) was designated to occur on study Day 7±2. Visit 4 (End of Study Visit, EOS) was designated to occur on study Day 28±4. The primary efficacy outcome time point for the study was EOS.

All signs and symptoms of sinusitis that were identified at baseline (Visit 1) were assessed and numerically graded as had been done previously. Vital signs, adverse events and concomitant drug and non-drug treatments were recorded. Study drug compliance was checked and clinical laboratory tests were performed at Visit 3. Clinical laboratory tests were performed at Visit 4 if a clinically significant abnormality was present or if the subject experienced a clinically significant adverse event.

A TAP and aspiration of the maxillary sinus and culture was strongly encouraged at Visits 3 or 4 only for those subjects who were failing to respond clinically to treatment.

At Visits 3 and 4, the investigator also determined the overall clinical outcomes based on predefined criteria: cure, improvement, failure, or unknown at Visit 3 and cure, failure, or unknown at Visit 4. The overall clinical success was defined by the sponsor as cure plus improvement at EOT (Visit 3, Day 7±2) and cure at EOS (Visit 4, Day 28±4). A sinus radiograph was repeated at Visit 3 only if the subject failed to respond clinically. A sinus radiograph was obtained for all subjects at Visit 4. The same radiographic view was obtained and read by the same radiologist as at Visit 1, whenever possible.

Study medications were returned to the investigator and study drug accountability was performed at Visit 3.

Bacteriologic

Sinus Aspiration

Transantral puncture and aspiration of maxillary sinuses for culture and susceptibility testing was to be performed at baseline. If the subject failed to respond clinically to treatment, a repeat TAP was strongly encouraged.

Specimens for culture should have been aspirated through the needle after maxillary sinus puncture according to standard procedures at the site. Endoscopically guided cultures without sinus puncture were not acceptable. When free fluid could not be obtained from the sinus cavity, up to 2.5 mL of normal saline (without preservative) solution could be instilled and aspirated to provide a specimen. The specimen should have been transported to the local laboratory for examination by Gram stain, quantitative aerobic culture and identification of pathogens. Pure culture of the isolated pathogen was then to be transported as rapidly as possible to the central laboratory for re-identification, susceptibility testing, and storage of the isolate.

Susceptibility Testing

Routine susceptibility testing of isolates was conducted locally as appropriate. If available, results were to be recorded in the case report form. During the course of the study, the central laboratory performed susceptibility testing for all isolates obtained during the study.

Subjects who did not have a pathogen isolated or if the pathogen was resistant to study medication need not have been discontinued from study drug provided they were improving clinically. Subjects with no baseline pathogen isolated were excluded from the bacteriological analysis.

Safety Assessments
Adverse Events

All adverse events, either reported by the subject or observed by the investigator, were recorded at each visit or phone contact on the adverse event page of the CRF with information on their severity (mild, moderate, severe), date of onset, duration, withdrawal from treatment and/or study, treatment required, seriousness, and the investigator's assessment of relationship to study drug. Adverse events included adverse drug reactions, illnesses with an onset during the study, or exacerbation of pre-existing illnesses (including the disease under study). Insufficient or lack of clinical response, benefit, efficacy, or therapeutic effect was not considered an adverse event. Thus the investigator had to distinguish between an exacerbation of disease under study (pre-existing illness) and lack of efficacy. Objective test findings (e.g., abnormal laboratory test results) specified in the protocol which resulted in a change in study drug dosage, treatment discontinuation, or intervention/diagnostic evaluation to assess risk were also recorded as adverse events, as were clinically significant changes in physical examination findings. Subjects were to be followed until adverse events (or their sequelae) resolved or stabilized.

Serious Adverse Events

A serious adverse event (SAE) included any adverse drug experience occurring at any dose that:

- resulted in death
- was life-threatening
- resulted in inpatient hospitalization or prolongation of an existing hospitalization
- resulted in persistent or significant disability/incapacity
- resulted in congenital anomaly/birth defect.

Detailed definitions associated with these events are provided in the protocol.

Additionally, important medical events that did not result in death, were not life-threatening, or did not require hospitalization may have been considered serious

adverse drug experiences when, based on appropriate medical judgement, they jeopardized the subject and required medical or surgical intervention to prevent one of the outcomes listed in this definition. Regardless of the above criteria, any adverse experience which the sponsor or an investigator considered serious was to be immediately reported to the sponsor and included in the corporate safety database system.

Any serious adverse event or death was to be reported immediately independent of circumstances or suspected cause if it occurred or came to the attention of the investigator during the study through the last follow-up visit required by the protocol or 35 days after the last administration of study drug, whichever was later. Any serious adverse event occurring at any time after completion of the study was to be promptly reported when study drug was the suspected cause. The investigator was to make an assessment of causality (unknown causality was attributed to azithromycin) and provide sufficient information about the case to allow for an independent medical assessment of possible causality.

Clinical Laboratory Tests

All clinically important abnormal laboratory tests that occurred during the study were repeated at appropriate intervals until they returned either to baseline or to a level deemed acceptable by the investigator and sponsor's clinical monitor (or his/her designated representative), or until a diagnosis that explained them was made. An abnormal laboratory test result was to be recorded as an adverse event if any one of following criteria was met:

- the test result was associated with accompanying symptoms
- the test result required additional diagnostic testing or medical/surgical intervention
- the test result led to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy
- the test result led to any of the outcomes included in the definition of a serious adverse event
- the test result was considered to be an adverse event by the investigator or sponsor

The following laboratory tests were performed at baseline (Visit 1, Day1), at EOT (Visit 3, Day 7±2), or at the time of discontinuation for an adverse event.

Hematology	**Clinical Chemistry**	**Urinalysis (by Dipstick)**
Hemoglobin	SGOT/AST	Protein
Hematocrit	SGPT/ALT	Glucose
Red blood cells	Total bilirubin	Ketones
Platelet count	LDH	Bilirubin
WBC count with differential	Alkaline phosphatase	pH
	Urea (BUN)	Urobilinogen
	Creatinine	Blood
	Total protein	Nitrite
	Albumin	
	Sodium	
	Potassium	
	Bicarbonate	
	Chloride	
	Random blood glucose	

In addition, at baseline (Visit 1) a pregnancy test (blood or urine gonadotropin) was performed on female subjects of child-bearing potential.

Clinical laboratory tests, including blood chemistry, hematology and dipstick urinalysis, were obtained at Visit 4 (EOS, Day 28±4) only if clinically significant abnormalities were present at Visit 3, or if the subject was experiencing a clinically significant adverse event.

Moderate and marked liver function abnormalities were defined as follows:

	SGOT/SGPT	Alkaline Phosphatase	Total Bilirubin
Moderate	>1.5 x ULN	>1.2 x ULN	>1.5 x ULN
Marked	>3 x ULN	>1.5 x ULN	>2.0 x ULN

where ULN was defined as the upper limit of normal, if the pretreatment baseline was normal or the pretreatment baseline if it was abnormal.

Moderately abnormal liver function tests were repeated within three to seven days. If confirmed, liver function tests were repeated at weekly intervals until they resolved. Subjects with marked liver function abnormalities discontinued treatment immediately, and the sponsor's appointed clinical monitor was notified. The abnormal tests were repeated within 48 hours, and then at three to seven day intervals until they resolved. After consultation with the sponsor's appointed clinical monitor, additional evaluation of subjects with marked abnormalities that persisted after study drug treatment was discontinued was arranged. The additional evaluation may have included GI consultation and additional laboratory tests (e.g., HBV, HAV, or CMV serology, CPK, reticulocyte count). Subjects with moderate and marked abnormal liver function tests were to be followed until the abnormalities resolved or the sponsor's appointed clinician

agreed that the abnormal findings stabilized and additional testing would be of no value in clarifying the findings.

In addition, any of the following marked laboratory abnormalities led to automatic additional local laboratory testing on stored samples.

Bilirubin increase from Baseline	≥1.0 mg/dL or ≥17 μmol/L
Creatinine increase from Baseline	≥0.8 mg/dL or ≥73 μmol/L
Hemoglobin decrease from Baseline	≥2 g/dL or ≥1.24 mmol/L

These data were reviewed by the sponsor's clinician, and in consultation with the investigator, additional laboratory evaluation may have been performed.

Statistical Methods

Sample Size

In this multicenter trial each center was to continue to enroll subjects until at least 25 subjects with a positive bacterial culture for *H. influenzae* and at least 25 subjects with a positive bacterial culture for *S. pneumoniae* who were clinically and bacteriologically evaluable had been enrolled in each study arm. Centers were also to enroll at least 15 *M. catarrhalis* evaluable subjects per arm. However, the sponsor reserved the right to terminate the enrollment irrespective of the status of enrollment of *M. catarrhalis* subjects. It was anticipated that a total of 300 subjects would be needed to satisfy these criteria.

Statistical and Analytical Plans

The statistical analyses performed are summarized below:

Study Populations Analyzed

There were three analysis populations:

1. The safety population included all treated subjects.
2. The clinical modified intent-to-treat (MITT) population included subjects who had clinically documented acute bacterial infection of the maxillary sinuses at baseline, and who had received at least one dose of study medication. The bacteriological MITT population was defined as a subset of subjects in the clinical MITT population with a positive baseline culture for *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, or *S. aureus* (when isolated in pure culture with a colony count of $\geq 10^4$ CFU/mL).
3. The clinically evaluable population included all subjects in the MITT population, unless any one or more of the following criteria applied: a) Did not meet all inclusion and exclusion criteria, b) Received less than 80% of study medication except if failed and discontinued, c) Received more than 120% of study medication.

   In addition, subjects who met the following criteria were excluded from the clinically evaluable analyses at the relevant visit(s): a) Received concomitant

systemic antibiotic treatment for intercurrent illness prior to the evaluation point, b) Had no visit at the primary evaluation time point (EOS visit) unless the subject was previously designated as a treatment failure, c) Had a visit date outside the analysis visit window, d) Had no radiology data at Visit 4 unless the subject was considered a clinical failure prior to Visit 4 or the subject had an x-ray at Visit 3 and was a cure at both Visit 3 and Visit 4, e) Had an inappropriate, susceptible baseline pathogen (bacteriological evaluable subset only).

The bacteriologically evaluable population was defined as a subset of subjects in the clinically evaluable population with a positive baseline culture for *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, or *S. aureus* (when isolated in pure culture with a colony count of $\geq 10^4$ CFU/mL).

All evaluability determinations were made on groups of clean subject data at regular intervals during the study prior to database release.

Efficacy Parameters

Two populations, the clinical MITT and clinically evaluable populations were analyzed for efficacy in this study.

Primary Efficacy Parameter:

The primary measure of efficacy was the sponsor's assessment of bacteriological response at the EOS visit (Visit 4, Day 28±4) for the bacteriological MITT population.
Secondary Efficacy Parameters: The secondary measures of efficacy were:

- Clinical response at the EOT visit (Visit 3, Day 7±2)
- Clinical response at the EOS visit (Visit 4, Day 28±4)
- Bacteriological response at the EOT visit (Visit 3, Day 7±2) for the bacteriological MITT and bacteriologically evaluable populations and at EOS for the bacteriologically evaluable population.

Bacteriological Response:

Bacteriological response was summarized on a by-subject and by-pathogen basis for the bacteriological MITT and bacteriologically evaluable populations.

For those subjects for whom a pathogen was isolated at baseline, bacteriological response was determined by the sponsor and evaluated at the EOT visit (Visit 3, Day 72) and EOS visit (Visit 4, Day 28±4) as follows:

Documented Eradication—Absence of the original baseline pathogen in a sinus puncture culture at Visit 3, Visit 4 or relevant visit.

Presumed Eradication—Absence of repeat sinus puncture culture results, and the subject was a clinical cure at Visit 4 or a clinical improvement or cure at Visit 3.

Documented Persistence—Presence of the original baseline pathogen in a sinus puncture culture at Visit 3,Visit 4 or relevant visit.

Presumed Persistence—Absence of repeat sinus puncture culture and the subject was a clinical failure.

Superinfection—Baseline pathogen(s) gone but another pathogen present in a sinus puncture culture. By-subject bacteriological response assessment was based on the following hierarchy in the event that more than one outcome applied:

1. Documented Persistence
2. Superinfection
3. Presumed Persistence
4. Presumed Eradication
5. Documented Eradication

The by-pathogen bacteriological response assessments were similar to those described above for the by-subject bacteriological response with the exception that "Superinfection" was not included as a response category.

Clinical Response:

Clinical response was determined by the investigator at the EOT visit (Visit 3, Day 7±2) and the EOS visit (Visit 4, Day 28±4) and was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point. The investigator classified the clinical presentation of the subject at the evaluation time point using the criteria listed below.

Cure—Resolution of signs and symptoms of acute sinusitis to the level that existed prior to the occurrence of the acute illness. No worsening in the radiographic appearance of the sinuses noted (applicable to Visit 4 or where radiographic information is available). No antibiotics (other than study drug) were given.

Improvement—Improvement but incomplete resolution of the signs and symptoms of acute sinusitis as defined above and no requirement for additional antibiotic. This was applicable at Visit 3 only.

Failure—Persistence of one or more signs or symptoms of sinusitis or appearance of new signs or symptoms. Need for additional antimicrobials or change in antimicrobial therapy.

Unknown—Subject response cannot be assessed due to missed visit or failure to record clinical outcome.

The occurrence of any of the following conditions superceded the evaluation of response as Cure, Improvement, Failure or Unknown and resulted in the reassignment of outcome by the sponsor as follows:

a) For subjects who were previously assessed as failures, the outcome was always failure at subsequent time points.

b) For subjects who were given a concomitant antibiotic prior to or during the analysis visit windows, response was classified as failure if the concomitant antibiotic was given for incomplete clinical response or failure.

All reassignments of outcome by the Sponsor were completed prior to database release.

Efficacy Analyses

Level of Statistical Significance:
Descriptive statistics were presented separately for the two treatment groups. No statistical comparisons or inferences between treatment groups were made.

Subject Clinical Response:
Subject clinical response was summarized for both the MITT and clinically evaluable populations. Clinical response was evaluated at the EOT visit (Visit 3, Day 7±2) as Cure, Improvement, Failure or Unknown; and at the EOS visit (Visit 4, Day 28±4) as Cure, Failure or Unknown. Clinical response was based primarily on the global assessment of the clinical presentation of the subject made by the investigator at the evaluation time point.

The number and percentage of subjects classified as Success (Cure + Improvement at Visit 3, Cure at Visit 4) and Failure were displayed and a 95% confidence interval of the success rate was computed for each treatment group separately using the normal approximation to the binomial distribution. Summaries were presented for all subjects combined as well as separately by baseline pathogen. Results were also displayed by geographical region.

Bacteriological Response:
Bacteriological eradication rates and 95% confidence intervals (Documented Eradication + Presumed Eradication) were displayed by treatment group for all bacteriological MITT and bacteriologically evaluable populations combined as well as by baseline pathogen separately (where numbers of pathogens were sufficiently large). Results were also displayed by country.

Baseline Susceptibility:
All baseline pathogens received by the central laboratory were tested for susceptibility to study drug. The MIC values, categorized as susceptible, intermediate and resistant, were summarized and displayed. A tabulation of baseline susceptibility and clinical outcome was constructed by country. In addition, a correlation between susceptibility based on minimum inhibitory concentration (MIC) and zone size is presented.

Missing Values:
In the summaries of clinical response (clinical MITT and clinically evaluable populations) and bacteriologic response (bacteriological MITT and bacteriologically evaluable populations), subjects with missing observations were excluded except for evaluable failures due to the use of concomitant antibiotics. Subjects designated as a failure at a prior visit were not excluded. Additional presentation of the clinical response data with the missing values included and set to failure and set to cure were provided for the clinical MITT population.

Other Efficacy Variables:
Summary of signs and symptoms consisted of a display by treatment group of frequencies in the different score categories and the corresponding percentages, or means, as appropriate.

Clinical response results were presented in strata defined by presence or absence of allergic rhinitis at baseline for each treatment group.

Visit Windows:
Day 1 (Baseline) was the first day of treatment. For analysis purposes, the windows for evaluability were defined as follows:

Visit	Day Range
Baseline (Day 1)	N/A
EOT (Visit 3)	6 to 12
EOS (Visit 4)	22 to 36

Safety Parameters and Analyses

All safety parameters were summarized by treatment group for all treated subjects (safety population). No statistical comparisons were made.

Adverse Events:

All adverse events that occurred after the first dose of study medication regardless of suspected causality to study drug were summarized according to Pfizer Worldwide Safety Standards (WSS). The number and percentage of subjects reporting an adverse event after the first dose of study medication, were summarized within each COSTART (coding symbols for thesaurus of adverse reaction terms) body system, preferred term, and treatment. All adverse events were summarized by severity. Similar displays were generated for all treatment-related adverse events. Premature discontinuations were also included.

Serious Adverse Events:

A listing is provided from the Pfizer, Inc. serious adverse events database of all subjects with serious adverse events.

Laboratory Data:

The incidence of clinically significant laboratory test abnormalities for each laboratory parameter and the median change from baseline to last observation were summarized for each treatment group according to Pfizer Worldwide Safety Standards.

Vital Signs:

Median changes from baseline to the last observation for each vital sign were summarized for each treatment group.

Changes in the Conduct of the Study or Planned Analyses

There were no changes in the conduct of the study or planned analyses.

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/s/

Nasim Moledina
1/14/04 01:08:43 PM
MEDICAL OFFICER

John, my review of NDA 50-784/S004 for Zithromax 500 mg/indication ABS

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