

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-797

MEDICAL REVIEW

**Division Director/Team Leader Memorandum for NDA 50-797
Zmax (Azithromycin Extended Release) for Oral Suspension**

Azithromycin, a macrolide antibiotic, first gained US marketing approval in November, 1991. Approved indications in adults include community-acquired pneumonia, acute sinusitis, acute exacerbation of chronic bronchitis, and pharyngitis. Azithromycin is available in multiple oral formulations (tablets, oral sachet, powder for oral suspension), as well as intravenously. Duration of treatment for adult respiratory infections ranges from 3-5 days, with a total cumulative dose, regardless of formulation, of 1500 mg.

The sponsor of this NDA, Pfizer Inc., developed a new formulation of azithromycin, an extended release powder for oral suspension ("azithromycin ER"), given as a 2-gram single dose. Fourteen phase 1 studies were performed to define the clinical pharmacology profile of the formulation (e.g., bioavailability, food effect, GI tolerance, and pharmacokinetics), and 4 phase 3 studies in adults were conducted to assess efficacy and safety of this 2 gram single dose oral suspension in respiratory indications: community-acquired pneumonia, and acute bacterial sinusitis. Safety data from a phase 3 pharyngitis study were also included.

The relative bioavailability of azithromycin extended release, compared to azithromycin immediate release sachet, is approximately 86%. A direct comparison of the relative bioavailability of azithromycin ER to azithromycin tablets has not been performed. Since four azithromycin 250mg tablets are bioequivalent to the 1 gram sachet, the relative bioavailability of azithromycin ER may also be 86% compared to tablets. Thus, the exposure (AUC) following administration of 2 g azithromycin extended release will likely exceed the AUC for the approved azithromycin tablet 3-day and 5-day regimens. After a 2-gram azithromycin ER dose, peak serum concentrations are reached 2 hours later, compared to the sachet, and better tolerated with less nausea and vomiting. Administration of azithromycin ER with food results in higher peak serum concentrations and systemic exposure, but is less well tolerated in terms of GI side effects, compared to taking it on an empty stomach. In the phase 3 studies, patients were given azithromycin ER at least one hour before or 2 hours after a meal. Pharmacokinetic studies of azithromycin ER 2 grams, compared to azithromycin 1500 mg as immediate release (250 or 500 mg) tablets over 3-5 days, reveal "front-end" loading, with higher peak serum concentration and greater systemic exposure on the first day of dosing with the extended release formulation.

Phase 3 clinical studies assessed patient safety and efficacy in adults with mild to moderate outpatient respiratory infections. Adults with signs, symptoms, and radiographic evidence of community-acquired pneumonia (CAP) were studied in two randomized, double-blind, double-dummy, multicenter international trials. In one CAP study, azithromycin ER 2-gram single dose was compared to clarithromycin ER 1 gram daily for 7 days. In the second study, levofloxacin 500 mg daily for 7 days was the comparator. In both CAP studies, clinical cure rates for azithromycin ER and comparators were 90-95%, and the lower limit of the 95% confidence interval (CI) for the difference in cure rates was greater than -10%, indicating non-inferiority of azithromycin extended release to comparators. Pathogens in pneumonia included *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

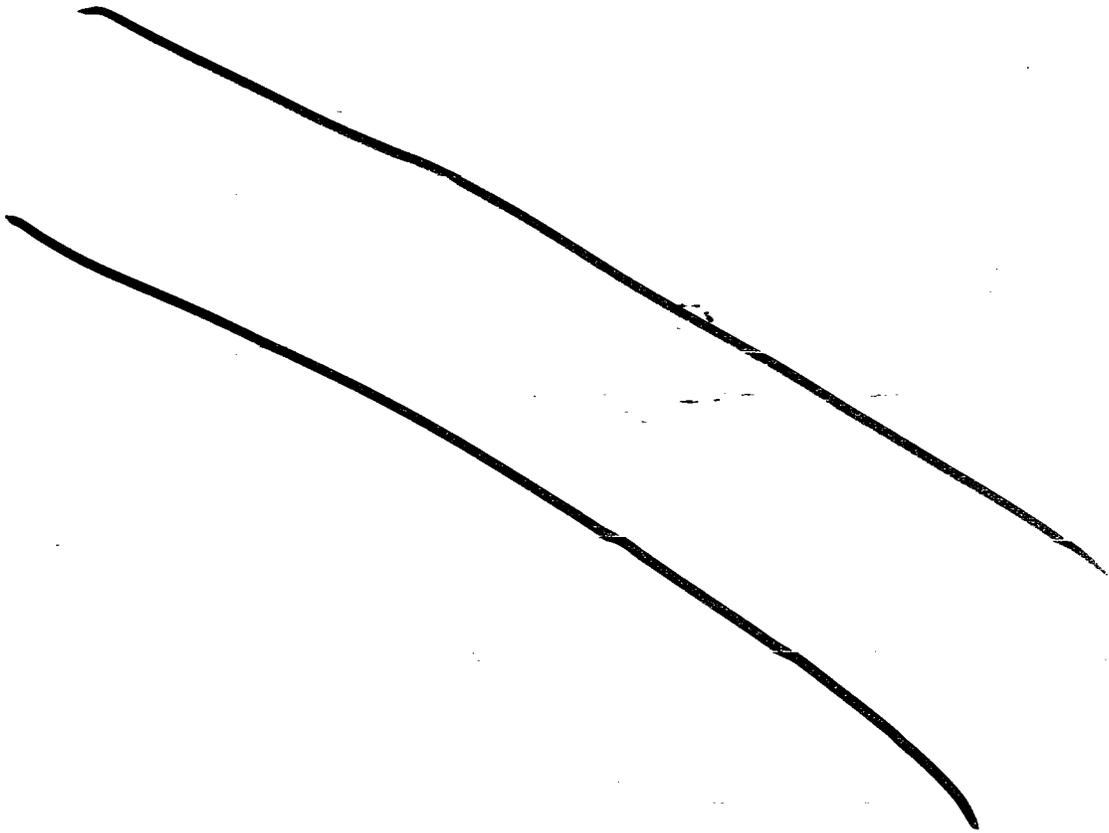
Clinical Cure Rates in Community Acquired Pneumonia at Test of Cure (day 14-21)

	<u>Azithromycin extended release</u>	<u>Comparator</u>	<u>95% CI</u>
	n/N (%)	n/N (%)	
Study 1	187/202 (93)	198/209 (95)	(-6.9, 2.6)
Study 2	156/174 (90)	177/189 (94)	(-9.7, 1.7)

For acute bacterial sinusitis (ABS), a single randomized, double-blind, double-dummy, multicenter international trial in adults was performed, comparing azithromycin ER 2-gram single dose with levofloxacin 500 mg daily for 10 days. The clinical cure rates for azithromycin and levofloxacin were roughly 90%, and the lower limit 95% CI supported that azithromycin ER is non-inferior to levofloxacin in the treatment of acute bacterial sinusitis. Pathogens in sinusitis included *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

Clinical Cure Rates in Acute Bacterial Sinusitis at Test of Cure (day 17-24)

<u>Azithromycin extended release</u>	<u>Levofloxacin</u>	<u>95% CI</u>
n/N (%)	n/N (%)	
238/254 (94)	232/252 (92)	(-2.8, 6.1)



A total of 1292 patients received azithromycin ER 2 grams and were assessed for safety. The most common adverse events reported were related to the GI-tract (21%), and included diarrhea/loose stools (13%), nausea (4%), and vomiting (2%). Known adverse effects with other marketed formulations of azithromycin include warnings related to allergic reactions, Stevens Johnson syndrome and toxic epidermal necrolysis. Since the full course of treatment with azithromycin extended release is a single dose, vomiting raises the concern of whether or not to re-treat patients. Overall, no patients in the phase 3 studies vomited within the first 30 minutes after taking azithromycin ER, and no blood samples were obtained to assess the impact of vomiting on absorption. If a patient vomits immediately after taking azithromycin ER, the patient needs to be retreated. If a patient vomits after 1 hour, additional therapy is not routinely recommended. Patients who otherwise vomit within the first hour should contact their physician for further care.

In summary, the sponsor has studied azithromycin extended release for oral suspension, given as a 2 gram single dose, and provided substantial evidence of safety and efficacy in the treatment of adults with outpatient community acquired pneumonia and acute bacterial sinusitis.

There are no phase 4 commitments with this NDA approval. A pediatric development program is on-going with the extended release formulation.

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/s/

John Alexander
6/10/05 03:00:18 PM
MEDICAL OFFICER

Janice Soreth
6/10/05 03:07:29 PM
MEDICAL OFFICER

Table of Contents

1	EXECUTIVE SUMMARY.....	8
1.1	RECOMMENDATION ON REGULATORY ACTION	8
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	8
1.2.1	Risk Management Activity	8
1.2.2	Required Phase 4 Commitments.....	8
1.2.3	Other Phase 4 Requests.....	8
1.3	SUMMARY OF CLINICAL FINDINGS	8
1.3.1	Brief Overview of Clinical Program.....	8
1.3.2	Efficacy.....	9
1.3.3	Safety.....	16
1.3.4	Dosing Regimen and Administration.....	20
1.3.5	Drug-Drug Interactions.....	20
1.3.6	Special Populations.....	21
2	INTRODUCTION AND BACKGROUND.....	23
2.1	PRODUCT INFORMATION	23
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	23
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES.....	23
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS.....	25
2.5	PRESUBMISSION REGULATORY ACTIVITY	25
2.6	OTHER RELEVANT BACKGROUND INFORMATION.....	27
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....	28
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE).....	28
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	28
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....	29
4.1	SOURCES OF CLINICAL DATA	29
4.2	TABLES OF CLINICAL STUDIES	29
4.3	REVIEW STRATEGY	30
4.4	DATA QUALITY AND INTEGRITY	30
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES.....	31
4.6	FINANCIAL DISCLOSURES.....	31
5	CLINICAL PHARMACOLOGY.....	32
5.1	PHARMACOKINETICS.....	33
5.2	PHARMACODYNAMICS.....	33
5.3	EXPOSURE-RESPONSE RELATIONSHIPS	33
6	INTEGRATED REVIEW OF EFFICACY.....	34
6.1	INDICATION: COMMUNITY-ACQUIRED PNEUMONIA.....	34
6.1.1	Methods.....	34
6.1.2	General Discussion of Endpoints.....	34
6.1.3	Study Design.....	35
6.1.4	Efficacy Findings.....	35
6.1.5	Efficacy Conclusions.....	50
6.2	INDICATION: ACUTE BACTERIAL SINUSITIS.....	51
6.2.1	Methods.....	51
6.2.2	General Discussion of Endpoints.....	51
6.2.3	Study Design.....	53
6.2.4	Efficacy Findings.....	58

6.2.5	Clinical Microbiology.....	70
6.2.6	Efficacy Conclusions.....	77
<hr/>		
7	INTEGRATED REVIEW OF SAFETY.....	94
7.1	METHODS AND FINDINGS.....	94
7.1.1	Deaths.....	97
7.1.2	Other Serious Adverse Events.....	98
7.1.3	Dropouts and Other Significant Adverse Events.....	99
7.1.4	Other Search Strategies.....	100
7.1.5	Common Adverse Events.....	101
7.1.6	Less Common Adverse Events.....	111
7.1.7	Laboratory Findings.....	111
7.1.8	Vital Signs.....	121
7.1.9	Electrocardiograms (ECGs).....	122
7.1.10	Immunogenicity.....	122
7.1.11	Human Carcinogenicity.....	122
7.1.12	Special Safety Studies.....	123
7.1.13	Withdrawal Phenomena and/or Abuse Potential.....	123
7.1.14	Human Reproduction and Pregnancy Data.....	123
7.1.15	Assessment of Effect on Growth.....	123
7.1.16	Overdose Experience.....	123
7.1.17	Postmarketing Experience.....	123
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS.....	123
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety.....	123
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	128
7.2.3	Adequacy of Overall Clinical Experience.....	128
7.2.4	Adequacy of Special Animal and/or In Vitro Testing.....	128
7.2.5	Adequacy of Routine Clinical Testing.....	128
7.2.6	Adequacy of Metabolic, Clearance, and Interaction Workup.....	128
7.2.7	Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.....	129
7.2.8	Assessment of Quality and Completeness of Data.....	129
7.2.9	Additional Submissions, Including Safety Update.....	129
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS.....	129
7.4	GENERAL METHODOLOGY.....	129
8	ADDITIONAL CLINICAL ISSUES.....	129
8.1	DOSING REGIMEN AND ADMINISTRATION.....	129
8.2	DRUG-DRUG INTERACTIONS.....	129
8.3	SPECIAL POPULATIONS.....	130
8.4	PEDIATRICS.....	131
8.5	ADVISORY COMMITTEE MEETING.....	132
8.6	LITERATURE REVIEW.....	132
8.7	POSTMARKETING RISK MANAGEMENT PLAN.....	132
8.8	OTHER RELEVANT MATERIALS.....	132

Clinical Review
Nasim Moledina, M.D.
NDA 50-797
Azithromycin (Zithromax®)

9	OVERALL ASSESSMENT.....	132
9.1	CONCLUSIONS	132
9.2	RECOMMENDATION ON REGULATORY ACTION	133
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	133
9.3.1	Risk Management Activity	133
9.3.2	Required Phase 4 Commitments.....	133
9.3.3	Other Phase 4 Requests.....	133
9.4	LABELING REVIEW	133
9.5	COMMENTS TO APPLICANT.....	137
10	APPENDICES.....	138
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS	147
10.2	LINE-BY-LINE LABELING REVIEW.....	147
	REFERENCES	148

Appears This Way
On Original

List of Tables

Table 1: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects).....	11
Table 2: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects).....	12
Table 3: Sponsor’s Assessment [Number (%)] of Clinical Response (Clinical Per Protocol Subjects) at TOC visit.....	13
Table 4: Sponsor’s Summary of Bacteriologic Eradication Rates of All Baseline Pathogens at the TOC visit in Bacteriologic Per protocol Subjects.....	14
Table 5: Bacteriologic Eradication Rate (%) By Pathogen at TOC (Bacteriologic per Protocol Subjects).....	14
Table 6: Summary of Common (≥1%) Adverse Events (All Causality) in Adult Phase 3 Studies.....	17
Table 7: Summary of Common (≥1%) Adverse Events (Treatment Related) in Adult Phase 3 Studies by.....	19
Table 8: Adult Indications.....	24
Table 9: FDA Approval for Zithromax.....	24
Table 10: Key Biopharmaceutic Studies:.....	29
Table 11: Key Clinical Pharmacology Studies:.....	29
Table 12: Efficacy and Safety studies of Indications for Adults.....	30
Table 13: Subject Disposition.....	36
Table 14: Drug Administration:.....	37
Table 15: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects).....	38
Table 16: Clinical Response at TOC, MITT Population.....	38
Table 17: Investigator Assessment of Clinical Response at TOC, Number (%) of Subjects ^a (Clinical Per Protocol Subjects).....	39
Table 18: Clinical Cure Rates by Baseline Pathogen (Bacteriologic-Per Protocol Subjects).....	40
Table 19: Commonly Used Concomitant Medications, by Decreasing Frequency.....	41
Table 20: Evaluation Groups.....	43
Table 21: Drug Administration:.....	44
Table 22: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects).....	45
Table 23: Sponsor Assessment of Clinical Response at TOC, MITT Population.....	46
Table 24: Investigator Assessment of Clinical Response at TOC, Number (%) of Subjects ^a	46
Table 25: Clinical Cure Rates at TOC by Baseline Pathogen.....	47
Table 26: CAP: Bacteriologic Eradication and Clinical Cure Rates at TOC in Azithromycin ER Subjects with Azithromycin Non-Susceptible <i>S. pneumoniae</i> at Baseline (A0661075, A0661103) –Bacteriologic Per Protocol Subjects.....	49
Table 27: Commonly Used Concomitant Medications, by Decreasing Frequency.....	50
Table 28: Study and Analysis Visit Windows.....	56
Table 29: Commonly Used Concomitant Medications (All Treated Subjects).....	57
Table 30: Number of Subjects Receiving Additional Antimicrobial Medications.....	58
Table 31: Sponsor’s Table: Number (%) of Subjects Discontinued or Lost to follow up.....	59

Table 32: Modified Sponsor’s Discontinuations from Study (ITT Population).....	59
Table 33: Number of Subjects Involved in Protocol Deviation and Reasons for Deviation.....	60
Table 34: Modified Sponsor’s Table of Subject Demographic Characteristics at Baseline [All Treated (ITT) subjects]	61
Table 35: Sponsor’s Table of Subject Demographic Characteristics (Clinical Per Protocol subjects at TOC)	62
Table 36: Modified Sponsor’s Table of Prognostic Factors and Other Baseline Characteristics (All Treated Subjects).....	63
Table 37: Sponsor’s Overall Subject Evaluation Groups, Number (%) ^a of Subjects.....	64
Table 38: Reasons for discontinuation from evaluation – Patient Profile	65
Table 39: Sponsor’s Assessment [Number (%)] of Clinical Response (Clinical Per Protocol Subjects) at TOC visit.....	66
Table 40: Investigator’s Assessment of Clinical Response (Clinical Per Protocol Subjects) at TOC Visit.....	67
Table 41: Listing of Re-Classified Patients in the Reviewer’s Analysis	68
Table 42: Reviewer’s Assessment [Number (%)] of Clinical Response (Clinical Per Protocol Subjects) at the TOC visit.....	68
Table 43: Clinical Cure Rates at the TOC visit by Baseline Characteristics (Clinical Per Protocol Subjects).....	69
Table 44: Sponsor’s Primary Efficacy Outcome in Clinical ITT Population.....	70
Table 45: Reviewer’s Primary Efficacy Outcome in Clinical ITT Population.....	70
Table 46: Overall Growth of Baseline Pathogens.....	71
Table 47: Sponsor’s Summary of Bacteriologic Eradication Rates of All Baseline Pathogens at the TOC visit in Bacteriologic Per protocol Subjects.....	72
Table 48: Bacteriologic Eradication Rate (%) By Pathogen at TOC (Bacteriologic per Protocol Subjects).....	72
Table 49: * Summary of Bacteriologic Eradication Rates of overall Baseline	73
Table 50: Clinical Response versus Bacteriologic Response at the TOC visit in the Bacteriologic Per Protocol Subjects (Sponsor Assessment)	74
Table 51: Susceptibility of baseline pathogens versus Sponsor-Assessed Bacteriologic Response [Number of Pathogens = Bacteriologic Per Protocol Subjects].....	75
Table 52: Susceptibility of Baseline Pathogens, Number of Pathogens (All-Randomized Subjects Without Regard to Treatment Group).....	76
Table 53: Sponsor-Assessed Susceptibility of baseline pathogens versus Clinical Response	76

Table 55: 2 x 2 Table	90
Table 56: Kappa 2x2 Table for Clinically Evaluable Population	91
Table 57: Kappa for Per Protocol Analysis	91
Table 58: Bacteriologic Eradication Rates at TOC (Bacteriologic Per Protocol Subjects).....	93
Table 59: Phase 3 Azithromycin ER Studies.....	97
Table 60: Summary of Serious Adverse Event Cases in Adult Phase 3 Studies, Including Deaths	98
Table 61: Number of Subjects with Adverse Events Resulting in Discontinuation From	99
Table 62: Discontinuations from Study - All Phase 3 Clinical Studies - All Adult Subjects.....	100

Table 63: Summary of Common (>1%) Adverse Events (All Causality) in Phase 3 Studies	102
Table 64: Summary of Common (>1%) Adverse Events (All Causality) in Azithromycin.....	104
Table 65: Summary of Common (>1%) Treatment-Related Adverse Events in Phase 3.....	106
Table 66: Summary of Common (>1%) Treatment-Related Adverse Events in Phase 3.....	107
Table 67: Number of Treatment-Emergent, Treatment-Related GI AEs with >1%.....	109
Table 68: Summary of Treatment-Related Vomiting in Phase 3 studies.....	110
Table 69: Summary of Diarrhea (All Causality and Treatment-Related) in Phase 3 Studies.....	111
Table 70: Overall Incidence of Clinically Significant Abnormalities in Phase 3 Studies.....	111
Table 71: Incidence of Clinically Significant Abnormalities (Without Regard to Baseline).....	113
Table 72: Clinically Significant Laboratory Abnormalities by Demographic.....	115
Table 73: Summary of Adverse Events (All Causality) in Phase 3 Studies by Gender.....	117
Table 74: Summary of Adverse Events (All Causality) for Subjects ≥16 Years of Age in.....	118
Table 75: Summary of Adverse Events (All Causality) for Subjects 13-16 Years of Age in.....	119
Table 76: Summary of Adverse Events (All Causality) in Phase 3 Studies by Race.....	120
Table 77: Summary of Adverse Events (All Causality) in Phase 3 Studies by Geographic.....	121
Table 78: Subject Evaluation Groups in Phase 3 Studies by Treatment Group.....	124
Table 79: Subject Evaluation Groups in Phase 3 Studies for Azithromycin ER-Treated.....	124
Table 80: Demographic Characteristics in Phase 3 Studies by Treatment Group.....	125
Table 81: Demographic Characteristics in Phase 3 Studies for Azithromycin ER-Treated.....	126
Table 82: Duration of Active Treatment in Phase 3 Studies by Treatment Group.....	127
Table 83: Number of Active Doses in Phase 3 Studies by Treatment Group.....	127

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the review of safety and efficacy data submitted in this NDA, the following recommendations are made by the Medical Officers (Dr. Charles Cooper, Dr. Menfo Imoisili and Dr. Nasim Moledina):

Azithromycin ER is recommended for approval for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

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

Community-acquired pneumonia due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*, in patients appropriate for oral therapy.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Given prior experience with azithromycin products, no special risk management activity is required.

1.2.2 Required Phase 4 Commitments

No clinical Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

None requested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Indications and Study Design

The applicant presented data supporting the efficacy of azithromycin ER in the treatment

of █████ CAP and ABS. All Phase 3 studies supporting these indications were multicenter, randomized, double-blind, double-dummy, comparative studies designed to confirm the hypothesis that azithromycin ER was at least as clinically effective as the active comparator. Each comparator had demonstrated efficacy against the specific diseases under study, and had relevant regulatory approval in the U.S.

Endpoints and Analysis

The primary endpoint in █████ CAP, and ABS was the sponsor's assessment of clinical response at the Test of Cure (TOC) visit. Non-inferiority of azithromycin ER was based on the lower boundary of the 95% confidence interval around the percent difference in clinical cure rates (azithromycin ER – comparator) being greater than -10%. For the major secondary analysis of overall bacteriologic response, confidence intervals were determined around the percent difference in eradication (documented and presumed) rates. In addition, the long-term follow-up assessment of clinical cure and relapse was also analyzed in the primary population for █████ CAP. There were no center adjustments given that the primary efficacy parameter in each study was defined by the sponsor based on signs/symptoms and antibiotic use.

Primary Population

In █████ CAP, and ABS studies, the primary efficacy population was the Clinical Per Protocol population, defined as:

- Satisfying the diagnostic criteria for the disease under study
- Dosed for at least 80% of days with active drug/placebo for subjects who are cured, and dosed for at least three days for subjects who fail
- Received no systemic antibiotics active against relevant pathogens (unless for treatment failure)
- Assessed in the pre-defined visit window

Analyses were conducted on other populations, including Clinically-Eligible (modified intent-to-treat) and Bacteriologic Per Protocol. A subject in the latter population met the definition of Clinical Per Protocol and had a pathogen identified at baseline.

1.3.2 Efficacy

Indication: Community-Acquired Pneumonia

Efficacy and safety data using a single 2.0 gram dose of Azithromycin ER in mild-to-moderate CAP were obtained in two independent, Phase 3, randomized, multicenter, double-blind, double dummy, comparative international studies, A0661075 and A0661103.

The primary efficacy endpoint in either study was the sponsor assessment of clinical response for the Clinical Per Protocol population at the test of cure visit (TOC; study days 14-21). Secondary endpoints determined for the Clinical Per Protocol population included clinical relapse at long-term follow-up (LTFU; Days 28-35). Clinical and bacteriologic responses by

baseline pathogen at TOC in the Bacteriologic Per Protocol population were also assessed. Other efficacy assessments included sponsor assessment of clinical response by baseline pathogen versus baseline susceptibility.

Study A0661075 was a randomized, double-blind, double-dummy, active-controlled, multicenter, international study in which subjects were assigned to receive either a single, 2.0 g dose of Azithromycin ER or clarithromycin ER tablets, 1.0 g once daily for 7 days. Of 551 subjects screened, a total of 501 subjects were randomized at 61 centers in North America, Latin America, Europe and India. A total of 499 subjects were treated: 247 subjects received Azithromycin ER and 252 received clarithromycin.

Study A0661103 was a randomized, double-blind, double-dummy, active-controlled, multicenter, international study in which subjects were assigned to receive either a single, 2.0 g dose of Azithromycin ER or levofloxacin tablets, 500 mg once daily for 7 days. Of 470 subjects screened, a total of 427 subjects were randomized at 62 centers in North America, Latin America, Europe and India. A total of 423 subjects were treated: 211 subjects received Azithromycin ER and 212 received levofloxacin.

Efficacy Findings

Study A0661075

Subject Disposition:

Five hundred and one subjects were enrolled in this study. Two subjects who were randomized were withdrawn prior to receiving study medication and were not included in the All Treated population.

Of the 499 treated subjects, 411 (82.4%) were included in the Clinical Per Protocol population. All treated subjects were analyzed for adverse events and the majority of subjects had 1 or more clinical laboratory observation during the study.

Efficacy Results: Subjects treated with azithromycin ER had a clinical cure rate of 92.6% compared with a cure rate of 94.7% for subjects treated with clarithromycin ER (CI = -6.9%, 2.6%). The lower limit of this 95% CI was greater than -10%, indicating that azithromycin ER therapy was non-inferior to clarithromycin ER therapy in the treatment of CAP. Only 1 azithromycin ER-treated subject was considered to have relapsed at the LTFU visit.

Table 1: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects)

	Azithromycin ER	Clarithromycin ER	Difference (%)	95% CI ^a
Subjects at TOC, N (%)	202	209		
Cure	187 (92.6)	198 (94.7)	-2.2	(-6.9, 2.6)
Failure	15 (7.4)	11 (5.3)		
Subjects at LTFU ^b	176	177		
Cure	175 (99.4)	172 (97.2)		
Relapse	1 (0.6)	5 (2.8)		

^a 95% confidence interval for the difference in cure rates between treatment groups;

^b Includes subjects who are cured at TOC and have LTFU assessments.

TOC = Test of Cure visit; LTFU = Long Term Follow-Up visit.

Clinical response is sponsor assessed.

The overall bacteriologic eradication rate (for all pathogens) was similar for azithromycin ER (91.8%) and clarithromycin ER (90.5%) at the TOC visit. The 95% CI for the difference in eradication rates (difference =1.3; 95% CI of -5.2%, 7.7%) was consistent with that for the analysis of clinical response. Bacteriologic eradication and clinical cure rates for *S. pneumoniae*, *H. influenzae*, ~~isolates~~ isolates was 89.5, 93.3, and 100%, respectively, within the azithromycin ER treatment group. Presumed eradication and response rates for subjects with evidence of CAP caused by *C. pneumoniae* and *M. pneumoniae* were 90.5 and 96.2%, respectively, in azithromycin ER-treated subjects. The majority of eradicated pathogens in both treatment groups were assigned a response of presumed eradication.

Study A0661103

Four hundred and twenty-seven subjects were enrolled in this study. Four subjects who were

randomized were withdrawn prior to receiving study medication and were not included in the All Treated population.

Of the 423 treated subjects, 363 (85.8%) were included in the Clinical Per Protocol population. All treated subjects were analyzed for adverse events and the majority of subjects had 1 or more clinical laboratory observation during the study.

Efficacy Results: Subjects treated with azithromycin ER had a clinical cure rate of 89.7% compared with a cure rate of 93.7% for subjects treated with levofloxacin (CI = -9.7%, 1.7%). The lower limit of this 95% CI was greater than -10%, indicating that azithromycin ER therapy was non-inferior to levofloxacin therapy in the treatment of CAP. None of the azithromycin ER-treated subjects and 1 levofloxacin-treated subject was considered to have relapsed at the LTFU visit.

Table 2: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects)

	Azithromycin ER		Levofloxacin		Difference (%)	95% CI ^a
Subjects at TOC, N (%)	174		189			
Cure	156	(89.7)	177	(93.7)	-4.0	(-9.7, 1.7)
Failure	18	(10.3)	12	(6.3)		
Subjects at LTFU ^b	146		170			
Cure	146	(100.0)	169	(99.4)		
Relapse	0	0	1	(0.6)		

^a 95% confidence interval for the difference in cure rates between treatment groups;

^b Includes subjects who are cured at TOC and have LTFU assessments.

TOC = Test of Cure visit; LTFU = Long Term Follow-Up visit.

Clinical response is sponsor assessed.



Indication: Acute Maxillary Sinusitis

The study was a randomized, double-blind, double-dummy, multi-center, international comparative trial conducted at sixty study sites in North America, S. America, Europe, and Asia, in eligible subjects (18 years of age or older), with clinical and radiological evidence of ABS. Patients were randomized to receive either a single (one time only), 2 gm dose of azithromycin ER or a daily 500 mg dose of levofloxacin for 10 days.

Clinical and bacteriologic responses were assessed at the Test of Cure (TOC) visit (17-24 days of treatment). Total time-period of participation for each subject was approximately 4 weeks. In this study, out of the 271 patients randomized to azithromycin group, 270 received azithromycin. Out of the 270 patients randomized to the levofloxacin group, 268 patients received levofloxacin.

According to the sponsor’s assessment, subjects in the Clinical Per Protocol population treated with azithromycin ER had a clinical cure rate of 94.5% compared with 92.8% for subjects treated with levofloxacin. The 95% CI for the difference in cure rates was reported to be -2.5 % to 5.9%. The lower limit of this CI was greater than -10%, the chosen delta prior to the study. This indicates that azithromycin ER therapy was non-inferior to levofloxacin therapy in the treatment of acute, uncomplicated bacterial maxillary sinusitis. The Investigator’s assessment was similar to that of the sponsor.

Primary Efficacy Outcome in Clinical Per Protocol Subjects

Table 3: Sponsor’s Assessment [Number (%)] of Clinical Response (Clinical Per Protocol Subjects) at TOC visit

Characteristics	Azithromycin ER	Levofloxacin	Difference	95% CI*
No of Subjects @ TOC	256	251		
Cure	242 (94.5)	233 (92.8)	1.7	-2.5, 5.9
Failure	14 (5.5)	18 (7.2)		

- CI* = Confidence Interval (for the difference in cure rates between treatment groups)
- From Sponsor’s Table 15

The bacteriologic eradication rate at the TOC visit was 100% each for *S. pneumoniae* and *M. catarrhalis* in azithromycin ER-treated subjects and 92.3% and 90.9% in levofloxacin-treated subjects respectively. The eradication rate is 96.3 % for *H. influenzae* in azithromycin-treated subjects and 100% in levofloxacin-treated subjects in clinical cure rates by baseline pathogen for the Bacteriologic Per Protocol population at the TOC visit. These rates were similar across treatment groups for subjects with *S. pneumoniae* isolates, *H. influenzae* (including beta-lactamase positive and negative isolates), and *M. catarrhalis*.

Table 4: Sponsor's Summary of Bacteriologic Eradication Rates of All Baseline Pathogens at the TOC visit in Bacteriologic Per protocol Subjects

	Azithromycin ER	Levofloxacin	Difference	95% CI
	n (%)	n (%)		
Pathogens (Total)	114	129		
Eradication	112 (98.2)	120 (93.0)	5.2	0.21, 10.2
Persistence	2 (1.8)	9 (7.0)		

TOC= Test of Cure; n= No of pathogens eradicated/persisted (documented or presumed) at the TOC visit; 95% CI = 95% confidence interval for differences in eradication rates between treatment groups

[From Sponsor's table 5.5, Page 486 of the submitted application]

Table 5: Bacteriologic Eradication Rate (%) By Pathogen at TOC (Bacteriologic per Protocol Subjects)

Pathogen	Azithromycin ER	Levofloxacin
	n/N (%)	n/N (%)
Total Pathogens ^b	112/114 (98.2)	120/129 (93.0)
<i>S. pneumoniae</i>	37/37(100.0)	36/39 (92.3)
Penicillin Susceptible	18/18 (100.0)	24/25 (96.0)
Penicillin Intermediate	12/12(100.0)	7/8 (87.5)
Penicillin Resistance	7/7(100.0)	5/6 (83.3)
<i>H. influenzae</i>	26/27 (96.3)	30/30 (100.0)
Beta-lactamase +	5/5 (100.0)	7/7 (100.0)
Beta-lactamase -	21/22 (95.5)	23/23 (100.0)
<i>M. catarrhalis</i> ^c	8/8 (100.0)	10/11 (90.9)
Beta-lactamase +	7/7 (100.0)	9/10 (90.0)
Beta-lactamase -	0/0	1/1 (100.0)
Beta-lactamase unknown	1/1	0/0

OC = Test of Cure; n= number of pathogens eradicated or presumed eradicated (within the pathogen category) at post Baseline visit. N = Number of pathogens isolated at Baseline.
^b A subject may have more than one pathogen isolated at Baseline
^c In some cases, isolates of *M. catarrhalis* were not tested for the presence of beta-lactamase at the central lab. Therefore the number of isolates classified as either beta-lactamase positive or negative may not add up to the total number of isolates for this pathogen.

The number of total pathogens exceeds the number of patients with one of the three key pathogens. Some subjects had multiple pathogens. Many other microorganisms (including various Gram-negative rods) were added by the sponsor as pathogens to their analysis. The number of subjects (8) used to determine the clinical response of *M. catarrhalis* in the Bacteriologic Per Protocol population should be put in context. The FDA's Draft Guidance and Points to Consider documents recommend at least 15 subjects on the study drug arm (azithromycin ER in this case) to demonstrate clinical efficacy for *M. catarrhalis* for the indication of acute bacterial sinusitis. In this study, only 8 subjects grew *M. catarrhalis* from their sinus aspirate cultures in the azithromycin arm, which falls short of the recommended

Clinical Review
Nasim Moledina, M.D.
NDA 50-797
Azithromycin (Zithromax®)

number. There was a 100% cure rate in this arm. That notwithstanding, considered in isolation, 8 subjects still would be less than adequate. But azithromycin is not a new molecular entity. In the NDA 50784 for the indication of ABS reviewed by Dr. Moledina, and approved recently, the bacteriologic eradication rate for patients with ABS due to *M. catarrhalis* was 14/15 (93.3%) in the MITT patients treated with azithromycin, 500 mg per day x 3 days. Given the similarities in the pharmacokinetic profile for a single 2-gm dose of azithromycin ER and other dose regimens of azithromycin, the number of *M. catarrhalis* provided in this study is acceptable.

1.3.3 Safety

Safety Profile in Adults

Exposure in Adults

In the five adult Phase 3 studies, 1292 subjects received a single 2.0 g dose of azithromycin ER and 1304 received multiple-dose comparative agents (252 clarithromycin ER, 754 levofloxacin, 298 azithromycin 3-day). Between 91-92% of these subjects completed the study. One study (pharyngitis/tonsillitis A0661119) had a lower age limit of 13 years, and thus contributed 49 pediatric subjects (i.e., <16 years of age) to the adult database. Nineteen of these pediatric subjects received azithromycin ER and 30 received a 3-day regimen of azithromycin. Just under half the subjects were from the U.S./Canada and the balance from Europe, Latin America, and India. All treated subjects were assessed for adverse events, and approximately half for laboratory test abnormalities, since only three protocols (██████████ CAP studies) required routine laboratory safety testing. Summary data include adverse events and laboratory test abnormalities up to 35 days following the end of treatment.

Discontinuation

Overall rates of discontinuation from study were similar between the pooled azithromycin ER (8.9%, 115 of 1292) and comparator (8.2%, 107 of 1304) groups. CAP subjects had the highest overall rate of discontinuation from study. Treatment-related discontinuations from study (due to either adverse events or lack of efficacy) were comparable between the pooled azithromycin ER (2.9%, 37 of 1292) and comparator (3.0%, 39 of 1304) groups. In an analysis of discontinuations from treatment due to all-cause adverse events, the rates were 1.9% (24 of 1292) for azithromycin ER and 2.3% (30 of 1304) for pooled comparators. Discontinuation rates due to treatment-related adverse events were very low: 0.2% (3 of 1292) and 0.5% (6 of 1304), respectively.

Incidence of All Causality Adverse Events (AE) in Adult Studies

The following table summarizes adverse events due to all causes reported at a rate of ≥1% in either the pooled azithromycin ER or comparator groups.

Table 6: Summary of Common (≥1%) Adverse Events (All Causality) in Adult Phase 3 Studies by Pooled Treatment Groups

	Number (%) of Subjects	
	Azithromycin ER (N=1292)	All Comparators (N=1304)
Subjects with ≥1 AE	526 (40.7)	518 (39.7)
Subjects discontinued due to an AE	24 (1.9)	30 (2.3)
<i>Body System</i>		
Event (preferred term)		
<i>Body as a Whole</i>	183 (14.2)	171 (13.1)
Abdominal pain	44 (3.4)	37 (2.8)
Asthenia	17 (1.3)	20 (1.5)
Back pain	13 (1.0)	10 (0.8)
Fever	13 (1.0)	7 (0.5)
Headache	48 (3.7)	52 (4.0)
Pain	11 (0.9)	14 (1.1)
<i>Digestive</i>	267 (20.7)	176 (13.5)
Diarrhea	156 (12.1)	69 (5.3)
Nausea	56 (4.3)	39 (3.0)
Vomiting	25 (1.9)	24 (1.8)
<i>Nervous</i>	30 (2.3)	55 (4.2)
Dizziness	14 (1.1)	26 (2.0)
Insomnia	5 (0.4)	13 (1.0)
<i>Respiratory</i>	173 (13.4)	197 (15.1)
Asthma	12 (0.9)	25 (1.9)
Cough Increased	22 (1.7)	24 (1.8)
Dyspnea	18 (1.4)	15 (1.2)
Pharyngitis	22 (1.7)	19 (1.5)
Pneumonia	13 (1.0)	15 (1.2)
Respiratory Disorder	27 (2.1)	33 (2.5)
Respiratory Tract Infection	25 (1.9)	29 (2.2)
Rhinitis	31 (2.4)	32 (2.5)
<i>Skin and Appendages</i>	34 (2.6)	39 (3.0)
Rash	13 (1.0)	13 (1.0)
<i>Special Senses</i>	22 (1.7)	34 (2.6)
Taste Perversion	4 (0.3)	13 (1.0)
Source: Section 2.7.4, Summary of Clinical Safety, Appendix I, Tables 5.1 and 6.1		
Studies included: ██████████ A0661103, A0661075, A0661119, A0661078		
Comparators include: levofloxacin (Studies ██████████ A0661103, A0661078), clarithromycin ER (Study A0661075) azithromycin 3-day (Study A0661119)		

In the analysis of all causality adverse events, the overall incidence of adverse events and the incidence of specific adverse events (other than diarrhea), were generally comparable for the pooled azithromycin ER and comparator groups. Adverse events affecting the digestive system, “body as a whole”, and the respiratory system were the most common categories in both treatment groups.

Table 7: Summary of Common (≥1%) Adverse Events (Treatment Related) in Adult Phase 3 Studies by Pooled Treatment Groups

	Number (%) of Subjects				
	Azithromycin ER (N=1292)	Comparators			
		All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azithromycin 3 Day (N=298)
Subjects with ≥1 AE	295 (22.8)	229 (17.6)	62 (24.6)	109 (14.5)	58 (19.5)
Discontinued for AE	3 (0.2)	6 (0.5)	1 (0.4)	5 (0.7)	0 (0.0)
<i>Body System</i>					
<i>Event (preferred term)</i>					
<i>Body as a Whole</i>	78 (6.0)	61 (4.7)	17 (6.7)	28 (3.7)	16 (5.4)
Abdominal pain	35 (2.7)	27 (2.1)	3 (1.2)	10 (1.3)	14 (4.7)
Headache	17 (1.3)	8 (0.6)	3 (1.2)	4 (0.5)	1 (0.3)
<i>Digestive</i>	222 (17.2)	127 (9.7)	32 (12.7)	55 (7.3)	40 (13.4)
Diarrhea	141 (10.9)	63 (4.8)	17 (6.7)	18 (2.4)	28 (9.4)
Dyspepsia	8 (0.6)	8 (0.6)	1 (0.4)	3 (0.4)	4 (1.3)
Nausea	51 (3.9)	28 (2.1)	8 (3.2)	16 (2.1)	4 (1.3)
Loose Stools	10 (0.8)	8 (0.6)	2 (0.8)	2 (0.3)	4 (1.3)
Vomiting	14 (1.1)	9 (0.7)	2 (0.8)	5 (0.7)	2 (0.7)
<i>Nervous</i>	10 (0.8)	21 (1.6)	3 (1.2)	15 (2.0)	3 (1.0)
Dizziness	6 (0.5)	13 (1.0)	2 (0.8)	8 (1.1)	3 (1.0)
<i>Skin and Appendages</i>	19 (1.5)	15 (1.2)	4 (1.6)	6 (0.8)	5 (1.7)
Rash	10 (0.8)	7 (0.5)	1 (0.4)	2 (0.3)	4 (1.3)
<i>Special Senses</i>	5 (0.4)	17 (1.3)	9 (3.6)	8 (1.1)	0 (0.0)
Taste Perversion	4 (0.3)	13 (1.0)	9 (3.6)	4 (0.5)	0 (0.0)

Source: Section 2.7.4, Summary of Clinical Safety, Appendix I, Tables 7.1, 7.2, 8.1 and 8.2; Studies are ██████████ A0661103, A0661075, A0661119, A0661078 Comparators are levofloxacin (Studies ██████████ A0661103, A0661078), clarithromycin ER (Study A0661075), and azithromycin 3-day (Study A0661119)

In the analysis of treatment-related adverse events, the incidence of overall adverse events and of specific adverse events (other than diarrhea), were generally comparable for the pooled azithromycin ER and comparator groups. Again, the incidence of digestive system adverse events was higher in the azithromycin ER group (17.2%) than in the pooled comparator group (9.7%), and this is driven by the rate of treatment related diarrhea (10.9% vs. 4.8%). Few subjects reported severe diarrhea. Azithromycin ER maintained a consistent profile of treatment-related adverse events across the various indications studied ██████████ CAP, ABS, ██████████ Clarithromycin ER had a similar overall rate of treatment-related adverse events as azithromycin ER, and only a slightly lower rate of digestive system events (including diarrhea), but had more treatment-related taste perversion relative to any of the other agents, including azithromycin ER. Levofloxacin had the best gastrointestinal

tolerability of all the study agents, with an incidence of treatment-related diarrhea ranging from 1.5-4.7% in the three studies in which it was the comparative agent. Lastly, the overall rates of treatment-related adverse events and treatment-related digestive system adverse events were comparable between azithromycin IR 3-day and azithromycin ER.

Roughly two-thirds of treatment-related adverse events were mild in all treatment groups; approximately 3-4% of events were severe in the two azithromycin and levofloxacin groups and 7% were severe in the clarithromycin ER group.

Treatment-related vomiting, a potential point of concern for a single dose therapy, was infrequent among adults receiving azithromycin ER (14/1292, 1.1%).

1.3.4 Dosing Regimen and Administration

In Phase 3 clinical trials of adults, the azithromycin ER dose of 2.0 grams as a single dose was studied. Patients were to receive the study drug at least one hour before or two hours after a meal. This should be the recommended dose regimen in the package insert.

1.3.5 Drug-Drug Interactions

The current labeling for azithromycin products addresses the drug-drug interactions. The following statements can be found in the labeling for azithromycin products:

_____ co-administration of nelfinavir at steady-state results in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of azithromycin is warranted. (See **ADVERSE REACTIONS**.)

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. (See **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**.) When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz, or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is co administered with any of the above agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products.

Clinical Review
Nasim Moledina, M.D.
NDA 50-797
Azithromycin (Zithromax®)

Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin—elevated digoxin concentrations.

Ergotamine or dihydroergotamine—acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

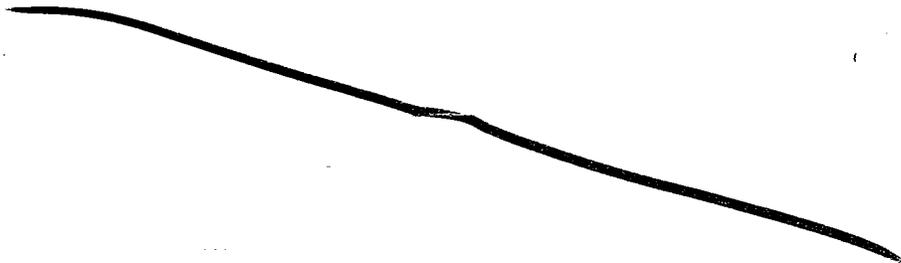
Cyclosporine, hexobarbital and phenytoin concentrations.

Laboratory Test Interactions: There are no reported laboratory test interactions.

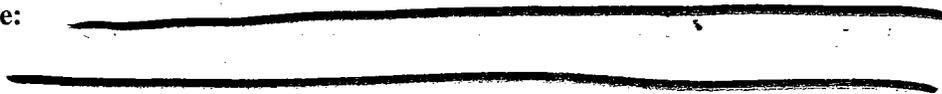
1.3.6 Special Populations

Based on the studies conducted, the proposed label for Zmax under the CLINICAL PHARMACOLOGY section is as follows:

Renal Insufficiency



Geriatric Use:



In clinical trials of Zmax, 16.6% of subjects were at least 65 years of age (214/1292) and 4.6% of subjects (59/1292) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Clinical Review
Nasim Moledina, M.D.
NDA 50-797
Azithromycin (Zithromax®)

Gender

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Under **DOSAGE AND ADMINISTRATION** section of the package insert, the following statement has been proposed:

Special Populations

Renal Insufficiency:

No dosage adjustment is recommended for patients with renal impairment (GFR 10-80 mL/min). Caution should be exercised when Zmax is administered to patients with severe renal impairment (GFR <10 mL/min). (See **CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency.**)

Hepatic Insufficiency:

The pharmacokinetics of azithromycin in patients with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function (See **CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency.**)

Appears This Way
On Original

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Azithromycin extended release ER powder for oral suspension is a newly developed extended release formulation consisting of matrix microspheres of azithromycin dihydrate, which is administered as a single 2.0 g. dose.

According to the sponsor, this novel formulation offers:

- Antimicrobial activity against the common community-acquired respiratory pathogens;
- The potential to treat *S. pneumoniae* with low-level azithromycin resistance;
- Greater compliance, with the potential benefits of reducing treatment failure and decreasing the emergence of resistance that may occur when patients fail to complete their prescribed regimen;
- The ability to front-load the dose, which may reduce the emergence of resistance;

2.2 Currently Available Treatment for Indications

There are multiple antimicrobials of several classes approved for treatment of CAP ██████ and ABS, including previously approved formulations of azithromycin.

2.3 Availability of Proposed Active Ingredient in the United States

Azithromycin is currently available in immediate release formulations administered orally by capsule, tablet, sachet, and powder for oral suspension (hereafter referred to as azithromycin IR), and in an intravenous formulation. Initial marketing licenses for azithromycin IR were obtained for adults in the U.S. and Europe in the early 1990s. At the time of the initial filing, a 5-day regimen was approved in the U.S., but based largely on a pharmacokinetic argument, a 3-day regimen was approved in Europe. Depending on the country, the recommended duration of treatment for common respiratory tract infections in adults ranges from 3-5 days, but all of the regimens deliver the same total dose.

Azithromycin IR approvals span the treatment of a number of community-acquired infectious diseases. In the U.S., it is currently approved for the treatment of adults with mild to moderate infections caused by susceptible strains of designated microorganisms in the following specific conditions.

Clinical Review
 Nasim Moledina, M.D.
 NDA 50-797
 Azithromycin (Zithromax®)

Table 8: Adult Indications

Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease	<i>H. influenzae, M. catarrhalis, S. pneumoniae</i>
CAP (in patients appropriate for oral therapy)	<i>H. influenzae, S. pneumoniae, M. pneumoniae, C. pneumoniae</i>
Pharyngitis/tonsillitis (alternative in individuals who cannot use first line therapy)	<i>S. pyogenes</i>
Uncomplicated skin and skin structure infections	<i>S. aureus, S. pyogenes, S. agalactiae</i>
Urethritis and cervicitis	<i>N. gonorrhoeae, C. trachomatis</i>
Genital ulcer (chancroid in men) disease	<i>H. ducreyi</i>
Prevention and treatment of <i>Mycobacterium Avium-intracellulare</i> infections in HIV infected patients	<i>Mycobacterium avium-intracellulare</i>
ABS	<i>H. influenzae, M. catarrhalis, S. pneumoniae</i>

Additionally, an intravenous/oral regimen of azithromycin is approved for treatment of CAP by *C. pneumoniae, H. influenzae, L. pneumophila, M. catarrhalis, M. pneumoniae, S. aureus* and *S. pneumoniae*. Intravenous azithromycin is also approved for treatment of pelvic inflammatory disease due to *C. trachomatis, N. gonorrhoeae,* and *M. hominis*.

The following table presents U.S. Food and Drug Administrations (FDA) registration approvals for adult use obtained to date.

Table 9: FDA Approval for Zithromax

NDA number	Filing	Submission Date	Approval Date
50-670	Capsules	Apr-90	Nov-91
50-693	Single Dose Adults (sachet)	Apr-92	Sep-94
50-711	Tablets (250 mg)	Feb-94	Jul-96
50-670/S-008 (Suppl)	Sexually Transmitted Diseases /1.0 g and 2.0g	Dec-94	Dec-95
50-730	<i>Mycobacterium avium</i> complex (MAC) (600 mg) Prophylaxis	Dec-95	Jun-96
50-670/S-010 (Suppl)	Atypical Pneumonia	Dec-95	Dec-96
50-733	Intravenous Formulation	Feb-96	Jan-97
50-730/S-005 (Suppl)	<i>Mycobacterium avium</i> complex (MAC) Treatment	Jan-00	Nov-00
50-784	Accelerated Dosing– 500 mg tablets, AECB	Jul-01	May-02
50-784/S-004 (Suppl)	ABS	Mar-03	Jan-04

2.4 Important Issues With Pharmacologically Related Products

Several formulations of azithromycin have been approved (Refer to table 9). The current package inserts for all oral azithromycin products and azithromycin I.V. address all the issues with azithromycin and macrolide products.

2.5 Presubmission Regulatory Activity

Clinical studies to define the appropriate pharmaceutical formulation, as well as two proofs of concept studies that delineated the product's pharmacokinetic and GI tolerability profile, were conducted prior to September 2002 under IND-24,999. An End-of-Phase 2 meeting was held with the Division to discuss clinical issues (October 4, 2002) and for CMC discussion (October 1, 2002). Subsequently, a new IND was submitted on November 14, 2002 (IND-66,194) to cover the Phase 3 program and any additional Phase 1 studies deemed necessary to support the program.

Dialog on trial design, comparator selection and statistical considerations was held as teleconferences on November 13 and December 20, 2002, and April 8, 2003. As a result of these discussions:

- Pfizer and the Division agreed on the design of the trials for CAP and ABS. Delta selection for these non-inferiority trials was be -10%. Sample sizes were adjusted, where necessary, to achieve these deltas with 80% power.

Agreements included the following items:

- CMC documents for adult ~~_____~~ unless a submission for both patient populations is made at the same time
- Limits for specified and unspecified degradation products for Azithromycin ER drug product will be based on the data presented with proper justification and qualification
- Results from primary stability studies conducted through at least six months for the adult dosage strength presentation will be made at the time of submission of the NDA; Pfizer also agreed to provide additional results (12 to 18 months stability data) from primary stability studies during FDA review, but no later than three months prior to the action date
- Pfizer provided acceptable information to demonstrate adequate process control of the drug product during commercial manufacturing; a comprehensive rationale for the drug development manufacturing process would be provided in the NDA.
- There was discussion of equivalence between batches of drug product manufactured for Phase 1 and Phase 3 clinical studies, stability studies, and commercial; there was discussion on the comparisons of dissolution data, process controls, and PK profiles being sufficient to compare the Phase 1 and 2 batches with Phase 3 batches, but the Division strongly recommended that the Sponsor conduct a pivotal clinical bioequivalence study to

demonstrate equivalence between the Phase 3 batches and product manufactured by the commercial process; a request was also made for the Sponsor to provide individual dissolution profiles from all relevant batches to support a proposed dissolution method and acceptance criteria; it was agreed the Sponsor would provide (1) a tabular summary that clarifies the comparisons provided in Table 12 of the briefing package (where changes in the manufacture of batches of drug product used in clinical and stability studies were delineated and Pfizer explained that the differences were relatively minor and the uses of the batches not entirely clear; Pfizer further explained that all of the batches of the ER product used in clinical and stability studies were manufactured with the same formulation and essentially the same process, but adjustments to operating parameters were made to optimize the process) and (2) a detailed proposal for rigorously evaluating pharmacokinetic results to demonstrate equivalence for drug product used in all clinical and stability studies

An administrative Pre-NDA teleconference was held on December 3, 2003. The purpose of the teleconference was to discuss and seek agreement on the Levofloxacin trial blinding proposal, to share examples of tables and data formats; obtain agreement on providing Clinical Study Reports for indicated studies, and to share the CTD/NDA submission plans. Items discussed included the following:

- Acceptance of Pfizer's proposal on the bioequivalence of levofloxacin comparators
- Discussion on the adequacy of the laboratory safety data being collected and its inclusion in the label

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- Examples of tables and data formats were shared with the Division
 - Sharing of plans for organization of the CTD/NDA
 - Agreement that no new toxicology information would be required in the new NDA
 - Supplying of clinical study reports, electronic data sets, and CRF's, with electronic CRF's to be submitted for all pivotal study subjects and for serious and life-threatening AE's and discontinuations due to treatment-related AE's for non-pivotal studies (as discussed with the Project Manager on July 6, 2004)
 - Labeling issues on the description of clinical study results and adverse reactions.
 - A paper copy for the field will be supplied (subsequently it was determined that it would be sufficient to send a letter to Pfizer's home district certifying that the electronic CMC section had been submitted to CDER).
 - Pfizer clarified the technique used to collect blood samples from patients who vomited.

Following up on the administrative Pre-NDA teleconference, a Pre-NDA meeting was held on May 19, 2004 to review issues relating to the upcoming NDA submission for Azithromycin ER. Items discussed included the following:

- Geographical distribution of subjects in the Phase 3 program – Division acceptance of forty eight percent of subjects enrolled in the Phase 3 program were from sites in the U.S. and Canada.

- Azithromycin ER as an Advisory Committee topic – an AC meeting is not necessarily a given; the decision on the need for an AC will be made based on the data submitted with the NDA.
- Labeling – the Division indicated it would be open to the inclusion of compliance statements and alternative display of adverse event data, indicating that the location of such data would be dependent on the overall quality of the data and the impact of these data on clinical outcomes.
- Pfizer's proposals on (1) submitting safety narratives for deaths that occurred on therapy or within 35 days of completion/discontinuation of therapy, all treatment-related SAE's, and discontinuations for SAE's and (2) since there are no ongoing studies for this NDA, in lieu of a formal 4-Month Safety Update, only updates on data from subjects with SAE's from the original Azithromycin ER NDA will be submitted – the Division was in agreement with these proposals.

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- Pfizer will provide data on the susceptibility of clinical *Streptococcus pneumoniae* isolates to azithromycin, erythromycin, and penicillin and isolates will be evaluated using NCCLS recommended procedures.
 - The Division will consider inclusion of compliance statements in the labeling if the data submitted support these claims; information on adverse events by onset and duration could be included in the CLINICAL TRIALS section of the package insert.
 - There is currently no procedure for inclusion of pharmacoeconomic data in the label
 - The Division requested Pfizer to provide an analysis of the ITT and MITT for the primary endpoints.
- There was a conversation on July 21, 2004 between Ms. Judit Milstēin, Project Manager, and Donald Jaffe of Pfizer,

The adult indications (sinusitis, and CAP) are included in the current adult NDA submission.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

According to the sponsor azithromycin ER powder for oral suspension is provided as a single-dose oral powder for suspension. The formulation is composed of azithromycin dihydrate microspheres, vehicle blend, and sucrose. The drug product is packaged in [REDACTED] bottles with a child-resistant closure [REDACTED]. For the adult Azithromycin ER 2.0 g dose, 60 mL of water is added to the bottle to form a suspension. The entire suspension is administered orally.

CHEMICAL NAME

1-oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)-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]-, [2R-(2R*, 3S*, 4R*, 5R*, 8R*, 10R*, 11R*, 12S*, 13S*, 14R*)] - (USAN 1); (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 - (USAN 2); 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A - (USAN 3).

MOLECULAR FORMULAE AND WEIGHTS

Azithromycin has the molecular formula $C_{38}H_{72}N_2O_{12}$, molecular weight of [REDACTED]. Azithromycin dihydrate has the molecular formula $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$, molecular weight of 785.0 daltons.

The sponsor originally proposed an established name for this product of Azithromycin [REDACTED]. However, this microsphere terminology had not been recognized in USP or by CDER. Given that the product contained other powder materials, CDER proposed the name azithromycin for extended-release oral suspension. Pfizer and FDA agreed on the name, Zmax (azithromycin extended release) for oral suspension. For detailed review of CMC, please refer to the review by Dr. Suresh Pagay.

3.2 Animal Pharmacology/Toxicology

Reference is made to the approved NDA 50-670, azithromycin capsules. No new pharmacology/toxicology data were submitted to support the new formulation of azithromycin.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This NDA (50-797) contains clinical data and information of chemistry, manufacturing, and controls supporting the use of a unique single-dose formulation of azithromycin. Pfizer has conducted four Phase 3 respiratory tract infection studies to evaluate azithromycin ER for the treatment of adults with ~~acute bacterial maxillary sinusitis [ABS]~~, acute bacterial maxillary sinusitis [ABS], and mild to moderate community acquired pneumonia [CAP].

4.2 Tables of Clinical Studies

Table 10: Key Biopharmaceutic Studies:

Study	Type	Design	Treatments	Subjects Enrolled
A0661084	POC Bioavailability (fasted)	Open-label Crossover (2-way)	AER alone (2.0 g SD) AER + Mg(OH) ₂ (2.0 g SD) IR Azithromycin (2.0 g SD)	32
A0661124	Bioequivalence (fasted)	Open-label Crossover (2-way)	AER* Primary ICH (2.0 g SD) AER Supportive ICH (2.0 g SD)	46
A0661107	Food Effect (high-fat)	Open-label Crossover (2-way)	AER* Fed state (2.0 g SD) AER Fasted state (2.0 g SD)	16
A0661114	Food Effect (standard meal)	Open-label Crossover (2-way)	AER* Fed state (2.0 g SD) AER Fasted state (2.0 g SD)	92

Table 11: Key Clinical Pharmacology Studies:

Study	Type	Design	Treatments	Subjects
A0661086	POC Toleration (fasted)	Parallel, Observer Blind	AER alone (2.0 g SD) AER + Mg(OH) ₂ (2.0 g SD) IR Azithromycin (2.0 g SD)	320
A0661115	Maalox® Interaction (fasted)	Open-label Crossover (2-way)	AER* 2 gm With Maalox® Without Maalox®	39

AER=Azithromycin Extended Release; SD=Single Dose; IR=Immediate Release (by commercial sachet); POC=Proof of Concept

* Azithromycin ER includes Mg(OH)₂

Table 12: Efficacy and Safety studies of Indications for Adults

Study	Indication	Study Population	Comparator	Subjects Randomized/Treated*
A0661075	Mild/Mod CAP (Fine ≤70)	Adults	Clarithromycin ER	501/499
A0661103	Mild/Mod CAP (Fine ≤90)	Adults/Adolescents	Levofloxacin	427/423
A0661078	ABS	Adults	Levofloxacin	541/538

ER = Extended Release; Fine Score ≤ 70 – Fine Classes I and II; Fine Score ≤90 – Fine Classes I, II, III; * - Randomization was 1:1 to azithromycin ER or the active comparator.

Pfizer also provided safety data from a fifth Phase 3 study of azithromycin ER. Study A0661119 was a multi-center, randomized study comparing azithromycin ER to azithromycin 500 mg tablets (500 mg per day for 3 days) in adults with pharyngitis. Efficacy data were not provided for this study in this submission.

4.3 Review Strategy

The review of data for all studies began with detailed review of case report forms (CRF) for a 12% sample of randomly-selected patients. After blinded review of the CRF, the assessments of the reviewer were compared with those of the sponsor. The reviewer for each indication then determined whether additional CRF review or additional analyses were warranted.

Safety review included assessment of all adverse events and analyses of AEs by various subgroups and indications. CRFs for all deaths were reviewed in detail. Case-report forms of all patients that were discontinued due to an adverse event were also reviewed in detail for all indications.

4.4 Data Quality and Integrity

Based on the blinded review of the random sample, the outcome designation by the applicant of evaluable patients, cure/failure designation and reason for discontinuation in both the arms of the studies was similar to the outcome designation by the reviewer. It was determined that the data analyses by the applicant for the two CAP studies were acceptable.

The Division of Scientific Investigations inspected several clinical sites and also performed a monitoring inspection of Pfizer's Groton, CT. facility. In the clinical site inspections, DSI was unable to satisfactorily verify some data from site [REDACTED]

Medical Officer's Comments:

Three other clinical sites, participating in CAP studies, were found to have varying degrees of minor violations. The data from these clinical sites were acceptable.

The inspection of the Pfizer facility was performed because of concerns arising from the clinical inspections with the electronic data capture methods. One concern that arose from the Pfizer inspection was related to the completion of Monitoring Reports in accordance with timeframes specified in Pfizer's SOPs. The inspection noted some backdated reports at a couple of clinical sites. Pfizer was able to document that this was not a systemic problem in the CAP studies. The electronic data capture methods employed by Pfizer led to some concerns about the overall data quality. These methods included prepopulating certain fields in the electronic CRFs and using CRFs sent from Pfizer back to investigators as source data documents.

Medical Officer's Comments:

The Division was reasonably assured that the data submitted by Pfizer were adequately monitored. The Division notes that as electronic CRFs become more prevalent, methods such as prepopulating fields on electronic CRFs could lead to problems with data quality. Investigators should also maintain separate source documents that record information supplied to the sponsor.

4.5 Compliance with Good Clinical Practices

All clinical studies in this NDA involving human subjects were conducted in compliance with institutional review board regulations in 21 C.F.R. Part 56 and the informed consent regulations in 21 C.F.R. Part 50, or in accordance with the Declaration of Helsinki, as referenced in 21 C.F.R. Part 312.

4.6 Financial Disclosures

There are eleven covered studies for this NDA. The covered studies were not funded via variable compensation and none of the investigators in the studies hold any form of propriety interest in ZITHROMAX®.

Pfizer has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2.

With a total of 1318 investigators listed in the eleven covered studies, 14 of the listed investigators had financial information to disclose. Ten of these investigators have equity in Pfizer Inc. and four of the investigators received significant payments of other sorts. Note: two investigators, [REDACTED] participated in more than one protocol; therefore, they have multiple 3455 forms.

All Independent Grants associated with the investigators are paid directly to the Institution rather than to the individual investigator.

5 CLINICAL PHARMACOLOGY

Refer to Dr. Charles Bonapace's review for this section. In summary, the sponsor stated that data from clinical pharmacology studies show:

- Overall exposure was similar following administration of azithromycin ER as a single 2.0 gram (g) dose and azithromycin IR as a 1.5 g total dose over 3- or 5- days. The C_{max} and AUC_{0-24} achieved on Day 1 with azithromycin ER (2.0 g) were approximately two and three times higher respectively, than those achieved with multiple dose Zithromax® IR regimens (1.5 g total). T_{max} was delayed by approximately 2 hours with azithromycin ER.
- The bioavailability of 2.0 g azithromycin ER relative to 2.0 g Zithromax® IR commercial sachet is 83%. The peak serum concentrations were achieved later (~2 hours later) following azithromycin ER administration. A single 2.0 g dose of azithromycin ER significantly lowered the frequency of GI adverse events, particularly nausea, vomiting and diarrhea, compared to a single 2.0 g dose of the commercial Zithromax® IR sachet (2.0 g dose).
- Data from pharmacokinetic studies of Azithromycin ER in healthy adult subjects, compared to results from previous pharmacokinetic studies, indicate that a higher peak serum concentration (C_{max}) and greater systemic exposure (AUC) of azithromycin are achieved on the first day of dosing following a single 2.0 g Azithromycin ER dose versus 1.5 g of Zithromax IR given over 3 or 5 days. Consequently, Azithromycin ER and conventional 3-day (500 mg daily) and 5-day (500 mg on Day 1 and 250 mg daily on Days 2-5) Zithromax IR dosing regimens are not interchangeable.
- When a 2.0 g dose of Azithromycin ER was administered with a high-fat meal, peak serum concentration increased by 115% and systemic exposure increased by 23%. When a 2.0 g dose of Azithromycin ER was administered with a standard meal, peak serum concentration increased by 119%; however, systemic exposure was not affected. Azithromycin ER was better tolerated by the GI tract when administered in a fasting state.
- In pediatric subjects with non-life-threatening respiratory tract or uncomplicated skin or soft tissue infections, serum azithromycin exposure was comparable across all age groups (aged 3 months to 16 years) following a single oral dose of 60 mg/kg (maximum of 2.0 g) of azithromycin ER. Overall, azithromycin exposure in pediatric subjects following a single oral dose of 60 mg/kg (maximum of 2.0 g) was comparable to that observed in adults (single dose 2.0 g) following administration of azithromycin ER.
- Maalox®, an antacid containing aluminium and magnesium hydroxides, did not affect the pharmacokinetics of azithromycin ER.

The proposed label recommends administration of azithromycin in the fasted state. The original protocol stated that azithromycin can be administered without regard to food. The protocols were then amended to administer azithromycin in a fasted state. The applicant was

asked to provide the number of patients that were enrolled and received azithromycin ER in each of the Phase 3 clinical trials before and after the protocols were amended to restrict azithromycin ER dosing to 1 hour before or 2 hours after a meal, and to provide information regarding the percentage of patients that were administered azithromycin ER in the fed state before the protocols were amended.

Study A0661103 (CAP) did not enroll any subjects until after implementation of the food effect amendment. For the other three Phase 3 trials, less than 5% of the per protocol subjects were enrolled prior to the food effect amendment.

Medical Officer's Comments:

Since the majority of patients were enrolled after the food effect amendment, the labeling statement proposed by the applicant that azithromycin should be given 1 hour before or 2 hours after a meal is acceptable. These labeling instructions represent how the drug was given in the Phase 3 studies. For detailed review of the food effect study, please refer to Dr. Charles Bonapace's review.

5.1 Pharmacokinetics

Refer to section 5 above and for detailed review, refer to Dr. Charles Bonapace's review.

5.2 Pharmacodynamics

Refer to section 5 above and for detailed review, refer to Dr. Charles Bonapace's review.

5.3 Exposure-Response Relationships

Refer to Dr. Charles Bonapace's review.

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6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION: COMMUNITY-ACQUIRED PNEUMONIA

Efficacy and safety data using a single 2.0 gram dose of Azithromycin ER in mild-to-moderate CAP were obtained in two independent, Phase 3, randomized, multicenter, double-blind, double dummy, comparative international studies, A0661075 and A0661103.

6.1.1 Methods

The primary objective of these two trials was to confirm the hypothesis that a single oral 2.0 g dose of Azithromycin ER is clinically non-inferior to standard comparators: either clarithromycin

ER tablets, given at a dose of 1 g once daily for 7 days, or levofloxacin, given at a dose of 500 mg once daily for 7 days. Secondary objectives were to assess bacteriologic efficacy and safety of the two treatment regimens. Both comparators are accepted standard treatments for mild-to moderate CAP. The comparator drug in Study A0661075, clarithromycin extended release tablets (clarithromycin ER), is a macrolide antibiotic with demonstrated efficacy in CAP. The comparator drug in Study A0661103, levofloxacin, is a fluorinated carboxyl quinolone with demonstrated efficacy in CAP.

Inclusion criteria for the two studies were similar, except for Modified Fine Risk Scores, as described below. Male or female outpatients, ≥ 16 years of age (Study A0661075), or ≥ 18 years of age (Study A0661103), a clinical diagnosis of pneumonia, as demonstrated by a productive cough and at least 2 of the following signs and symptoms: rales and/or evidence of pulmonary consolidation; dyspnea or tachypnea; elevated body temperature; or elevated total peripheral white blood cell count (WBC $>10,000/\text{mm}^3$) or greater than 15% immature neutrophils, were enrolled into the trials. All subjects underwent a sputum culture for the purpose of determination of a causative pathogen and a chest radiograph to confirm the presence of a pulmonary infiltrate.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint in either study was the sponsor assessment of clinical response for the Clinical Per Protocol population at the test of cure visit (TOC; study days 14-21).

Secondary endpoints determined for the Clinical Per Protocol population included clinical relapse at long-term follow-up (LTFU; Days 28-35). Clinical and bacteriologic responses by baseline pathogen at TOC in the Bacteriologic Per Protocol population were also assessed. Other efficacy assessments included sponsor assessment of clinical response by baseline pathogen versus baseline susceptibility.

6.1.3 Study Design

Study A0661075 was a randomized, double-blind, double-dummy, active-controlled, multicenter, international study in which subjects were assigned to receive either a single, 2.0 g dose of Azithromycin ER or clarithromycin ER tablets, 1.0 g once daily for 7 days. Of 551 subjects screened, a total of 501 subjects were randomized at 61 centers in North America, Latin America, Europe and India. A total of 499 subjects were treated: 247 subjects received Azithromycin ER and 252 received clarithromycin.

Study A0661103 was a randomized, double-blind, double-dummy, active-controlled, multicenter, international study in which subjects were assigned to receive either a single, 2.0 g dose of Azithromycin ER or levofloxacin tablets, 500 mg once daily for 7 days. Of 470 subjects screened, a total of 427 subjects were randomized at 62 centers in North America, Latin America, Europe and India. A total of 423 subjects were treated: 211 subjects received Azithromycin ER and 212 received levofloxacin.

6.1.4 Efficacy Findings

Study A0661075

Study Dates: 13 Jan 2003 – 24 Mar 2004

Phase of Development: Phase 3

Study Objectives: The primary study objective was to confirm the hypothesis that a single, 2.0 g oral dose of azithromycin extended release (ER) is clinically non-inferior to 7-days of clarithromycin extended release (ER), 1.0 g PO QD, when used to treat adults with mild to moderate community acquired pneumonia (CAP). Secondary objectives included assessments of bacteriologic efficacy and safety of both treatment regimens.

Study Design: Randomized, double-blind, double-dummy, active-controlled, multicenter, international study in which subjects were randomly assigned to receive azithromycin ER or clarithromycin ER. Clinical and bacteriologic response were assessed at the Test of Cure (TOC) visit (14-21 days post first dose).

Subject Disposition:

Five hundred and one subjects were enrolled in this study. Two subjects who were randomized were withdrawn prior to receiving study medication and were not included in the All Treated population.

Of the 499 treated subjects, 411 (82.4%) were included in the Clinical Per Protocol population. All treated subjects were analyzed for adverse events and the majority of subjects had 1 or more clinical laboratory observations during the study.

Table 13: Subject Disposition

Evaluation Group, N (%) of Subjects ^a	Azithromycin ER	Clarithromycin ER	Total
Screened 551			
All Randomized	247 (100.0)	254 (100.0)	501 (100.0)
All Treated	247 (100.0)	252 (99.2)	499 ^b (99.6)
Completed Study	214 (86.6)	223 (88.5)	437 (87.6)
Discontinued From Study	33 (13.4)	29 (11.5)	62 (12.4)
Evaluated for Primary Efficacy ^c	202 (81.8)	209 (82.9)	411 (82.4)
Analyzed for Safety:			
Adverse Events	247 (100.0)	252 (100.0)	499 (100.0)
Laboratory Data ^d	229 (92.7)	234 (92.9)	463 (92.8)

^a Percentages in the All Randomized and All Treated populations based on All Randomized; otherwise, percentages are based on the All Treated Subjects.

^b Two subjects (10331009 and 10341005) were randomized but were withdrawn prior to receiving treatment

^c Clinical Per Protocol Population: Clinically eligible subjects who received at least 6 days of study medication, including active plus placebo doses, received no concomitant systemic antibiotic potentially effective against CAP pathogens and received an assessment in the appropriate visit window.

^d Number of treated subjects with at least 1 laboratory observation during the study (subjects must have had at least one baseline and one post-therapy laboratory observation for inclusion in this summary).

Diagnoses and Criteria for Inclusion of Subjects: Male or female outpatients, >16 years of age, with pneumonia were enrolled. The diagnosis of pneumonia was demonstrated by a productive cough and at least 2 of the following signs and symptoms: rales and/or evidence of pulmonary consolidation; dyspnea or tachypnea; elevated body temperature; or elevated total peripheral white blood cell count (WBC >10,000/mm³ or greater than 15% immature neutrophils). Subjects were to have a chest radiograph demonstrating evidence of a new infiltrate or consolidation, and a Modified Fine Risk score of ≤70 (Fine Class I and II). Overall, the two treatment groups were similar with respect to baseline characteristics. Approximately 49% of all treated subjects were men and 51% were women. There was a higher percentage of males in the clarithromycin ER treatment arm (53%) as compared to the azithromycin ER treatment group (45%). A majority of all subjects were white (76%) and were < 65 years of age (88%), with a mean age of 45.6 (±15.9) years of age (range = 17-81) for the azithromycin ER group and 43.6 (±15.3) years of age (range = 16-77) for the clarithromycin ER treatment group.

Baseline characteristics and other prognostic factors were also similar across both treatment groups in the Clinical Per Protocol population.

Table 14: Drug Administration:

Medication	Lot No.	Formulation
Azithromycin ER, 2.0 g powder ^a	T0582V-G1, ED-O-195-703,	G02701AA
Matching Placebo, 2.0 g powder	ED-O-228-702, ED-O-072-203	G02676BA
Clarithromycin ER, 500 mg capsule ^b	ED-O-153-502, 09971.01-G1	G02643AA
Matching Placebo, 500 mg capsule	ED-O-158-502	G02088AA

^aAll azithromycin ER and azithromycin ER placebo was provided as white to off-white, single-dose powder for oral suspension in a 100 ml bottle.

^bAll clarithromycin (extended release) and clarithromycin placebo was provided as size 000, gray capsules (two 500 mg capsules administered orally once daily, for a duration of 7 days).

The study regimens were administered in a double-blind, double dummy fashion. Subjects assigned to receive azithromycin ER received their single dose of active azithromycin ER and 2 capsules of clarithromycin ER placebo on Day 1 and then continued with QD dosing of clarithromycin ER placebo for the next 6 days. Subjects assigned to receive clarithromycin ER received azithromycin ER placebo and 2 capsules of active clarithromycin ER on Day 1 and then continued with QD dosing of active clarithromycin ER for the next 6 days.

Efficacy and Safety Evaluations: The primary efficacy endpoint was the sponsor assessment of clinical response (clinical cure rate) at the TOC visit (Clinical Per Protocol subjects). Secondary efficacy endpoints included: bacteriological response (eradication rate) at the TOC visit; investigator assessment of clinical response at the TOC visit; sponsor assessment of clinical response by baseline pathogen at the TOC visit; and sponsor assessment of clinical response in the non-primary populations. Susceptibilities of baseline pathogens were also summarized.

Subject Populations

Analyses were conducted on the following 5 subject populations; the primary population of interest was the Clinical Per Protocol population.

- All Randomized Subjects: All subjects who received a randomization number from the central randomization system.
- All Treated Subjects: All Randomized Subjects who received at least one dose of study medication.
 - Clinically Eligible Subjects: All Treated Subjects with a clinical diagnosis of CAP
 - Clinical Per Protocol Subjects: Clinically Eligible Subjects meeting the following criteria:
 - o Received at least 6 days of study medication, including active and placebo doses;
 - o Received no concomitant systemic antibiotic potentially effective against key CAP pathogens;
 - o Received an assessment in the appropriate visit window;

A subject was also considered to be in the Clinical Per Protocol population if the subject was clinically eligible and was a treatment failure with at least 3 days of dosing, including active and placebo doses.

- Bacteriologic Per Protocol Subjects: Clinical Per Protocol Subjects with a baseline

bacterial pathogen identified by culture, PCR, and/or serology.

Safety parameters: Vital signs and physical examinations were assessed at Baseline; vital signs were also assessed at the On Treatment (Day 3-5) and TOC (Day 14-21) visits. Clinical laboratory assessments (blood chemistry and hematology) were recorded at Baseline and the TOC visit. Azithromycin drug concentrations were to be determined for subjects who vomited within 30 minutes of receiving the first dose of azithromycin ER/placebo.

Statistical Methods: The primary efficacy analysis compared the clinical cure rates (based on sponsor-assessed clinical response) of the azithromycin ER and clarithromycin ER regimens at the TOC visit (Days 14-21) in the Clinical Per Protocol population. Azithromycin ER was considered non-inferior to clarithromycin ER if the lower boundary of the 95% confidence interval for the difference in cure rates (azithromycin ER minus clarithromycin ER) was greater than -10%. Other analyses included comparisons of clinical cure rates by pathogen and the bacteriologic eradication rates in the Bacteriologic Per Protocol population.

Efficacy Results: Subjects treated with azithromycin ER had a clinical cure rate of 92.6% compared with a cure rate of 94.7% for subjects treated with clarithromycin ER (CI = -6.9%, 2.6%). The lower limit of this 95% CI was greater than -10%, indicating that azithromycin ER therapy was non-inferior to clarithromycin ER therapy in the treatment of CAP. Only 1 azithromycin ER-treated subject was considered to have relapsed at the LTFU visit.

Table 15: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects)

	Azithromycin ER		Clarithromycin ER		Difference (%)	95% CI ^a
Subjects at TOC, N (%)	202		209			
Cure	187	(92.6)	198	(94.7)	-2.2	(-6.9, 2.6)
Failure	15	(7.4)	11	(5.3)		
Subjects at LTFU ^b	176		177			
Cure	175	(99.4)	172	(97.2)		
Relapse	1	(0.6)	5	(2.8)		

^a 95% confidence interval for the difference in cure rates between treatment groups

^b Includes subjects who are cured at TOC and have LTFU assessments.

TOC = Test of Cure visit; LTFU = Long Term Follow-Up visit.

Clinical response is sponsor assessed.

Table 16: Clinical Response at TOC, MITT Population

	Azithromycin ER		Clarithromycin ER		Difference	95% CI ^a
Clinically Eligible Subjects at TOC, (N %)	226		234			
Cure	197	(87.2)	205	(87.6)	-0.4	(-6.5, 5.6)
Failure	29	(12.8)	29	(12.4)		

Medical Officer's Comments:

The Medical reviewer concurs with the applicant's results.

Investigator Assessment of Clinical Response

The assessment of clinical response by the investigator was very similar to the assessment by the sponsor (Table 17). There were 2 discrepancies between the investigator and sponsor assessment of clinical response at TOC in the Clinical Per Protocol population (Subjects 10541017 and 10541029). Both subjects were in the clarithromycin ER treatment arm; the clinical response was assessed as cure by the sponsor based on signs and symptoms improved or resolved, no additional antibiotic treatment provided, and a stable chest radiograph.

Table 17: Investigator Assessment of Clinical Response at TOC, Number (%) of Subjects (Clinical Per Protocol Subjects)

	Azithromycin ER		Clarithromycin ER	
	N=202	(%)	N=209	(%)
Cure	187	(92.6)	196	(93.8)
Failure	11	(5.4)	13	(6.2)
Signs and Symptoms				
Persisted/Worsened	9	(4.5)	12	(5.7)
New Signs/Symptoms	1	(0.5)	0	
Progression of Pneumonia	1	(0.5)	1	(0.5)
Death Due to Pneumonia	0		0	
Not Done	0		0	
Missing	4	(2.0)	0	

TOC=Test of Cure

Number (%) of subjects considered by the investigator as cure or failure at the TOC visit.

The overall bacteriologic eradication rate (for all pathogens) was similar for azithromycin ER (91.8%) and clarithromycin ER (90.5%) at the TOC visit. The 95% CI for the difference in eradication rates (difference =1.3; 95% CI of -5.2%, 7.7%) was consistent with that for the analysis of clinical response. Bacteriologic eradication and clinical cure rates for *S. pneumoniae*, *H. influenzae*, [redacted] isolates was 89.5, 93.3, and 100%, respectively, within the azithromycin ER treatment group. Presumed eradication and response rates for subjects with evidence of CAP caused by *C. pneumoniae* and *M. pneumoniae* were 90.5 and 96.2%, respectively, in azithromycin ER-treated subjects. The majority of eradicated pathogens in both treatment groups were assigned a response of presumed eradication.

Table 18: Clinical Cure Rates by Baseline Pathogen (Bacteriologic Per Protocol Subjects)

Baseline Pathogen	Azithromycin ER		Clarithromycin ER	
	n/N ^b	Cure Rate (%)	n/N ^b	Cure Rate (%)
Total Subjects with Pathogens		100		127
Total Pathogens ^a		134		169
<i>H. influenzae</i>	14/15	(93.3)	23/26	(88.5)
Beta-lactamase ⁺	3/3	(100.0)	4/4	(100.0)
Beta-lactamase ⁻	11/12	(91.7)	19/22	(86.4)
<hr/>				
<i>S. pneumoniae</i>	17/19	(89.5)	25/27	(92.6)
Penicillin Susceptible	11/12	(91.7)	17/18	(94.4)
Penicillin Intermediate	6/6	(100.0)	7/8	(87.5)
Penicillin Resistant	0/1	(0.0)	1/1	(100.0)
<i>C. pneumoniae</i>	19/21	(90.5)	29/31	(93.5)
<i>M. pneumoniae</i>	25/26	(96.2)	20/21	(95.2)

TOC = Test of Cure.

^a A subject may have had more than one pathogen isolated.

^b Number of subjects within the pathogen category with a sponsor-assessed clinical response of Cure at the post-Baseline visit (n) / Number of subjects with the pathogen isolated at Baseline (N)

Pathogen strains may not add to the total for a given pathogen as a subject may have more than one strain of the pathogen.

Clinical Cure is sponsor assessed.

Medical Officer's Comments:

Concomitant Medications and Non-Drug Treatments

The majority of subjects (92% azithromycin ER group, 90% clarithromycin ER group) received one or more concomitant medication(s) during the study (Table 19). The most commonly used concomitant medications (excluding antibiotics) in both treatment groups included: analgesics, bronchodilators, agents for symptomatic relief of upper respiratory tract infections (including cough suppressants, expectorants, mucolytics, and combinations containing antihistamines or sympathomimetics), medications used in rheumatic diseases and gout (includes anti-inflammatory analgesics) and antihypertensives.

Table 19: Commonly Used Concomitant Medications, by Decreasing Frequency (All Treated Subjects)

	Azithromycin ER	Clarithromycin ER
Number of Subjects	247	252
Number (%) of Subjects with any Concomitant Drug Treatment	226 (91.5)	226 (89.7)
Analgesics	122 (49.4)	103 (40.9)
Systemic Treatment of Symptoms of URT Infections	93 (37.7)	97 (38.5)
Drugs used in Rheumatic Diseases and Gout	81 (32.8)	96 (38.1)
Bronchodilators	79 (32.0)	84 (33.3)
Antihypertensive Drugs	43 (17.4)	44 (17.5)

URT = Upper Respiratory Tract

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Clinical Review
Nasim Moledina, M.D.
NDA 50-797
Azithromycin (Zithromax®)

Study A0661103

Study Dates: 24 Apr 2003 – 28 Apr 2004

Phase of Development: Phase 3

Study Objectives: The primary objective was to confirm the hypothesis that a single, 2.0 g oral dose of azithromycin sustained release (ER) was clinically non-inferior to a 7-day treatment of levofloxacin (500 mg, PO QD) for the treatment of mild to moderate community-acquired pneumonia (CAP). The secondary objectives include assessments of bacteriologic efficacy and safety of both treatment regimens.

Study Design: Randomized, double-blind, double-dummy, and multicenter, international study in which subjects were randomly assigned to receive azithromycin ER, given as a single 2.0 g dose, or levofloxacin (500 mg, PO QD), with a dosing duration of 7 days. Clinical and bacteriologic response were assessed at the Test of Cure (TOC) visit (14-21 days post first dose).

Evaluation Groups:

Four hundred and twenty-seven subjects were enrolled in this study. Four subjects were randomized but withdrew prior to receiving study medication and were not included in the All Treated population.

Of the 423 treated subjects, 363 (85.8%) were included in the Clinical Per Protocol population. All treated subjects were analyzed for adverse events and the majority of subjects had 1 or more clinical laboratory observations during the study.

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Table 20: Evaluation Groups

Evaluation Group, N (%) of Subjects ^a	Azithromycin ER	Levofloxacin	Total
Screened 470			
All Randomized	213 (100.0)	214 (100.0)	427 (100.0)
All Treated	211 ^b (99.1)	212 ^b (99.1)	423 ^b (99.1)
Completed Study	180 (85.3)	190 (89.6)	370 (87.5)
Discontinued From Study	31 (14.7)	22 (10.4)	53 (12.5)
Evaluated for Primary Efficacy ^c	174 (82.5)	189 (89.2)	363 (85.8)
Analyzed for Safety:			
Adverse Events Laboratory Data ^d	211 (100.0)	212 (100.0)	423 (100.0)
	198 (93.8)	200 (94.3)	398 (94.1)

^a Percentages in the All Randomized and All Treated populations based on All Randomized; otherwise, percentages are based on the All Treated Subjects.

^b Four subjects (2 azithromycin ER [10201009, 10561029], 2 levofloxacin [10671001, 10441009]) were randomized but were withdrawn prior to receiving treatment.

^c Clinical Per Protocol Population: Clinically eligible subjects who received at least 6 days of study medication, including active plus placebo doses, received no concomitant systemic antibiotic potentially effective against CAP pathogens, and received an assessment in the appropriate visit window.

^d Number of treated subjects with at least 1 laboratory observation during the study (subjects must have had at least one baseline and one post-therapy laboratory observation for inclusion in this summary).

Diagnoses and Criteria for Inclusion of Subjects: Males or females, ≥ 18 years of age, with pneumonia were enrolled. The diagnosis of pneumonia was demonstrated by a productive cough and at least 2 of the following signs and symptoms: rales and/or evidence of pulmonary consolidation; dyspnea or tachypnea; elevated body temperature; or elevated total peripheral while blood cell count (WBC $>10,000/\text{mm}^3$) or greater than 15% immature neutrophils. Subjects were to have a chest radiograph indicating pneumonia and a Modified Fine Risk score of ≤ 90 (Fine Class I, II, and III).

Overall, the two treatment groups were similar with respect to baseline characteristics.

Approximately 54% of all treated subjects were men and 46% were women.

There was a higher percentage of males in the azithromycin ER treatment arm (57%) as compared to the levofloxacin treatment group (51%). A majority of all subjects were white (63%) and were < 65 years of age (77%), with a mean age (SD) of 48.2 (± 18.1) years of age (range = 18-95) for the azithromycin ER group and 49.0 (± 18.6) years of age (range = 18-87) for the levofloxacin treatment group.

Table 21: Drug Administration:

Medication*	Lot No.	Formulation
Azithromycin ER, 2.0 g powder	T0582V-G1, ED-O-195-703	G02701AA
Matching Placebo, 2.0 g powder	ED-O-228-702, ED-O-072-203	G02676BA
Levofloxacin, 250 mg capsule	ED-O-157-502	G01739AA
Matching Placebo, 250 mg capsule	ED-O-008-101, ED-O-141-403, ED-O-386-Z02	G00699AA
Levofloxacin (Tavanic) 250mg capsule**	E02484-001E01	G02902AA
Matching placebo for Levofloxacin (Tavanic) 250 mg capsule**	09773.01	G02899AA

*All azithromycin ER and azithromycin ER placebo was provided as white to off-white, single-dose powder for oral suspension in a 100 ml bottle. All levofloxacin and levofloxacin placebo was provided as size 0, black/blue capsules (two 250 mg capsules, administered orally, for duration of 7 days).

**Levofloxacin (Tavanic) and corresponding placebo was provided as size 0, gray capsules to Belgium and Eastern European countries only.

The study regimens were administered in a double-blind, double dummy fashion. Subjects assigned to receive azithromycin ER received their single dose of active azithromycin ER and 2 capsules of levofloxacin placebo on Day 1 and then continued with QD dosing of levofloxacin placebo for the next 6 days. Subjects assigned to receive levofloxacin received azithromycin ER placebo and 2 capsules of active levofloxacin on Day 1 and then continued with QD dosing of active levofloxacin for the next 6 days.

Efficacy and Safety Evaluations: The primary efficacy endpoint was sponsor assessment of clinical response (clinical cure rate) at the TOC visit (Clinical Per Protocol subjects). Secondary efficacy endpoints included bacteriological response (eradication rate) at the TOC visit, investigator assessment of clinical response at the TOC visit, sponsor assessment of clinical response by baseline pathogen at the TOC visit, sponsor assessment of clinical response at the LTFU visit (Clinical Per Protocol subjects), and sponsor assessment of clinical response in the non-primary populations. Susceptibilities of baseline pathogens were also summarized.

Subject Populations

Five study populations were analyzed; the primary population of interest was the Clinical Per Protocol population.

- All Randomized Subjects: All subjects who received a randomization number from the central randomization system.
- All Treated Subjects: All Randomized Subjects who received at least one dose of study medication.
- Clinically Eligible Subjects: All Treated Subjects with a clinical diagnosis of CAP.
- Clinical Per Protocol Subjects: Clinically Eligible Subjects meeting the following criteria:
 - Received at least 6 days of study medication, including active and placebo doses;
 - Received no concomitant systemic antibiotic potentially effective against key

CAP pathogens;

- Received an assessment in the appropriate visit window;

A subject was also considered to be in the Clinical Per Protocol population if the subject was clinically eligible and was a treatment failure with at least 3 days of dosing, including active and placebo doses.

- Bacteriologic Per Protocol Subjects: Clinical Per Protocol Subjects with a baseline bacterial pathogen identified by culture, PCR, and/or serology.

Safety parameters: Vital signs and physical examinations were assessed at Baseline; vital signs were also assessed at the On Treatment (Day 3-5) and TOC (Day 14-21) visits. Clinical laboratory assessments (blood chemistry and hematology) were recorded at Baseline and the TOC visit. Azithromycin drug concentrations were to be determined for subjects who vomited within 30 minutes of receiving the first dose of azithromycin ER/placebo.

Statistical Methods: The primary efficacy analysis compared the clinical cure rates (based on the sponsor-assessed clinical response) of the azithromycin ER and levofloxacin regimens at the TOC visit (Day 14-21) in the Clinical Per Protocol population. Azithromycin ER was considered non-inferior to levofloxacin if the lower boundary of the 95% confidence interval for the difference in cure rates (azithromycin ER minus levofloxacin) was greater than -10%. Other analyses included comparisons of clinical cure rates by pathogen and the bacteriologic eradication rates in the Bacteriologic Per Protocol population.

Efficacy Results: Subjects treated with azithromycin ER had a clinical cure rate of 89.7% compared with a cure rate of 93.7% for subjects treated with levofloxacin (CI = -9.7%, 1.7%). The lower limit of this 95% CI was greater than -10%, indicating that azithromycin ER therapy was non-inferior to levofloxacin therapy in the treatment of CAP. None of the azithromycin ER-treated subjects and 1 levofloxacin-treated subject was considered to have relapsed at the LTFU visit.

Table 22: Summary of Clinical Response, Number (%) of Subjects (Clinical Per Protocol Subjects)

	Azithromycin ER		Levofloxacin		Difference (%)	95% CI ^a
Subjects at TOC, N (%)	174		189			
Cure	156	(89.7)	177	(93.7)	-4.0	(-9.7, 1.7)
Failure	18	(10.3)	12	(6.3)		
Subjects at LTFU ^b	146		170			
Cure	146	(100.0)	169	(99.4)		
Relapse	0	0	1	(0.6)		

^a 95% confidence interval for the difference in cure rates between treatment groups

^b Includes subjects who are cured at TOC and have LTFU assessments.

TOC = Test of Cure visit; LTFU = Long Term Follow-Up visit.

Clinical response is sponsor assessed.

Clinical Review
 Nasim Moledina, M.D.
 NDA 50-797
 Azithromycin (Zithromax®)

Table 23: Sponsor Assessment of Clinical Response at TOC, MITT Population

	Azithromycin ER	Levofloxacin	Difference	95% CI ^a
Clinically Eligible Subjects at TOC, (N %)	195	199		
Cure	165 (84.6)	179 (89.9)	-5.3	(-11.9, 1.2)
Failure	30 (15.4)	20 (10.1)		

Medical Officer's Comments:

The Medical Officer concurs with the applicant's results.

Investigator Assessment of Clinical Response

The assessment of clinical response by the investigator was very similar to the assessment by the sponsor (Table 24). A discrepancy between investigator and sponsor assessment of clinical response was documented for 1 subject in the Clinical Per Protocol population. Subject 10111007 (azithromycin ER treatment group) was considered a clinical cure at TOC by the investigator, yet took an antibiotic at TOC for the disease under study and therefore was considered a clinical failure by the sponsor. The number of clinical cures in the azithromycin ER treatment group is however, identical in both the sponsor and investigator assessment of clinical response summary tables. The clinical response for 1 additional subject, (10691007) considered 'missing' in Table 24, was subsequently considered a cure by the study sponsor. Hence, there was no net change in the number of clinical cures at TOC in the azithromycin ER treatment group.

Table 24: Investigator Assessment of Clinical Response at TOC, Number (%) of Subjects^a
(Clinical Per Protocol Subjects)

	Azithromycin ER N=174		Levofloxacin N=189	
	n	(%)	n	%
Cure	156	(89.7)	177	(93.7)
Failure	13	(7.5)	6	(3.2)
Signs and Symptoms				
Persisted/Worsened	10	(5.7)	6	(3.2)
New Signs/Symptoms	2	(1.1)	0	
Progression of Pneumonia	1	(0.6)	0	
Death Due to Pneumonia	0		0	
Not Done	0		1	(0.5)
Missing	5	(2.9)	5	(2.6)

TOC=Test of Cure

^aNumber (%) of subjects considered by the investigator as cure or failure at the TOC visit.

The overall bacteriologic eradication rate (for all pathogens) was similar for the azithromycin ER (90.7%) and levofloxacin (92.3%) treatment groups at the TOC visit. The 95% CI for the difference in eradication rates [difference = -1.7; 95% CI of (-8.8, 5.5)] was consistent with that for the analysis of clinical response. Bacteriologic eradication rates for *S. pneumoniae*, *H. influenzae*, [REDACTED] isolates were 85.7, 93.3, and 100%, respectively, within the azithromycin ER treatment group. Clinical cure rates were similar across treatment groups for subjects with *S. pneumoniae*, *H. influenzae*, [REDACTED] isolates. Presumed eradication and clinical response rates for subjects with evidence of CAP caused by *C. pneumoniae* and *M. pneumoniae* were 94.7 and 71.4%, respectively, in azithromycin ER-treated subjects. In both treatment groups, the majority of pathogens were assigned a response of presumed eradication.

Table 25: Clinical Cure Rates at TOC by Baseline Pathogen (Bacteriologic Per Protocol Subjects)

Baseline Pathogen	Azithromycin ER		Levofloxacin	
	n/N ^b Cure Rate (%)		n/N ^b Cure Rate (%)	
Total Subjects with Pathogens	91		104	
Total Pathogens ^a	107		130	
<i>H. influenzae</i>	14/15	(93.3)	8/8	(100.0)
Beta-lactamase +	3/3	(100.0)	0/0	
Beta-lactamase -	11/12	(91.7)	8/8	(100.0)
<hr/>				
<i>S. pneumoniae</i>	11/14	(78.6)	10/12	(83.3)
Penicillin Susceptible	8/9	(88.9)	7/8	(87.5)
Penicillin Intermediate	3/4	(75.0)	3/4	(75.0)
Penicillin Resistant	0/1	(0.0)	0/0	
<i>C. pneumoniae</i>	18/19	(94.7)	21/22	(95.5)
<i>M. pneumoniae</i>	5/7	(71.4)	18 /18	(100.0)

TOC = Test of Cure.

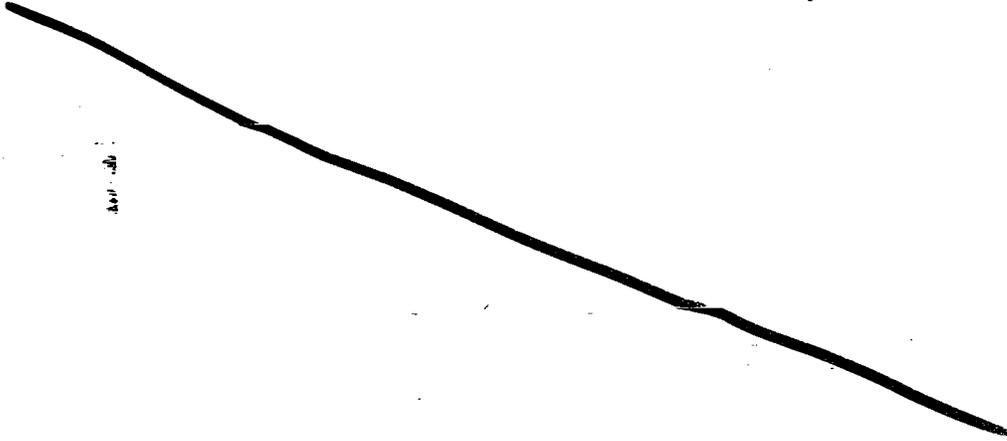
^a A subject may have had more than one pathogen isolated.

^b Number of subjects within the pathogen category with a sponsor-assessed clinical response of Cure at the post-Baseline visit (n) / Number of subjects with the pathogen isolated at Baseline (N)

Pathogen strains may not add to the total for a given pathogen as subject may have more than one strain of that pathogen.

Clinical Cure is sponsor assessed.

Medical Officer's Comments:



Due to the single-dose nature of the azithromycin ER active regimen, all subjects who received treatment with azithromycin ER (99.1% of those randomized) were compliant with the full course of active treatment; 2 of 213 subjects randomized to receive azithromycin ER (0.9%) were not treated. In contrast, 12 of 214 subjects (5.6%) in the levofloxacin group did not complete the entire 7-day course of active treatment, suggesting that the shorter the dosing schedule, the more likely subjects were to complete the full course of treatment. As expected, compliance with the dosing schedule over the study duration (active + placebo) was similar for both treatment groups.

Clinical Microbiology

The bacteriologic results have been discussed as part of the efficacy review in section 6.1.4. For detailed microbiology review, please refer to Dr. Peter Coderre's review.

The following table shows efficacy at TOC by MIC and genotype for azithromycin ER subjects with *S. pneumoniae* isolated at baseline that was non-susceptible to azithromycin. All *S. pneumoniae* isolates except for six (see below) and all *H. influenzae* isolates, were susceptible to azithromycin in the azithromycin ER group (NCCLS criteria).

Table 26: CAP: Bacteriologic Eradication and Clinical Cure Rates at TOC in Azithromycin ER Subjects with Azithromycin Non-Susceptible *S. pneumoniae* at Baseline (A0661075, A0661103) –Bacteriologic Per Protocol Subjects

Genotype/MIC*	No. Isolates Eradicated**/	Subjects Cured***/	Country
	No. Isolates	Subjects with Isolates	
All Non-Susceptible Isolates	4/6	3/6	--
No genotype specified			
>4 µg/mL	1/1	1/1	Lithuania
mef only			
2 µg/mL	1/1	1/1	Canada
4 µg/mL	1/2	1/2	Canada, U.S.
ermB only			
>256 µg/mL	1/1	0/1	U.S.
mef + erm-TR			
4 µg/mL	0/1	0/1	U.S.

Source: Applicant's data
 TOC=Test of Cure; * MIC's based on NCCLS criteria; ** Eradication=documented/presumed eradication;
 *** Clinical cure rates are based on the total number of subjects who have an isolate with that particular MIC value.

In the Bacteriologic Per Protocol analysis, only six azithromycin ER subjects had azithromycin non-susceptible *S. pneumoniae* isolated at baseline. Three of these subjects were clinically cured. The subject with the highly resistant pathogen (MIC >256 µg/mL) was a clinical failure but had documented eradication of the organism. For all other isolates, bacteriologic response was presumed from the clinical response. With the exception of one European subject, all resistant isolates came from North America. One additional subject, who was excluded from the Per Protocol analysis at TOC, had azithromycin-resistant *S. pneumoniae* (MIC = 4 µg/mL) isolated at baseline. The subject was cured and the pathogen was eradicated.

Medical Officer's Comments:

*The applicant has not requested inclusion of resistant pathogens in the INDICATIONS AND USAGE section of the package insert. Based on the data submitted, the number of non-susceptible *S. pneumoniae* isolates in CAP studies was small; thus, the medical officer concurs with the applicant for not including the information in the package insert.*

Concomitant Medications and Non-Drug Treatments

The majority of subjects (85% azithromycin ER group, 86% levofloxacin group) received one or more concomitant medication(s) excluding antibiotics during the study (Table 27). The most commonly used concomitant medications in both treatment groups included: analgesics, agents for symptomatic relief of upper respiratory tract infections (including cough suppressants, expectorants, mucolytics, and combinations containing antihistamines or sympathomimetics),

bronchodilators, and medications used in rheumatic diseases and gout (includes anti-inflammatory analgesics).

Table 27: Commonly Used Concomitant Medications, by Decreasing Frequency (All Treated Subjects)

	Azithromycin ER	Levofloxacin
Number of Subjects	211	212
Number (%) of Subjects with any Concomitant Drug Treatment	180 (85.3)	182 (85.8)
Analgesics	84 (39.8)	77 (36.3)
Systemic Treatment of Symptoms of URT Infections	66 (31.3)	79 (37.3)
Bronchodilators	56 (26.5)	56 (26.4)
Drugs used in Rheumatic Diseases and Gout	50 (23.7)	70 (33.0)

URT = Upper Respiratory Tract

Source: Applicant's data

6.1.5 Efficacy Conclusions

In study A0661075, a single, 2.0 g dose of azithromycin ER is clinically non-inferior to 7 days of clarithromycin ER (1.0 g QD for 7 days) in the treatment of mild to moderate CAP. For subjects who had documented infections with key CAP pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, clinical cure rates were comparable in the two treatment groups.

In study A0661103, a single, 2.0 g dose of azithromycin ER is clinically non-inferior to 7 days of levofloxacin (500 mg QD for 7 days) in the treatment of mild to moderate CAP. For subjects who had documented infections with key CAP pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Chlamydia pneumoniae*, clinical cure rates were comparable in the two treatment groups.

6.2 INDICATION: ACUTE BACTERIAL SINUSITIS

This section was reviewed by Dr. Menfo Imoisili.

6.2.1 Methods

This application contains reports from study A0661078, a pivotal Phase 3 clinical trial (hereafter referred to as study 1078) submitted by the sponsor to support the indication of acute bacterial sinusitis (ABS).

The study is a randomized, double-blind, double-dummy, multi-center, international comparative trial conducted at sixty study sites in North America, S. America, Europe, and Asia, in eligible subjects (18 years of age or older), with clinical and radiological evidence of ABS. Patients were randomized to receive either a single (one time only), 2 gm dose of azithromycin ER or a daily 500 mg dose of levofloxacin for 10 days.

Clinical and bacteriologic responses were assessed at the Test of Cure (TOC) visit (17-24 days of treatment). Total time-period of participation for each subject was approximately 4 weeks.

A 500-mg tablet formulation of azithromycin was recently FDA- approved for the treatment of acute bacterial sinusitis. Specifically, the approved dose for adults was one 500-mg tablet once daily for three days. Given the pharmacokinetics of azithromycin and the recent approval of the 500-mg tablet formulation for treatment of ABS, the Division of Anti-Infective Drug Products agreed that one study would be sufficient to evaluate the extended release formulation for approval of the ABS indication.

6.2.2 General Discussion of Endpoints

Efficacy Endpoints Evaluations

The **Primary Endpoint** was assessed for each evaluable patient at the TOC visit and the sponsor's assessment of clinical response was assigned via a programmed algorithm that was developed based upon the following criteria:

1. Cure

Signs and symptoms related to the acute infection had resolved, or clinically improved such that additional antibiotic was unnecessary.

2. Failure

Typical Failure

- Signs and symptoms associated with ABS persisted or worsened, and additional antibiotic(s) was/ were necessary;

or

- New clinical signs and/or symptoms of ABS developed, warranting additional antibiotic treatment.

Partial Resolution

- In some cases where no additional antibiotics were prescribed and some signs or symptoms improved while others did not, a response of Cure or Failure could not be assigned. The sponsor then manually reviewed the subject's data and assigned a response.

Analysis of the Primary Endpoint

- Clinical Cure Rate – The percentage of patients in the Clinical Per Protocol population cured at the TOC visit (Days 17-24).
- Clinical Success Rate – The percentage of patients with clinical response of cure or improvement (needing no additional antibiotics) at the TOC visit.

MO Comments: The sponsor evaluates the primary efficacy of azithromycin versus the comparator (levofloxacin) by ascertaining the resolution or persistence (or worsening) of clinical signs and symptoms (i.e. facial pain, pressure, or tenderness and the presence of purulent discharge/drainage) in the Clinical Per Protocol population at the TOC visit. In addition, failure is determined by evaluation of records for concomitant antibiotic treatment at the TOC visit. That is consistent with the protocol and is considered by the reviewing MO as clinically reasonable. Clinical response rates were also determined for the ITT and Bacteriological Per Protocol populations, to demonstrate consistency with the Clinical Per Protocol population. Both the clinical and bacteriological definitions are consistent with the endpoints traditionally recommended by the Division for Acute Bacterial Sinusitis trials.

The effect of prognostic factors on treatment effects and clinical responses, as assessed by the sponsor, was examined. Prognostic factors evaluated included: smoking history, history of allergic rhinitis and the number of previous episodes in the previous 12 months. In addition, the sponsor's assessment of clinical responses was summarized by center, age, race, gender, and geographic area.

A **Secondary Endpoint** was the bacteriological outcome in bacteriologically evaluable patients at the TOC visit, based on the following:

- 1. Eradication:** The pathogen isolated at baseline was not identified in the sinus aspirate specimen obtained at the TOC visit (if done), and no additional antibiotics were given for ABS.
- 2. Presumed Eradication:** Where repeat sinus aspiration was not performed (most cases), the sponsor-assessed clinical resolution was equated with bacteriologic eradication.
- 3. Persistence:** The original pathogen was still present in the sinus aspirate specimen obtained at the TOC visit (only one repeat sinus aspirate in the Azithromycin group and 2 in the Levofloxacin group were performed in Study 1078).

4. Presumed Persistence: If a repeat sinus aspiration was not performed and the sponsor-assessed clinical response was failure, or additional antibiotics were given for ABS prior to the TOC visit (most failure cases).

Analysis of the Secondary Endpoint

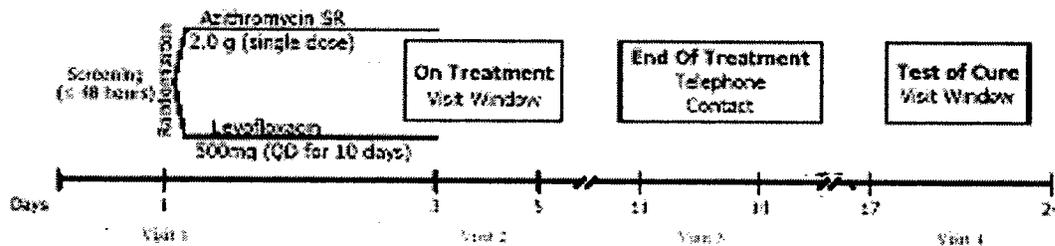
- **Bacteriologic Eradication Rate**-This refers to the percentage of pathogens eradicated (per pathogen) in the Bacteriologic Per Protocol population at the TOC visit (Days 17-24). This was an evaluation of the results of post-treatment culture, if done, relative to pathogens isolated at baseline from sinus aspirate specimen. Where post treatment culture was not done (as occurred in the majority of cases), or results were unavailable, the bacteriologic response was based on the clinical assessment at the TOC visit.

6.2.3 Study Design

Acute Bacterial Sinusitis study was a multi-center, international, randomized, double-blind, double-dummy, Phase 3 clinical trial in which subjects were assigned to receive azithromycin ER, 2 gm PO (single dose only) or levofloxacin, 500 mg daily for 10 days.

All subjects underwent maxillary sinus aspiration prior to treatment. Clinical and bacteriologic responses were assessed at the TOC visit.

Figure 1. Overall Study Design



STUDY OBJECTIVES

Primary: To show that a single, 2.0 gm dose of azithromycin extended release (ER), given orally, is clinically non-inferior to 10 days of levofloxacin 500 mg PO once a day (QD), when used to treat subjects (18 years or older) with uncomplicated, acute bacterial maxillary sinusitis.

Secondary: To assess the bacteriologic efficacy of azithromycin ER regimen and compare with that of the comparator drug.

Subject Eligibility

Inclusion Criteria

Subjects were eligible for inclusion in the study if they met the following criteria:

1. Written informed consent given by the subject or a legally authorized representative
2. Male or female outpatients, 18 years of age or older.
3. A clinical diagnosis of ABS, i.e. the presence of the following cardinal signs and symptoms for a minimum duration of 7 days:
 - Facial pain, pressure and/or tightness over one or both maxillary sinuses, and/or pain in one or both maxillary areas that worsens with movement or percussion, and
 - Presence of 1 or more of the following signs:
 - i. purulent nasal discharge,
 - ii. purulent drainage in the posterior pharynx,
 - iii. purulent discharge from the maxillary sinus orifice.
4. A sinus X-ray (Water's view) confirming the clinical diagnosis of maxillary sinusitis. At least one of the following must have been documented in one or both maxillary sinuses on radiological examination:
 - a. Complete or partial opacification,
 - b. An air/fluid level.
5. Two or more of the following:
 - a. Fever, as defined by:
 - i. Oral temperature: $>38^{\circ}\text{C}$ ($>100.4^{\circ}\text{F}$), or
 - ii. Tympanic temperature: $>38.5^{\circ}\text{C}$ ($>101.2^{\circ}\text{F}$);
 - b. Leukocytosis ($\text{WBC} >10,000/\text{mm}^3$ or $>15\%$ band forms);
 - c. Frequent coughing;
 - d. Headache;
 - e. Nasal congestion; and/or
 - f. Post-nasal drainage.
6. Willingness to undergo direct aspiration of the sinus cavity by maxillary sinus puncture.
7. Women of childbearing potential (WOCBP) with a negative urine pregnancy test within 48 hours prior to start of study medication [NOTE: WOCBP included any female who had experienced menarche and who had not undergone successful surgical sterilization or was not postmenopausal. Even women who were using oral, implanted or injectable contraceptive hormones or mechanical products (intrauterine devices; barrier methods) to prevent pregnancy, who were practicing abstinence, or who had a partner that is sterile (e.g., vasectomy), were considered to be of childbearing potential].

MO's Comments: *The inclusion criteria outlined by the sponsor are consistent with those given in the FDA draft guidance document on ABS.*

Exclusion Criteria:

1. Known or suspected hypersensitivity or intolerance to any macrolide or fluoroquinolone compound.
2. Previously diagnosed disease(s) of immune function, including:
 - Subjects with a baseline absolute neutrophil count $<1000/\text{mm}^3$;
 - HIV positive subjects with a CD4 count <200 ;
 - Any immunoglobulin or neutrophil disorder.
3. Pregnant or lactating women.
4. Treatment with any systemic antibiotic within 7 days prior to enrollment. Subjects receiving a systemic antifungal or antiviral agent for prophylaxis or for treatment of a non-respiratory infection (e.g., for vaginal yeast infection or HSV) were eligible for study entry and could continue those medications during the course of the study.
5. Gastrointestinal disturbances that might affect drug absorption (e.g., malabsorption syndromes).
6. Any medical condition which, in the opinion of the investigator, might interfere with the evaluation of the study drug and/or would make the subject unsuitable for enrollment.
7. Symptoms lasting for longer than 28 days.
8. Four or more episodes of acute sinusitis within the preceding 12 months.
9. Nasal or sinus surgery within 3 months prior to enrollment other than for a diagnostic procedure.
10. Complicated sinusitis (e.g., osteomyelitis, Pott's puffy tumor, malignancy involving the sinus, or the requirement for reconstructive surgery).
11. Nosocomial sinusitis.
12. Diagnosis of cystic fibrosis.
13. Known or suspected renal insufficiency.
14. Known or suspected hepatic disease.
15. Treatment with an investigational drug within 30 days prior to randomization.
16. Prior enrollment in either this study or any study utilizing azithromycin ER.

MO's Comments:

The exclusion criteria stated above generally agree with FDA draft guidance for industry for acute bacterial sinusitis.

Removal of Subjects from Treatment or Assessment

A subject may have been withdrawn from study therapy at any time for any of the following reasons:

- An adverse event;
- Persistence or worsening of signs and symptoms of acute infection;
- Intercurrent illness;
- Subject's decision not to participate further;
- In the Investigator's opinion, it was in the subject's best interest;
- If the study was terminated by Pfizer;
- Pregnancy.

Study Medications:

1. Study Drug: Azithromycin ER 2.0 g

Subjects assigned to the azithromycin ER arm received their single 2.0 g dose of active azithromycin ER (in the form of a slurry) and 2 capsules of levofloxacin placebo, administered orally on day 1, to be taken at least 1 hour before or 2 hours after a meal and then continued with 2 capsules of levofloxacin placebo daily for the next 9 days.

2. Comparator Drug: Levofloxacin 2 x 250-mg caps (= 500 mg/dose)

Subjects assigned to the levofloxacin arm received two capsules of active levofloxacin 250 mg and one azithromycin ER placebo on Day 1 and then continued with daily dosing of two active levofloxacin capsules (total 500 mg/day) for the following 9 days.

- The study regimens were administered in a double-blind, double dummy fashion.
- The first dose of each study medication was given in an observed setting such that subjects took the single dose of azithromycin ER/placebo slurry followed 30 minutes later by 2 capsules of levofloxacin/placebo. Subsequently, subjects were to take 2 capsules (levofloxacin/placebo) daily on Days 2 through 10.
- Following the administration of the azithromycin ER/placebo slurry, subjects were observed for a period of 30 minutes.

Vomiting Following Receipt of Study Medication

- If the subject vomited within 5 minutes of receiving the slurry, a second dose of azithromycin ER/placebo was administered. If a subject vomited more than 5 minutes after receiving the slurry, re-dosing was not necessary.
- If the subject vomited within 30 minutes, the site was to administer the levofloxacin/placebo capsules only after the subject felt comfortable enough to take them. Subjects who vomited within 30 minutes of dosing were to have a blood sample drawn after 2 hours to determine drug level concentration.

Visit Windows

The following windows were used to determine whether a subject's assessment was eligible for a given population.

Table 28: Study and Analysis Visit Windows

Visit	Schedule per Study Protocol	Window Used for Analyses
Baseline	Day 1	Day-1, Day 0, Day 1
OT	Day 3-5	Days 2-8
EOT	Day 11-13	Days 9-15
TOC	Day 17-24	Days 16-25

OT= On treatment; EOT= End of Treatment; TOC= Test of Cure. Days are as measured from baseline.

Concomitant Medications and Non-Drug Treatments

Most subjects (91.9% in azithromycin ER group and 92.2% in levofloxacin group) had one or more concomitant medication(s) during the study. The commonly used non-antibiotic concomitant medications comprise medications for upper respiratory tract (URT) infections, e.g. antihistamines, mucolytic agents, and nasal decongestants; drugs used in rheumatic fever and gout, such as anti-inflammatory analgesics; and drugs used for local anesthesia (Table 29).

Concomitant Antibiotics

Nineteen (7%) azithromycin ER-treated subjects and 23 (9%) levofloxacin-treated subjects received additional antibiotics during the study. In order of frequency, the classes of antibiotics subjects were receiving concomitantly included the fluoroquinolones, the penicillins /cephalosporins, and the macrolides (Table 30). Subjects receiving additional antibiotics for study treatment failure were assessed as Failures, if the antibiotic was received on or prior to the visit at which response was assessed. Subjects who received an antibiotic for treatment of intercurrent illnesses unrelated to sinusitis were excluded from the Clinical Per Protocol population, if the administered antibiotic was active against sinusitis pathogens and was received on or prior to the visit at which response was assessed. Nine (3%) azithromycin ER-treated subjects and 12 (5%) levofloxacin-treated subjects had received anti-bacterial medications prior to taking study medication. With the exception of one subject in the azithromycin ER group (10091004), all anti-bacterials were taken seven days or longer prior to enrollment, per protocol requirements.

Table 29: Commonly Used Concomitant Medications (All Treated Subjects)

	Azithromycin ER	Levofloxacin
Number of Subjects	270	268
Number (%) of Subjects with any Concomitant Drug Treatment	248 (91.9)	247 (92.2)
Systemic Treatment of Symptoms of URT Infections	105 (38.9)	101(37.7)
Drugs used in Rheumatic Diseases and Gout	99 (36.7)	93(34.7)
Analgesics	79 (29.3)	71(26.5)
Drugs used in Allergic Disorders	65 (24.1)	73(27.2)
Respiratory Corticosteroids	41 (15.2)	39 (14.6)
Drugs Acting on the Nose ^a	33 (12.2)	34 (12.7)
Bronchodilators	27 (10.0)	34 (12.7)

^a Includes anti-infective nasal preparations, other preparations used in the nose, and topical nasal decongestants; URT = Upper Respiratory Tract; Source: Table 3.2

Table 30: Number of Subjects Receiving Additional Antimicrobial Medications

	Azithromycin ER	Levofloxacin
Number of subjects	270	268
Number receiving Antibacterial Drugs	19 (7%)	23 (8.6)
Quinolones	8	10
Penicillins	6	7
Cephalosporins/cephamycin	3	1
Macrolides	2	4
Clindamycin/Lincomycin	1	1
Tetracyclines	1	0
Other Antibiotics	0	2

6.2.4 Efficacy Findings

Patient Disposition:

In Study 1078 the investigators set out to show that a single, 2.0 g dose of azithromycin ER (PO) for the treatment of ABS is clinically non-inferior to a 10-day course of levofloxacin 500 mg (PO) daily in the treatment of subjects (18 years or older) with uncomplicated, acute bacterial maxillary sinusitis.

In this study, out of the 271 patients randomized to azithromycin group, 270 received azithromycin. Out of the 270 patients randomized to the levofloxacin group, 268 patients received levofloxacin.

DISCONTINUATIONS

Table 31 shows the proportion of patients in each treatment group that discontinued treatment for insufficient clinical response or for adverse events. The table also shows the proportion of patients that failed to return for follow-up.

MO's Comments: *The number in each group is relatively small. And the proportions of patients in the treatment groups are fairly similar in all categories.*

Table 31: Sponsor's Table: Number (%) of Subjects Discontinued or Lost to follow up

	Treatment group n/N (%)		
	Azithromycin ER (%)	Levofloxacin (%)	Total (%)
All Discontinuations ⇒	7/270 (2.6)	7/268 (2.6)	14/538 (2.6)
Reasons Discontinued ↓ ↓ ↓			
Adverse Events	2/270 (0.74)	1/268 (0.37)	3/538 (0.56)
Therapeutic Failure	4/270 (1.5)	3/268 (1.1)	7/538 (1.3)
Lost to Follow-up	1/270 (0.37)	3/268 (1.1)	4/538 (0.74)

Table 32: Modified Sponsor's Discontinuations from Study (ITT Population)

	Azithromycin ER	Levofloxacin
Number (%) of Subjects	N = 270	N = 268
Discontinuations:		
Related to Study Drug ^a (total)	5 (1.9)	4 (1.5)
Adverse Event ^b	1 (0.4)	1 (0.4)
Lack of Efficacy	4 (1.5)	3 (1.1)
Not Related to Study Drug ^a (total)	2 (0.7)	3 (1.1)
Adverse Event ^b	1 (0.4)	0 (0.0)
Subject Defaulted ^c	1 (0.4)	3 (1.1)
Grand Total	7 (2.6)	7 (2.6)

a Relationship to Study Drug : Related if reason for discontinuation is Insufficient Clinical Response (Lack of Efficacy), or due to a treatment related adverse event; otherwise, relationship is described as 'Not Related' to Study Drug.

b Includes subjects discontinued for an adverse event (AE, per their case report forms [CRF]).

c Subjects discontinued for the following reasons: Lost to Follow-Up, No Longer Willing to Participate in Study.

PROTOCOL DEVIATIONS

Table 33 shows subjects with protocol deviations in the 2 study groups. The reasons for the deviations vary, and include failure to meet inclusion/exclusion criteria, lack of compliance with the prescribed dosing regimen, missed visits or visits which occurred outside of the scheduled visit window, informed consent deviations, etc.

Three subjects in the Levofloxacin arm were excluded from the Clinically Eligible population for insufficient signs and symptoms of sinusitis upon enrollment. Two subjects (10321009 and 10321010), both in the azithromycin ER treatment group, were incorrectly identified in the audit of site 1032 as having insufficient signs and symptoms at Baseline. While they were still considered as protocol deviations, they were included among the evaluable population in the sponsor's efficacy analyses. One subject (10371001) did not have a sinus aspirate obtained at Baseline and was excluded from the Bacteriologic Per Protocol population as well as from Clinical Per Protocol Population. Subject 10551001, who received placebo by error instead of