

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # : 50-797

Drug Name: Zmax complete (azithromycin microspheres), a single 2.0g dose taken orally.

Indication(s): Acute Bacterial Maxillary Sinusitis, Community Acquired Pneumonia

Applicant: Pfizer

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TABLE OF CONTENTS

LIST OF TABLES.....	3
1. EXECUTIVE SUMMARY	4
1.1 INTRODUCTION	4
1.2 CONCLUSIONS AND RECOMMENDATIONS	4
1.3 BRIEF OVERVIEW OF CLINICAL STUDIES	6
1.4 STATISTICAL ISSUES AND FINDINGS	6
2. INTRODUCTION.....	6
2.1 OVERVIEW.....	7
2.1.1 <i>Class and Indication.....</i>	<i>7</i>
2.1.2 <i>History of Drug Development</i>	<i>7</i>
2.1.3 <i>Sponsor's Rationale for Azithromycin SR.....</i>	<i>7</i>
2.2 DATA SOURCES	7
3. STATISTICAL EVALUATION	8
3.1 EVALUATION OF EFFICACY (STUDY A0661078 IN ABS).....	8
3.1.1 <i>Study Design and Endpoints (Study A0661078).....</i>	<i>8</i>
3.1.2 <i>Subject Disposition, Demographic and Baseline Characteristics (Study A0661078).....</i>	<i>10</i>
3.1.3 <i>Statistical Methodologies (Study A0661078)</i>	<i>12</i>
3.1.4 <i>Results and Conclusions (Study A0661078).....</i>	<i>12</i>
3.2 EVALUATION OF EFFICACY (STUDY A0661075 IN CAP)	15
3.2.1 <i>Study Design and Endpoints (Study A0661075).....</i>	<i>15</i>
3.2.2 <i>Subject Disposition, Demographic and Baseline Characteristics (Study A0661075).....</i>	<i>16</i>
3.2.3 <i>Statistical Methodologies (Study A0661075)</i>	<i>18</i>
3.2.4 <i>Results and Conclusions (Study A0661075).....</i>	<i>19</i>
3.3 EVALUATION OF EFFICACY (STUDY A0661103 IN CAP)	21
3.3.1 <i>Study Design and Endpoints (Study A0661103).....</i>	<i>21</i>
3.3.2 <i>Subject Disposition, Demographic and Baseline Characteristics (Study A0661103).....</i>	<i>22</i>
3.3.3 <i>Statistical Methodologies (Study A0661103)</i>	<i>24</i>
3.3.4 <i>Results and Conclusions (Study A0661103).....</i>	<i>24</i>
3.4 EVALUATION OF SAFETY.....	26
3.4.1 <i>Evaluation of Safety (Study A0661078).....</i>	<i>27</i>
3.4.2 <i>Evaluation of Safety (Study A0661075).....</i>	<i>27</i>
3.4.3 <i>Evaluation of Safety (Study A0661103).....</i>	<i>29</i>
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	30
4.1 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS (STUDY A0661078 IN ABS)	30
4.2 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS (STUDY A0661075 IN CAP).....	31
4.3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS (STUDY A0661103 IN CAP).....	32
5. SUMMARY AND CONCLUSIONS.....	34

LIST OF TABLES

Table 1: Visit Schedule (Study A0661078).....	8
Table 2: Subject Evaluation Groups, Number (%) ^a of Subjects (Study A0661078)	10
Table 3: Discontinuation from the Study, All Treated Subjects (Study A0661078).....	11
Table 4: Sponsor Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661078)	12
Table 5: Medical Officer’s Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661078).....	13
Table 6: Overall Bacteriologic Eradication Rates at TOC, Number (%) in Bacteriologic Per Protocol and Bacteriologic ITT Subjects (Study A001078).....	13
Table 7: Bacteriologic Eradication Rate (%) at TOC by Baseline Pathogen in Bacteriologic per Protocol Subjects (Study A0661078)	14
Table 8: Visit Schedule (Study A0661075).....	15
Table 9: Subject Evaluation Groups, Number (%) ^a of Subjects (Study A0661075).....	16
Table 10: Discontinuations from the Study, All Treated Subjects (Studies A0661075).....	17
Table 11: Sponsor Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661075)	19
Table 12: Overall Bacteriologic Eradication Rates at TOC, Number (%) in Bacteriologic Per Protocol and Bacteriologic ITT Subjects (Study A001075).....	19
Table 13: Bacteriologic Eradication Rate (%) at TOC by Baseline Pathogen in Bacteriologic Per Protocol Subjects (Study A0661075)	20
Table 14: Visit Schedule (Study A0661103).....	21
Table 15: Subject Evaluation Groups, Number (%) of Subjects (Study A0661103)	22
Table 16: Discontinuations from the Study, All Treated Subjects (Study A0661103)	23
Table 17: Sponsor Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661103)	25
Table 18: Overall Bacteriologic Eradication Rates at TOC, Number (%) in Bacteriologic Per Protocol and Bacteriologic ITT Subjects (Study A001103).....	25
Table 19: Bacteriologic Eradication Rate (%) at TOC by Baseline Pathogen in Bacteriologic per Protocol Subjects (Study A0661103)	26
Table 20 Sponsor Assessment of Clinical Response at TOC by Gender, Age, Race and Region in MITT Population (Study A0661078).....	30
Table 21 Sponsor Assessment of Clinical Response at TOC by Gender, Age, Race and Region in MITT Population (Study A0661075).....	31
Table 22 Sponsor Assessment of Clinical Response at TOC, Number (%) of Clinical Per Protocol Subjects, U.S vs. Non-U.S (Study A0661075).....	32
Table 23 Sponsor Assessment of Clinical Response at TOC by Gender, Age, Race and Region in MITT Population (Study A0661103).....	32
Table 24 Sponsor Assessment of Clinical Response at TOC, Number (%) of Clinical Per Protocol Subjects, U.S vs. Non-U.S (Study A0661103).....	33

1. EXECUTIVE SUMMARY

1.1 Introduction

This NDA submission (NDA 50797) seeks to gain approval for the use of azithromycin sustained release (SR) taken as a single 2.0 g dose taken orally. NDA 50797 submits data from four pivotal Phase 3 clinical trials conducted in support of three clinical indications: [REDACTED]

[REDACTED] Community-Acquired Pneumonia (CAP) (Studies A0661075 and A0661103) and Acute Bacterial Sinusitis (Study A0661078). This statistical review considers ABS (Study A0661078) and CAP (Studies A0661075 and A0661103) indications. [REDACTED]

All studies included in this review (Study A0661078 (ABS), Studies A0661075 (CAP) and A0661103 (CAP)) attempt to demonstrate the non-inferiority of azithromycin SR to comparator therapy within a 10% non-inferiority margin. However, the sponsor's primary analysis considers clinical response at TOC in the per protocol population as the only primary efficacy outcome. Note that the division recommends and traditionally considers the following as co-primary outcomes in non-inferiority trials: a) clinical response at TOC in the per protocol population and b) clinical response at TOC in the intent-to-treat (ITT) (or modified ITT population). Therefore, the primary analysis for studies in this statistical review considers the primary efficacy endpoint analyzed in the clinical per protocol and MITT populations as co-primary endpoints. Note that the 'clinically eligible population' as defined in the Sponsor's submission is referred to as the 'MITT population' throughout this statistical review. Similarly, the 'all randomized population' as defined by the sponsor is referred to as the 'ITT population' in this review.

1.2 Conclusions and Recommendations

Study A0661078 (ABS)

Study A0661078 demonstrated the non-inferiority of azithromycin SR therapy to levofloxacin therapy in the treatment of acute, uncomplicated bacterial maxillary sinusitis (ABS). According to the FDA analysis, clinical per protocol population (co-primary endpoint), subjects had cure rates at TOC of 94.5% (azithromycin SR) versus 92.9% (levofloxacin), a 1.6% difference with 95% CI (-2.6% to 5.8%). In the clinical MITT population (co-primary endpoint), subjects had cure rates at TOC of 91.1% (azithromycin SR) versus 89.1% (levofloxacin), a 1.9% difference with 95% CI (-3.1%, 7.0%). Non-inferiority of Azithromycin SR was demonstrated since the lower limit of the 95% CI of the treatment difference was greater than -10% in both the per-protocol and MITT population analyses.

Secondary analyses were also consistent with the primary analysis and show Azithromycin SR therapy to be noninferior to levofloxacin therapy in the bacteriologic per protocol, bacteriologic ITT, ITT and all treated analysis populations. Similar differences in cure rates between azithromycin SR and clarithromycin therapy were also observed in subjects with documented infections of key CAP pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*. Note that the number of patients treated with Azithromycin SR having a baseline pathogen of *Haemophilus influenzae* and *Streptococcus pneumoniae* met the recommended number of patients set forth in the guidance for the treatment of ABS. (i.e. at least 25 bacteriologic ITT patients). However, the number of patients with a baseline pathogen of *Moraxella catarrhalis* (i.e. 8 bacteriological ITT patients) failed to meet the recommended number of patients set forth in the guidance (i.e. at least 15 bacteriologic ITT patients). Note that secondary analyses of Study A0661078 were not powered to demonstrate non-inferiority.

Studies A0661075 and A0661103 (CAP)

Study A0661075 demonstrated the non-inferiority of azithromycin SR therapy to clarithromycin therapy in the treatment of community acquired pneumonia (CAP). In the clinical per protocol population (co-primary endpoint), subjects had cure rates at TOC of 92.6% (azithromycin SR) versus 94.7% (clarithromycin ER), a -2.2% difference with 95% CI (-6.9% to 2.6%). In the clinical MITT population (co-primary endpoint), subjects had cure rates at TOC of 87.2% (azithromycin SR) versus 87.6% (clarithromycin ER), a -0.4% difference with 95% CI (-6.5% to 5.6%). Analyses of secondary endpoints were also consistent with the primary analysis and show Azithromycin SR therapy to be noninferior to clarithromycin therapy in the bacteriologic per protocol, bacteriologic ITT, ITT and all treated analysis populations. Note that secondary analyses of Study A0661075 were not powered to demonstrate non-inferiority.

Study A0661103 failed to demonstrate the non-inferiority of azithromycin SR therapy to levofloxacin therapy in the treatment of community acquired pneumonia (CAP) since non-inferiority within a 10% margin could not be demonstrated in the MITT population. In the primary analysis, clinical per-protocol population (co-primary population) subjects had cure rates at TOC of 89.7% (azithromycin SR) versus 93.7% (levofloxacin), a -4.0% difference with 95% CI (-9.7% to 1.7%). In the MITT population (co-primary population) subjects had cure rates at TOC of 84.6% (azithromycin SR) versus 89.9% (levofloxacin), a -5.3% difference with 95% CI (-11.9% to 1.2%). Since the lower bound of the 95% CI for the treatment difference is below -10% in one of the two co-primary endpoints (i.e. the MITT population analysis), the non-inferiority of azithromycin SR could not be demonstrated. Analyses of secondary endpoints also failed to provide strong evidence of non-inferiority since the non-inferiority of azithromycin SR therapy could not be shown in the ITT, all treated, bacteriologic per-protocol and bacteriologic MITT populations. Note that secondary analyses of Study A0661103 were not powered to demonstrate non-inferiority.

Although Study A0661103 failed to demonstrate the non-inferiority of azithromycin SR therapy to levofloxacin therapy using a margin of -10% in the MITT population, it did show non-inferiority in the per-protocol population analysis. Additionally, the lower bounds of the 95% CIs for the treatment differences in clinical cure rates were close to -10% in the ITT (-10.3%) and all treated (-10.2%) analysis populations. Across both studies, similar differences in cure

rates between azithromycin SR and comparator therapy were observed in subjects with documented infections of key CAP pathogens, such as *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.

1.3 Brief Overview of Clinical Studies

Study A066178 (ABS)

Study A0661078 (ABS) is a randomized, double-blind, double-dummy multi-center trial comparing azithromycin SR (a single 2 gram dose PO) to levofloxacin (500mg orally once daily for 10 days). Clinical efficacy was assessed at the Test of Cure (TOC) visit, which occurred 17-24 days after the first dose of the study drug. The primary outcome was sponsor assessment of clinical response at TOC.

Studies A0661075 and A0661103 (CAP)

Study A0661075 (CAP) and Study A0661103 (CAP) are randomized, double-blind, double-dummy multi-center trials comparing azithromycin SR (a single 2 gram dose PO) to clarithromycin ER (1.0 g orally once daily for 7 days) in Study A0661075 and azithromycin SR (a single 2 gram dose PO) to levofloxacin (500mg once daily for 7 days) in Study A0661103. Clinical efficacy was assessed at the Test of Cure (TOC) visit, which occurred 14-21 days after the first dose of the study drug. The primary outcome was sponsor assessment of clinical response at TOC.

1.4 Statistical Issues and Findings

The main statistical issue for all studies in this review (Study A066178 (ABS), Studies A0661075 and A0661103 (CAP)) is that the sponsor considered clinical response as TOC in the per protocol population as the only primary efficacy outcome. The division recommends and traditionally considers the following as co-primary outcomes: a) clinical response at TOC in the per protocol population and b) clinical response at TOC in the ITT (or MITT) population. The definition of these co-primary endpoints is particularly relevant in Study A0661103 where non-inferiority of azithromycin SR to levofloxacin was not established using the sponsor assessed clinical response at TOC in the MITT population. In Study A0661103, non-inferiority was also not established using the sponsor assessed clinical response at TOC in other populations such as the all treated, ITT, bacteriological per protocol, and bacteriological ITT populations.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Azithromycin, an azalide antibiotic, is a member of the macrolide class of antibiotics. Macrolides are primarily bacteriostatic and act by binding to the 50S ribosomal subunit of susceptible bacteria, thus disrupting microbial protein synthesis. Drugs in this class are generally active against aerobic and anaerobic gram-positive cocci (with the exception of enterococci) and against gram-negative anaerobes.

2.1.2 History of Drug Development

Zithromax® (azithromycin) is currently approved for the following indications:

- Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.
- Acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.
- Community -acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.
- Pharyngitis/tonsillitis in adults and pediatrics caused by *S. pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.
- Uncomplicated skin and skin structure infections due to *S.aureus*, *S.pyogenes*, or *Streptococcus agalactiae*.
- Urethritis and cervicitis in adults due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*
- Genital ulcer disease in adult men to *Haemophilus ducreyi* (chancroid).

Zithromax® (azithromycin) 500 mg tablets was approved for a 3-day dosing regimen (500 mg/day) to treat ABS and AECB in adults, under NDAs 50784 and NDA 50784/ SE1-004 respectively.

2.1.3 Sponsor's Rationale for Azithromycin SR

Azithromycin SR with a single 2.0 mg dosing regimen offers the potential to increase antibiotic exposure at the start of treatment, minimize the duration of treatment-related adverse effects, reduce the risk of propagation of antibacterial resistance, enhance patient convenience and ensure completion of therapy.

2.2 Data Sources

- Files of \\Cdsesub1\n50797\N_000\2004-08-12

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy (Study A0661078 in ABS)

3.1.1 Study Design and Endpoints (Study A0661078)

Objectives: To confirm the hypothesis that a single, 2.0 g dose of azithromycin SR is clinically non-inferior to 10 days of levofloxacin 500 mg (PO) QD, when used to treat adults with ABS. Secondary assessments included safety and the bacteriologic efficacy of both treatment regimens.

Design: This is a Phase 3, multi-center, international, double-blind study with in which subjects were randomly assigned to one of two active treatment arms, 2.0 g dose of azithromycin SR (single dose only) or 10 days of levofloxacin 500 mg (PO) QD . Eligible subjects were to be 18 years of age or older with clinical and radiological evidence of ABS. All subjects underwent maxillary sinus aspiration prior to treatment.

Table 1: Visit Schedule (Study A0661078)

Visit number	Visit name	Schedule per Study Protocol	Actual Window used for Analysis
1	Baseline	Day 1	Day -1, Day 0, Day 1
2	OT	Day 3-5	Days 2-8
3	EOT (telephone contact)	Day 11-13	Days 9-15
4	TOC	Day 17-24	Days 16-25

Day numbers are measured from baseline. OT- On treatment, EOT- End of Treatment, TOC- Test of Cure, Screening (≤ 48 hrs) preceded visit 1.

The visit schedule is shown in Table 1. Clinical efficacy was assessed at the Test of Cure (TOC) visit. Subjects from whom a baseline pathogen was identified were also assessed for bacteriologic response at the TOC visit. Subjects were contacted and symptoms were assessed by telephone at the End of Treatment (EOT) visit (Days 11-13). An office visit was scheduled if they had not yet clinically improved. All subjects who received at least 1 dose of study medication were assessed for safety.

Primary Efficacy Endpoint:

- Sponsor assessment of clinical response for the Clinical Per Protocol population at the Test of Cure visit (Days 17-24).

Secondary Efficacy Endpoints:

- Bacteriologic eradication rate analyzed on a per pathogen basis for the Bacteriologic Per Protocol population at the Test of Cure visit (Days 17-24).
- Sponsor assessment of clinical response at TOC for the remaining populations.

- Sponsor assessment of clinical response by baseline pathogen for the Bacteriologic Per Protocol population at TOC.
- Investigator assessment of clinical response for the Clinical Per Protocol population at TOC. Summaries of baseline pathogen susceptibilities.

Statistical Reviewer Comments: *The sponsor's primary analysis considers clinical response at TOC in the per protocol population as the only primary efficacy outcome. The division recommends and traditionally considers the following as co-primary outcomes in non-inferiority trials: a) clinical response at TOC in the per protocol population and b) clinical response at TOC in the intent-to-treat (ITT) (or modified ITT population). Therefore, the primary analysis for studies in this statistical review considers the primary efficacy endpoint analyzed in the clinical per protocol and MITT populations as co-primary endpoints.*

Populations Analyzed:

All Randomized (or ITT) Subjects: All subjects who received a randomization number from the central randomization system.

All Treated Subjects: ITT Subjects who received at least one dose of study medication.

Clinically Eligible (or MITT) Subjects: All Treated Subjects with a diagnosis of maxillary sinusitis based on the inclusion of the following signs and symptoms:

- Had a diagnosis of acute sinusitis where clinical evidence of sinusitis is demonstrated by the following 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 one or more of the following signs:
 - Purulent nasal discharge
 - Purulent drainage in the posterior pharynx
 - Purulent discharge from the maxillary sinus orifice.
 - Had a sinus X-ray confirming the clinical diagnosis of maxillary sinusitis where at least one of the following is documented in one or both maxillary sinuses on radiologic examination:
 - Complete or partial opacification
 - An air/fluid level, and;
- Had two or more of the following:
 - Fever, as defined by oral temperature $>38^{\circ}\text{C}$ ($>100.4^{\circ}\text{F}$) or tympanic temperature $>38.5^{\circ}\text{C}$ ($>101.2^{\circ}\text{F}$),
 - Leukocytosis,
 - Frequent coughing,
 - Headache,
 - Nasal congestion,
 - Post-nasal drainage.

Clinical Per Protocol Subjects: MITT subjects meeting the following criteria:

- Received at least 8 days of dosing of study medication, including both active and placebo doses.
- Received no concomitant systemic antibiotic with activity against key sinusitis pathogens.
- Received an assessment in the appropriate visit window. (Exception: A subject is considered to be in the Clinical Per Protocol population if the subject is included in the MITT population and is a treatment failure who has received at least three days of dosing, including active and placebo doses).
- Bacteriologic Per Protocol Subjects: Clinical Per Protocol Subjects with a baseline bacterial pathogen identified by culture.

Statistical Reviewer Comments: *Note that the 'clinically eligible population' as defined in the Sponsor's submission is referred to as the 'MITT population' throughout this statistical review. Similarly, the 'all randomized population' as defined by the sponsor is referred to as the 'ITT population'.*

3.1.2 Subject Disposition, Demographic and Baseline Characteristics (Study A0661078)

Subject Disposition

Table 2: Subject Evaluation Groups, Number (%)^a of Subjects (Study A0661078)

Evaluation Group	Azithromycin SR	Levofloxacin	Total
ITT	271 (100.0)	270 (100.0)	541 (100.0)
All Treated	270 (99.6)	268 (99.3)	538 ^d (99.4)
MITT	270 (100.0)	264 (98.5)	534 (99.3)
Excluded Reason ^b	0 (0.0)	4 (1.5)	4 (0.7)
Insufficient Signs and Symptoms of ABS	0 (0.0)	3 (1.1)	3 (0.6)
No X-ray Evidence of Sinusitis	0 (0.0)	1 (0.4)	1 (0.2)
Clinical Per Protocol at TOC	256 (94.8)	251 (93.7)	507 (94.2)
Excluded Reason ^b	14 (5.2)	17 (6.3)	31 (5.8)
Clinically Ineligible	0 (0.0)	4 (1.5)	4 (0.7)
No TOC Visit ^c	10 (3.7)	11 (4.1)	21 (3.9)
Received Other Antibiotics	4 (1.5)	2 (0.7)	6 (1.1)
Bacteriologic Per Protocol at TOC	102 (37.8)	111 (41.4)	213 (39.6)

^a Percentages are based on the ITT Subjects. ^b A subject is counted only for the primary reason of exclusion; reasons are listed in hierarchical order. ^c Visits that occurred outside pre-defined visit window or did not occur. ^d Three patients (10111009, 10321014, and 10501020) were randomized but were withdrawn prior to receiving treatment. Source: Sponsor's Table

Statistical Reviewer Comments: *Of the 541 subjects enrolled (ITT population), 538 subjects were treated with either azithromycin SR or levofloxacin. Of these treated subjects, 524 (97%)*

completed the study and 507 (94%) were included in the Clinical Per Protocol population at TOC.

Table 3: Discontinuation from the Study, All Treated Subjects (Study A0661078)

Discontinuations	Azithromycin SR N = 270		Levofloxacin N = 268	
	Number (%) of Subjects			
Related to Study Drug ^a	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	2	(0.7)	3	(1.1)
Adverse Event ^b	1	(0.4)	0	(0.0)
Subject Defaulted ^c	1	(0.4)	3	(1.1)
Total	7	(2.6)	7	(2.6)

a: Relationship to Study Drug is derived as Related if reason for discontinuation is Insufficient Clinical Response (Lack of Efficacy), or due to a treatment related adverse event; otherwise, Relationship is derived as Not Related. b: Includes only subjects who discontinued due to an adverse event (AE) according to their completed subject summary CRF. c: Includes subjects who discontinued due to the following reasons: Lost to Follow-Up or Subject No Longer Willing to Participate in Study. Source: Sponsor's Table

Statistical Reviewer Comments: *The number of discontinuations was similar between the azithromycin SR treatment group (3%) and the levofloxacin treatment group (3%). All subjects in both treatment groups were analyzed for safety. Clinical laboratory assessments were collected for 5 subjects in the study (1% in each treatment group).*

Demographics and Baseline Characteristics:

Overall, the 2 treatment groups were similar with respect to Baseline characteristics. Approximately 42% of all treated subjects were men and 58% were women. There was a higher proportion of women in the levofloxacin treatment group than the azithromycin treatment group (63% vs. 47%). A majority of all subjects were white (67%) and were less than 65 years of age (94%), with a mean age of 38.4 years for the azithromycin SR group and 39.4 years for the levofloxacin treatment group. Approximately 3% of the subjects were black. Prognostic factors and other Baseline characteristics were similar across both treatment groups in the Clinical Per Protocol population.

Protocol Deviations Affecting Sponsor's Primary Analysis: Two subjects (10321009 and 10321010), both in the azithromycin SR treatment group, were identified in the audit of site 1032 as having insufficient signs and symptoms at Baseline. However, in response to the audit, the sponsor made a decision to retain the data as originally entered. Therefore, these 2 subjects are listed as protocol deviations but are included in the MITT population. Subject 10551001 was dispensed the incorrect bottle number in error. This subject was randomized to receive active azithromycin SR and placebo levofloxacin. However, due to an error by the site, the subject received placebo azithromycin SR and placebo levofloxacin. Assessments of all endpoints for this subject were based on the initially assigned randomization to the active azithromycin SR arm. The inclusion of the two subjects in the azithromycin SR arm did not meaningfully affect results in the primary analysis.

Statistical Reviewer Comments: *Additional protocol deviations were identified by the medical officer, Dr. Menfo Imoisili, but did not meaningfully change the overall study results (table 5). The primary reason for these protocol deviations included the failure to meet inclusion/exclusion criteria.*

3.1.3 Statistical Methodologies (Study A0661078)

Primary Efficacy Assessment: Clinical efficacy was analyzed in the MITT population using 95% confidence intervals comparing the proportion of patients with a clinical response of success (sponsor assessed clinical cure at TOC). The confidence intervals on the differences in proportions were computed using the normal approximation to the binomial distribution. The agreed upon non-inferiority margin was -10%.

Additional Efficacy Assessments: Additional efficacy analyses included the following secondary endpoints:

- Sponsor assessment of clinical response at the TOC visit for the remaining study populations (all populations except Clinical Per Protocol). Missing values were imputed as failures. Additional sensitivity analyses were conducted on this same efficacy parameter with missing values imputed as cures.
- Sponsor assessment of clinical response by baseline pathogen for the Bacteriological Per Protocol population at the TOC visit.
- Investigator assessment of clinical response for the Clinical Per Protocol population at the TOC visit.
- Summary of baseline pathogen susceptibilities.

Other Assessments: The effect of prognostic factors on treatment effects for the sponsor assessment of clinical response was examined. Prognostic factors collected included: smoking history, history of allergic rhinitis, and number of previous episodes in the past 12 months. In addition, the sponsor assessment of clinical response was summarized by center, age, race, gender, and geographic area.

3.1.4 Results and Conclusions (Study A0661078)

Efficacy Results

Table 4: Sponsor Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661078)

	Azithromycin SR	Levofloxacin	Difference	95% CI ^a
* Clinical Per Protocol Subjects at TOC, N (%)	256	251		
Cure	242 (94.5)	233 (92.8)	1.7	(-2.5, 5.9)
Failure	14 (5.5)	18 (7.2)		
* MITT				

Subjects at TOC, N (%)	270	264		
Cure	246 (91.1)	235 (89.0)	2.1	(-3.0, 7.2)
Failure	24 (8.9)	29 (11.0)		
ITT				
Subjects at TOC, N (%)	271	270		
Cure	246 (90.8)	239 (88.5)	2.3	(-2.9, 7.4)
Failure	25 (9.2)	31 (11.5)		

* Co-primary endpoint. Source: FDA table

Statistical Reviewer Comments: *The non-inferiority of Azithromycin SR therapy to levofloxacin therapy is demonstrated since for both co-primary endpoints the lower limit of the 95% CI for the treatment difference is greater than -10%.*

Table 5: Medical Officer's Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661078)

	Azithromycin SR	Levofloxacin	Difference	95% CI ^a
*Clinical Per Protocol				
Subjects at TOC, N(%)	255	254		
Cure	241 (94.5)	236 (92.9)	1.6	(-2.6, 5.8)
Failure	14 (5.5)	18 (7.1)		
*MITT Subjects at TOC, N(%)	269	267		
Cure	245 (91.1)	238 (89.1)	1.9	(-3.1, 7.0)
Failure	24 (8.9)	29 (10.9)		
**ITT Subjects at TOC, N(%)	271	270		
Cure	246 (90.8)	239 (88.5)	2.3	(-2.9, 7.4)
Failure	25 (9.2)	31 (11.5)		

Source: FDA table, *Co-primary endpoints,

Statistical Reviewer Comments: *The medical officer's analysis incorporates specific protocol deviations that occurred equally across study groups. This re-analysis did not meaningfully change the overall study efficacy results.*

Table 6: Overall Bacteriologic Eradication Rates at TOC, Number (%) in Bacteriologic Per Protocol and Bacteriologic ITT Subjects (Study A001078)

	Azithromycin SR	Levofloxacin	Difference	95% CI ^a
Bacteriological Per Protocol				
Subjects at TOC, (N %)	114	129		
Cure	112 (98.2)	120 (93.0)	5.2	(-0.2, 11.4)
Failure	2 (1.8)	9 (7.0)		
Bacteriologic ITT				
Subjects at TOC, (N %)	120	139		
Cure	114 (95.0)	123 (88.5)	6.5	(-0.4, 13.6)
Failure	6 (1.8)	16 (7.0)		

Eradicated = Eradication + Presumed Eradication, Persistence = Persistence + Presumed Persistence. Due to small sample sizes and proportions close to the boundary exact 95% CIs are computed. a: n = Number Eradicated number of pathogens, within the pathogen category, eradicated at the post Baseline visit), N = Number Isolated number of pathogens isolated at Baseline). Note: A subject may have more than one pathogen isolated at Baseline. Source: Sponsor's Table

Statistical Reviewer Comments: *The overall bacteriologic eradication rate of azithromycin SR therapy was non-inferior to levofloxacin therapy in the Bacteriologic Per Protocol and Bacteriologic ITT population at the TOC visit, a difference in eradication rates of 5.2% (CI = -0.4% to 13.6%) and 6.5% (CI = -0.2% to 11.4%) respectively.*

Table 7: Bacteriologic Eradication Rate (%) at TOC by Baseline Pathogen in Bacteriologic per Protocol Subjects (Study A0661078)

Pathogen	Azithromycin SR			Levofloxacin		
	n/N ^a	%	95% CI	n/N ^a	%	95% CI
<i>H. influenzae</i>	26/27	96.3	(81.0, 99.9)	30/30	100.0	(88.4, 100.0)
<i>M. catarrhalis</i>	8/8	100.0	(63.1, 100.0)	10/11	90.9	(58.7, 99.8)
<i>S. pneumoniae</i>	36/37	97.3	(85.8, 99.9)	36/39	92.3	(79.1, 98.4)

Eradicated = Eradication + Presumed Eradication, Persistence = Persistence + Presumed Persistence, TOC = Test of Cure. ^a n = Number Eradicated number of pathogens, within the pathogen category, eradicated at the post Baseline visit), N = Number Isolated number of pathogens isolated at Baseline). Note: A subject may have more than one pathogen isolated at Baseline. Due to small sample sizes and proportions close to the boundary exact 95% CIs are computed. Source: Sponsor's Table

Statistical Reviewer Comments: *Eradication rates of H. influenzae, M. catarrhalis and S. pneumoniae isolates were similar between groups at 96.3%, 100% and 97.3% in the azithromycin SR treatment group versus 100%, 90.9%, 92.3% in the Levofloxacin group. Since follow-up sinus taps were not required, the majority of eradicated pathogens in both treatment groups (229 of 232) were assigned a response of presumed eradication.*

Conclusions:

The primary efficacy analysis of Study A0661078 demonstrated the non-inferiority of azithromycin SR therapy to levofloxacin therapy in the treatment of ABS for both co-primary endpoints. According to the FDA analysis, clinical per protocol population (co-primary endpoint) subjects had cure rates at TOC of 94.5% (azithromycin SR) versus 92.9% (levofloxacin), a 1.6% difference with 95% CI (-2.6% to 5.8%). In the clinical MITT population (co-primary endpoint), subjects had cure rates at TOC of 91.1% (azithromycin SR) versus 89.1% (levofloxacin), a 1.9% difference with 95% CI (-3.1%, 7.0%). Secondary analyses were consistent with the primary analysis and show Azithromycin SR therapy to be noninferior to levofloxacin therapy in the bacteriologic per protocol, bacteriologic ITT, ITT and all treated analysis populations. Note that secondary analyses were not powered to demonstrate non-inferiority. Similar differences in cure rates between azithromycin SR and clarithromycin

therapy were also observed in subjects with documented infections of key CAP pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*

3.2 Evaluation of Efficacy (Study A0661075 in CAP)

3.2.1 Study Design and Endpoints (Study A0661075)

Study Objectives: The primary study objective was to confirm the hypothesis that a single, 2.0 g oral dose of azithromycin sustained release (SR) is clinically non-inferior to clarithromycin (1.0 g orally once daily for 7 days). 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 SR or Clarithromycin ER. Clinical and bacteriologic response were assessed at the Test of Cure (TOC) visit (14-21 days post first dose).

Table 8: Visit Schedule (Study A0661075)

Visit number:	Visit name	Schedule per Study Protocol	Actual Window used for Analysis
1:	Baseline	Day 1	Day -1, Day 0, Day 1
2:	OT	Day 3 - 5	Days 2 - 6
3:	EOT (telephone contact)	Day 8 - 11	Days 7 - 12
4:	TOC	Day 14 - 21	Days 13 - 24*, Days 3 - 24**
5:	LTFU	Day 28 - 35	Days 25 - 38

* Window used for the assessment of cardinal signs and symptoms and bacteriologic response.

**Window used for the assessment of the chest x-ray. Source: Sponsor's Table

Primary Efficacy Endpoint: Sponsor assessment of clinical response for the Clinical Per Protocol population at the Test of Cure visit (Days 14-21).

Secondary Efficacy Endpoints:

- Bacteriologic eradication rate analyzed on a per pathogen basis for the Bacteriologic Per Protocol population at the Test of Cure visit (Days 14-21).
- Sponsor assessment of clinical response at TOC for the remaining populations.
- Sponsor assessment of clinical response by baseline pathogen for the Bacteriologic Per Protocol population at TOC.
- Investigator assessment of clinical response for the Clinical Per Protocol population at TOC.
- Summaries of baseline pathogen susceptibilities.
- Sponsor assessment of clinical response at Long Term Follow-Up for the Clinical Per Protocol population.

Analyzed Populations:

All Randomized (or ITT) Subjects: All subjects who received a randomization number from the central randomization system.

All Treated Subjects: ITT Subjects who received at least one dose of study medication.

Clinically Eligible (or MITT) Subjects: All Treated Subjects with an appropriate diagnosis with the following selected specific inclusion criteria:

- Males or females, 16 years of age or older, for whom oral therapy is indicated;
- Cough productive of sputum (must be sent to the lab for culture and sensitivity);
- Diagnosis of pneumonia as demonstrated by two or more of the following signs or symptoms:
 - Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, egophony);
 - Dyspnea or tachypnea;
 - Body temperature $>38^{\circ}\text{C}$ (100.4°F) orally; or $>38.5^{\circ}\text{C}$ (101.2°F) tympanically; $>39^{\circ}\text{C}$ (102.2°F) rectally; or $>37.2^{\circ}\text{C}$ (99.0°F) axillary;
 - An elevated total peripheral white blood cell count ($\text{WBC}>10,000/\text{mm}^3$) or greater than 15% immature neutrophils (bands);
 - Chest radiograph, PA and lateral, revealing the presence of a new infiltrate or consolidation that cannot be attributed to a process other than pneumonia;
 - Modified Fine Risk score of ≤ 70 (Fine Class I & II)
 - Women of child-bearing potential (WOCBP) must have a negative urine pregnancy test within 48 hours prior to start of study medication.

Clinical Per Protocol Subjects: Clinically eligible (MITT) subjects meeting the following criteria:

- Receive at least 80% of study medication, including both active and placebo doses.
- Receive no concomitant systemic antibiotic with activity against pathogens typical of the indication under study.
- Receive an assessment in the appropriate visit window.

Exception: A subject is considered to be in the clinical per protocol population if the subject is included in the MITT population and is a treatment failure who has received at least 3 days of dosing, including active and placebo doses.

Bacteriologic Per Protocol Subjects: Clinical Per Protocol Subjects with a baseline bacterial pathogen.

3.2.2 Subject Disposition, Demographic and Baseline Characteristics (Study A0661075)

Subject Disposition:

Table 9: Subject Evaluation Groups, Number (%)^a of Subjects (Study A0661075)

Evaluation Group	Azithromycin SR	Clarithromycin ER	Total
ITT	247 (100.0)	254 (100.0)	501 (100.0)
All Treated	247 (100.0)	252 ^A (99.2)	499 ^A (99.6)
MITT	226 (91.5)	234 (98.5)	460 (92.2)
Excluded Reason ^b	21 (8.5)	18 (7.1)	39 (7.8)
Insufficient Signs and Symptoms of ABS	13 (5.3)	10 (4.0)	23 (4.6)
No X-ray Evidence of Sinusitis	8 (3.2)	8 (3.2)	16 (3.2)
Clinical Per Protocol at TOC	202 (81.8)	209 (82.9)	411 (82.4)
Excluded Reason ^b	45 (18.2)	43 (17.1)	88 (17.6)
Clinically Ineligible	21 (8.5)	18 (7.1)	39 (7.8)
No TOC Visit ^c	23 (9.3)	25 (9.9)	48 (9.6)
Received Other Antibiotics	1 (0.4)	0 (0.0)	1 (0.2)
Bacteriologic Per Protocol at TOC	100 (40.5)	127 (50.4)	227 (45.5)

a: Two subjects (10331009 and 10341005) were randomized to the clarithromycin ER treatment group but were withdrawn prior to receiving treatment. Percentages are based on the ITT Subjects. b: Excluded Reason: A subject is counted only for the primary reason of exclusion; reasons are listed in hierarchical order. c: Visits occurred outside pre-defined visit window or did not occur. Source: Sponsor's Table

Statistical Reviewer Comments: *In study A0661075, 501 subjects enrolled (ITT population), 499 subjects were treated with either azithromycin SR or clarithromycin ER. Of these treated subjects, 226 (91.5%) were included in the MITT population and 202 (81.8%) were included in the Clinical Per Protocol at TOC.*

Table 10: Discontinuations from the Study, All Treated Subjects (Studies A0661075)

	Azithromycin SR	Clarithromycin ER	Total
Number (%) of Subjects	N = 247	N = 252	N=499
Discontinuations			
Subject Died	0 (0.0)	1 (0.4)	1 (0.2)
Related to Study Drug ^a	10 (4.0)	8 (3.2)	18 (3.6)
Adverse Event ^b	1 (0.4)	1 (0.4)	2 (0.4)
Lack of Efficacy	9 (3.6)	7 (2.8)	16 (3.2)
Not Related to Study Drug ^a	23 (9.3)	20 (7.9)	43 (8.6)
Adverse Event ^b	6 (2.4)	6 (2.4)	12 (2.4)
Other ^b	2 (0.8)	3 (1.2)	5 (1.0)
Subject Defaulted ^c	15 (6.1)	11 (4.4)	26 (5.2)
Total	33 (13.4)	29 (11.5)	62 (12.4)

a: Relationship to Study Drug is derived as Related if reason for discontinuation is Insufficient Clinical Response (Lack of Efficacy), or due to a treatment related adverse event; otherwise, Relationship is derived as Not Related. b: Includes subjects who discontinued due to the following reasons: Other, did not meet entrance criteria, or protocol violation. c: Includes subjects who discontinued due to the following reasons: Lost to follow-up or subject no longer willing to participate in study. Source: Sponsor's Table

Statistical Reviewer Comments: *In Study A0661075, 501 subjects enrolled (ITT population) and 499 subjects were treated with either azithromycin SR or clarithromycin ER. Of these treated subjects, 437 (88%) completed the study. The number of discontinuations was similar between the azithromycin SR treatment group (13%) and the clarithromycin ER treatment group (12%) (table 10). All patients in both treatment groups were analyzed for safety.*

Demographics and Baseline Characteristics:

Overall, the two treatment groups had similar baseline characteristics. Of all treated subjects, approximately 49% were men and 51% were women. A majority of all subjects were white (76%) and were < 65 years of age (88%). Comparing the two treatment groups, there was a higher percentage of males in the clarithromycin ER treatment arm (53%) than the azithromycin SR treatment group (45%) and a higher mean age of 45.6 (\pm 15.9) years of age (range = 17-81) for the azithromycin SR group versus 43.6 (\pm 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.

Protocol Deviations Affecting Primary Analysis: Protocol deviations that may have had the potential to impact the overall study results were recorded in the sponsor's Study A0661103 protocol (Section 11, Item 8). Deviations included failure to meet the inclusion/exclusion criteria (34), lack of compliance with the prescribed dosing regimen or administration of study drug treatment (10), and missed TOC visits (24). The protocol deviations were similar across treatment groups and did not impact the overall conclusions of the study.

3.2.3 Statistical Methodologies (Study A0661075)

Primary Efficacy Assessment: Clinical efficacy was analyzed in the clinically evaluable population using 95% confidence intervals comparing the proportion of patients with a clinical response of success (sponsor assessed clinical cure at TOC). The confidence intervals on the differences in proportions were computed using the normal approximation to the binomial distribution. The agreed upon non-inferiority margin was -10%.

Additional Efficacy Assessments: Additional efficacy analyses included the following secondary endpoints:

- Sponsor assessment of clinical response at the TOC visit for the remaining study populations (all populations except Clinical Per Protocol and MITT). Missing values were imputed as failures. Additional sensitivity analyses were conducted on this same efficacy parameter with missing values imputed as cures.
- Sponsor assessment of clinical response by baseline pathogen for the Bacteriological Per Protocol population at the TOC visit.
- Investigator assessment of clinical response for the Clinical Per Protocol population at the TOC visit.
- Summary of baseline pathogen susceptibilities.

Other Assessments: The effect of prognostic factors on treatment effects for the sponsor assessment of clinical response was examined. Prognostic factors collected included: smoking history, history of allergic rhinitis, and number of previous episodes in the past 12 months. In addition, the sponsor assessment of clinical response was summarized by center, age, race, gender, and geographic area.

3.2.4 Results and Conclusions (Study A0661075)

Results

Table 11: Sponsor Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661075)

	Azithromycin SR		Clarithromycin ER		Difference	95% CI ^a
*Clinical Per Protocol						
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)		
*MITT						
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)		
ITT						
Subjects at TOC, (N %)	247		254			
Cure	215	(87.0)	218	(85.8)	1.2	(-4.8, 7.2)
Failure	32	(13.0)	36	(14.2)		

* Co-primary endpoints. Source: FDA table

Statistical Reviewer Comments: *The non-inferiority of Azithromycin SR therapy to Clarithromycin ER therapy is demonstrated since the lower limit of the 95% CI for the treatment difference for both co-primary endpoints is greater than -10%. The medical reviewer, Dr. Nasim Moledina, agreed with the subject classifications and efficacy results reported by the sponsor.*

Table 12: Overall Bacteriologic Eradication Rates at TOC, Number (%) in Bacteriologic Per Protocol and Bacteriologic ITT Subjects (Study A001075)

	Azithromycin SR		Clarithromycin ER		Difference	95% CI ^a
Bacteriologic Per Protocol						
Subjects at TOC, (N %)	100		127			
Eradication	93	(93.0)	117	(92.1)	0.9	(-6.8, 8.0)
Persistence	7	(7.0)	10	(7.9)		
Bacteriologic ITT						
Subjects at TOC, (N %)	177		214			
Eradication	149	(84.2)	170	(79.4)	4.7	(-3.1, 12.5)
Persistence	28	(15.8)	44	(20.6)		

Eradicated = Eradication + Presumed Eradication, Persistence = Persistence + Presumed Persistence. Due to small sample sizes and proportions close to the boundary exact 95% CIs are computed using StatXact 5. n = Number Eradicated number of pathogens, within the pathogen category,

eradicated at the post Baseline visit), N = Number Isolated number of pathogens isolated at Baseline). Note: A subject may have more than one pathogen isolated at Baseline. Source: Sponsor's Table

Statistical Reviewer Comments: *In the bacteriologic per protocol population, the overall bacteriologic eradication rate was 93.0% for azithromycin SR-treated subjects and 92.1% for clarithromycin ER-treated subjects at the TOC visit, with a 95% CI of (-6.8, 8.0) and a difference of 0.9%. Non-inferiority of the azithromycin SR-treatment was also demonstrated in the bacteriologic ITT population.*

Table 13: Bacteriologic Eradication Rate (%) at TOC by Baseline Pathogen in Bacteriologic Per Protocol Subjects (Study A0661075)

Pathogen	Azithromycin SR			Clarithromycin ER		
	n/N	%	95% CI	n/N ^a	%	95% CI
<i>H. influenzae</i>	14/15	93.3	(68.1, 99.8)	23/26	88.5	(69.6, 97.6)
<i>S. pneumoniae</i>	17/19	89.5	(66.9, 98.7)	26/29	89.7	(72.7, 97.8)
<i>C. pneumoniae</i>	19/21	90.5	(69.6, 98.8)	29/31	93.5	(69.6, 98.8)
<i>M. pneumoniae</i>	25/26	96.2	(80.4, 99.9)	20/21	95.2	(76.2, 99.9)

Eradicated = Eradication + Presumed Eradication, Persistence = Persistence + Presumed Persistence. Due to small sample sizes and proportions close to the boundary exact 95% CIs are computed. n = Number Eradicated number of pathogens, within the pathogen category, eradicated at the post Baseline visit), N = Number Isolated number of pathogens isolated at Baseline). Note: A subject may have more than one pathogen isolated at Baseline. Source: Sponsor's Table

Statistical Reviewer Comments: *The bacteriologic eradication rate of H. influenzae, S. pneumoniae, C. pneumoniae, M. pneumoniae was 93.3%, 89.5%, 90.5% and 96.2%, respectively in the azithromycin SR treatment group; comparable rates for these 4 pathogens were seen in the Clarithromycin ER group.*

Conclusions

Clinical Per protocol subjects treated with azithromycin SR had a clinical cure rate of 92.6% compared with a cure rate of 94.7% for subjects treated with clarithromycin ER, a difference of -2.2% with 95% CI = (-6.9%, 2.6%). In the MITT population, azithromycin SR-treated subjects had a clinical cure rate of 87.2% compared with 87.6% for subjects treated with clarithromycin ER, a difference of -0.4% with 95% CI (-6.5%, 5.6%). Since the lower limit of this 95% CI was greater than -10% in both of these co-primary endpoints, azithromycin SR therapy demonstrated non-inferiority to clarithromycin ER therapy in the treatment of CAP. Azithromycin SR-treated subjects had also shown non-inferior clinical cure/eradication rates based upon secondary analyses of the ITT, All Treated, Bacteriologic Per Protocol and Bacteriologic ITT populations. Similar differences in cure rates between azithromycin SR and comparator therapy were observed in subjects with documented infections of key CAP pathogens, such as *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*. Note that secondary analyses were not powered to demonstrate non-inferiority.

3.3 Evaluation of Efficacy (Study A0661103 in CAP)

3.3.1 Study Design and Endpoints (Study A0661103)

Study Objectives: The primary study objective was to confirm the hypothesis that a single, 2.0 g oral dose of azithromycin sustained release (SR) is clinically non-inferior to levofloxacin (1.0 g orally once daily for 7 days). 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 SR or Clarithromycin ER. Clinical and bacteriologic response were assessed at the Test of Cure (TOC) visit (14-21 days post first dose).

Table 14: Visit Schedule (Study A0661103)

Visit number:	Visit name	Schedule per Study Protocol	Actual Window used for Analysis
1:	Baseline	Day 1	Day -1, Day 0, Day 1
2:	OT	Day 3 - 5	Days 2 - 6
3:	EOT (telephone contact)	Day 8 - 11	Days 7 - 12
4:	TOC	Day 14 - 21	Days 13 - 24*, Days 3 - 24**
5:	LTFU	Day 28 - 35	Days 25 - 38

* Window used for the assessment of cardinal signs and symptoms and bacteriologic response.

**Window used for the assessment of the chest x-ray. Source: Sponsor's Table

Primary Efficacy Endpoint: Sponsor assessment of clinical response for the Clinical Per Protocol population at the Test of Cure visit (Days 14-21).

Secondary Efficacy Endpoints:

- Bacteriologic eradication rate analyzed on a per pathogen basis for the Bacteriologic Per Protocol population at the Test of Cure visit (Days 14-21).
- Sponsor assessment of clinical response at TOC for the remaining populations.
- Sponsor assessment of clinical response by baseline pathogen for the Bacteriologic Per Protocol population at TOC.
- Investigator assessment of clinical response for the Clinical Per Protocol population at TOC.
- Summaries of baseline pathogen susceptibilities.
- Sponsor assessment of clinical response at Long Term Follow-Up for the Clinical Per Protocol population.

Analyzed Populations:

All Randomized (or ITT) Subjects: All subjects who received a randomization number from the central randomization system.

All Treated Subjects: ITT Subjects who received at least one dose of study medication.

Clinically Eligible (or MITT) Subjects: Defined as

- Males or females, 18 years of age or older, for whom oral therapy is indicated;
- Cough productive of sputum (must be sent to the lab for culture and sensitivity);
- Diagnosis of pneumonia as demonstrated by two or more signs or symptoms (as defined in section 3.2.2).

Clinical Per Protocol Subjects: Clinically eligible (MITT) subjects meeting the following criteria: *

- Receive at least 80% of study medication, including both active and placebo doses.
- Receive no concomitant systemic antibiotic with activity against pathogens typical of the indication under study.
- Receive an assessment in the appropriate visit window.

Exception: A subject is considered to be in the clinical per protocol population if the subject is included in the MITT population and is a treatment failure who has received at least 3 days of dosing, including active and placebo doses.

Bacteriologic Per Protocol Subjects: Clinical Per Protocol Subjects with a baseline bacterial pathogen.

3.3.2 Subject Disposition, Demographic and Baseline Characteristics (Study A0661103)

Table 15: Subject Evaluation Groups, Number (%) of Subjects (Study A0661103)

Evaluation Group	Azithromycin SR	Levofloxacin	Total
ITT	213 (100.0)	214 (100.0)	427 (100.0)
All Treated	211 (99.1)	212 ^a (99.1)	423 ^a (99.1)
MITT	195 (92.4)	199 (93.9)	394 (93.1)
Excluded Reason ^b	16 (7.6)	13 (6.1)	29 (6.9)
Insufficient Signs and Symptoms of ABS	6 (2.8)	5 (2.4)	11 (2.6)
No X-ray Evidence of Sinusitis	10 (4.7)	8 (3.8)	18 (4.3)
Clinical Per Protocol at TOC	174 (82.5)	189 (89.2)	363 (85.8)
Excluded Reason ^b	37 (17.5)	23 (10.8)	60 (14.2)
Clinically Ineligible	16 (7.3)	13 (6.1)	29 (6.9)
No TOC Visit ^c	19 (9.0)	9 (4.2)	28 (6.6)
Received Other Antibiotics	1 (0.4)	0 (0.0)	1 (0.2)
Improper/Inadequate Dosage	1 (0.5)	1 (0.5)	2 (0.5)
Bacteriologic Per Protocol at TOC	100 (40.5)	127 (50.4)	227 (45.5)

Percentages in the ITT and All Treated populations based on All Randomized; otherwise, percentages based on All Treated. a: Four subjects (2 azithromycin SR [10201009, 10561029], 2 levofloxacin [10671001, 10441009]) were randomized but were withdrawn prior to receiving treatment. b: Excluded Reason: A subject is counted only for the primary reason of exclusion; reasons are listed in hierarchical order. c: Visits that occurred outside pre-defined visit window or did not occur. Source: Sponsor's Table

Statistical Reviewer Comments: *For Study A0661103, 427 subjects were enrolled (ITT population), 423 (99.1%) subjects were treated with either azithromycin SR or clarithromycin ER. Of these treated subjects, 394 (93.1%) were included in the MITT population and 363 (85.8%) were included in the Clinical Per Protocol at TOC. There were no significant disparities with respect to the number of exclusions and reasons pertaining to the exclusion from the MITT and/or Clinical Per Protocol populations at TOC.*

Table 16: Discontinuations from the Study, All Treated Subjects (Study A0661103)

Number (%) of Subjects	Azithromycin SR N=211		Levofloxacin N=212		Total N=423	
Discontinuations						
Subject Died	1	(0.5)	0	(0.0)	1	(0.2)
Related to Study Drug ^a	11	(5.2)	8	(3.8)	19	(4.5)
Adverse Event ^b	0	(0.0)	0	(0.0)	0	(0.0)
Lack of Efficacy	11	(5.2)	8	(3.8)	19	(4.5)
Not Related to Study Drug ^a	19	(9.0)	14	(6.6)	33	(7.8)
Adverse Event ^b	2	(0.9)	5	(2.4)	7	(1.7)
Other ^b	5	(2.4)	2	(0.9)	7	(1.7)
Subject Defaulted ^c	12	(5.7)	7	(3.3)	19	(4.5)
Total	31	(14.7)	22	(10.4)	53	(12.5)

a: Relationship to Study Drug is derived as Related if reason for discontinuation is Insufficient Clinical Response (Lack of Efficacy), or due to a treatment related adverse event; otherwise, Relationship is derived as Not Related. b: Includes subjects who discontinued due to the following reasons: Other, did not meet entrance criteria, or protocol violation. c: Includes subjects who discontinued due to the following reasons: Lost to follow-up or subject no longer willing to participate in study. Source: Sponsor's Table

Statistical Reviewer Comments: *For Study A0661103, of the 427 subjects enrolled (ITT population), 423 subjects were treated with either azithromycin SR or levofloxacin. Of these treated subjects, 370 (87%) completed the study. There were 31 azithromycin SR-treated subjects (15%) discontinued from the study as compared with 22 subjects (10%) in the levofloxacin treatment group. All treated subjects in both treatment groups were analyzed for safety.*

Overall, the two treatment groups had similar baseline characteristics. Of the all treated subjects, approximately 54% were men and 46% were women and a majority of all subjects were white (63%) and were < 65 years of age (77%). Comparing the two treatment groups, there was a higher percentage of males in the azithromycin SR treatment arm (57%) than the levofloxacin treatment group (51%) and a slightly lower mean age (SD) of 48.2 (± 18.1) years of age (range = 18-95) for the azithromycin SR group versus 49.0 (± 18.6) years of age (range = 18-87) for the

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

Protocol Deviations Affecting Primary Analysis: Protocol deviations that may have had the potential to impact the overall study results were recorded in the sponsor's Study A0661103 protocol (Section 11, Item 8). These included deviations from the inclusion/exclusion criteria (29), lack of compliance with the prescribed dosing regimen or administration of study drug treatment (1), and missed TOC visits or visits outside the visit window (27). The protocol deviations were similar across treatment groups, and did not impact the overall conclusions of the study.

3.3.3 Statistical Methodologies (Study A0661103)

Primary Efficacy Assessment:

Clinical efficacy was analyzed in the clinically evaluable population using 95% confidence intervals comparing the proportion of patients with a clinical response of success (sponsor assessed clinical cure at TOC). The confidence intervals on the differences in proportions were computed using the normal approximation to the binomial distribution. The agreed upon noninferiority margin was -10%.

Additional Efficacy Assessments: Additional efficacy analyses included the following secondary endpoints:

- Sponsor assessment of clinical response at the TOC visit for the remaining study populations (all populations except Clinical Per Protocol). Missing values were imputed as failures. Additional sensitivity analyses were conducted on this same efficacy parameter with missing values imputed as cures.
- Sponsor assessment of clinical response by baseline pathogen for the Bacteriologic Per Protocol population at the TOC visit.
- Investigator assessment of clinical response for the Clinical Per Protocol population at the TOC visit.
- Summary of baseline pathogen susceptibilities.

Other Assessments: The effect of prognostic factors on treatment effects for the sponsor assessment of clinical response was examined. Prognostic factors collected included: smoking history, history of allergic rhinitis, and number of previous episodes in the past 12 months. In addition, the sponsor assessment of clinical response was summarized by center, age, race, gender, and geographic area.

3.3.4 Results and Conclusions (Study A0661103)

Results

Table 17: Sponsor Assessment of Clinical Response at TOC, Number (%) of Subjects (Study A0661103)

	Azithromycin SR	Levofloxacin	Difference	95% CI
*Clinical Per Protocol				
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)		
*MITT 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)		
ITT Subjects				
at TOC, (N %)	213	214		
Cure	180 (84.5)	189 (88.3)	-3.8	(-10.3, 2.7)
Failure	33 (15.4)	25 (11.7)		

Source: Sponsor's Table

Statistical Reviewer Comments: *Study A0661103 failed to demonstrate the non-inferiority of azithromycin SR therapy to levofloxacin therapy in the treatment of community acquired pneumonia (CAP) since non-inferiority within a 10% margin could not be demonstrated in both co-primary endpoints. The medical reviewer, Dr. Nasim Moledina, agreed with the subject classifications and efficacy results reported by the sponsor.*

Table 18: Overall Bacteriologic Eradication Rates at TOC, Number (%) in Bacteriologic Per Protocol and Bacteriologic ITT Subjects (Study A001103)

	Azithromycin SR	Levofloxacin	Difference	95% CI ^a
Bacteriologic Per Protocol				
Subjects at TOC, (N %)	91	104		
Cure	82 (90.1)	96 (92.3)	-2.2	(-11.0, 6.2)
Failure	9 (9.9)	8 (7.7)		
Bacteriologic ITT				
Subjects at TOC, (N %)	132	144		
Cure	113 (85.6)	129 (89.6)	-4.0	(-12.2, 4.0)
Failure	19 (14.4)	15 (10.4)		

Eradicated = Eradication + Presumed Eradication, Persistence = Persistence + Presumed Persistence. Due to small sample sizes and proportions close to the boundary exact 95% CIs are computed using StatXact 5. n = Number Eradicated number of pathogens, within the pathogen category, eradicated at the post Baseline visit), N = Number Isolated number of pathogens isolated at Baseline). Note: A subject may have more than one pathogen isolated at Baseline.

Statistical Reviewer Comments: *In the bacteriologic per protocol population, the overall bacteriologic eradication rate was 90.1% for azithromycin SR-treated subjects and 92.3% for levofloxacin-treated subjects at the TOC visit, a difference of -2.2% with 95% CI (-11.0, 6.2).*

Non-inferiority of the azithromycin SR-treatment was not demonstrated in either the bacteriologic Per Protocol or bacteriologic ITT populations.

Table 19: Bacteriologic Eradication Rate (%) at TOC by Baseline Pathogen in Bacteriologic per Protocol Subjects (Study A0661103)

Pathogen	Azithromycin SR			Levofloxacin		
	n/N	%	95% CI	n/N ^a	%	95% CI
<i>H. influenzae</i>	14/15	93.3	(88.1, 99.8)	8/8	100.0	(63.1, 100.0)
<i>S. pneumoniae</i>	12/14	85.7	(57.1, 98.2)	10/12	83.3	(51.6, 97.9)
<i>C. pneumoniae</i>	18/19	94.7	(74.0, 99.9)	21/22	95.5	(77.1, 99.9)
<i>M. pneumoniae</i>	5/7	71.4	(29.0, 96.3)	18/18	100.0	(81.5, 100.0)

Eradication = Eradication + Presumed Eradication, Persistence = Persistence + Presumed Persistence. n = Number Eradicated number of pathogens, within the pathogen category, eradicated at the post Baseline visit. N = Number Isolated number of pathogens isolated at Baseline. Note: A subject may have more than one pathogen isolated at Baseline. Due to small sample sizes and proportions close to the boundary exact 95% CIs are computed in StatXact 5. Source: Sponsor's table

Statistical Reviewer Comments: *The bacteriologic eradication rate of H. influenzae, S. pneumoniae, C. pneumoniae, M. pneumoniae was 93.3%, 85.7%, 94.7% and 71.4%, respectively in the azithromycin SR treatment group; comparable rates for these 4 pathogens were seen in the Levofloxacin group.*

Conclusions

In Study A0661103, the results of the primary efficacy parameter, sponsor assessment of clinical response for the Clinical Per Protocol population at the TOC visit (Days 14-21) are presented in Table 17. Subjects treated with azithromycin SR had a clinical cure rate of 89.7% compared with 93.7% for subjects treated with levofloxacin, a -4.0% difference with 95% CI (-9.7%, 1.7%). The lower limit of this CI was greater than -10%, indicating that azithromycin SR therapy was non-inferior to levofloxacin in the treatment of mild to moderate CAP. In the co-primary MITT population, azithromycin SR-treated subjects had a clinical cure rate of 84.6% compared with 89.9% for subjects treated with levofloxacin, a -5.3% difference with 95% CI (-11.9%, 1.2%). Since the lower limit of this CI was less than -10%, the evidence did not indicate that azithromycin SR therapy was non-inferior to levofloxacin in the treatment of mild to moderate CAP. The 95% CI for the difference in cure rates was also below -10% in the ITT, All Treated, Bacteriologic Per Protocol and Bacteriologic ITT populations. Note that secondary analyses were not powered to demonstrate non-inferiority.

3.4 Evaluation of Safety

All subjects who received at least one dose of study medication were included in the analysis of safety. Adverse events of all causalities and treatment related adverse events that occurred during therapy or up to 35 days after the last dose were summarized by the investigator's assessment of severity (mild, moderate, severe), and coded using COSTART. Adverse events with an unknown relationship to therapy were included with those judged to be treatment related.

3.4.1 Evaluation of Safety (Study A0661078)

Adverse Events: Adverse events (all causality) were reported by 96 of 270 (36%) azithromycin SR-treated subjects and 84 of 268 (31%) of levofloxacin-treated subjects. Overall, 23.3% of subjects in the azithromycin SR treatment group and 15.3% of subjects in the levofloxacin treatment group experienced adverse events considered by the investigator to be treatment related.

Discontinuations and Dose Reductions Due to Adverse Events: The number of study discontinuations due to adverse events was low (<2%) in both treatment groups. Five azithromycin SR-treated subjects (2%) and 3 levofloxacin-treated subjects (1%) discontinued the study due to adverse events. Worsening of acute sinusitis, sinusitis, and sinus pain were the most frequently occurring adverse event that resulted in discontinuation from the study. Two of the 5 azithromycin SR-treated subjects who were discontinued experienced adverse events of worsening of sinusitis. All adverse events that led to discontinuation in levofloxacin treated subjects were treatment related, whereas only 1 azithromycin SR-treated subject had a treatment related adverse event that led to discontinuation.

All-Causality Adverse Events: Azithromycin SR-treated subjects experienced a slightly higher rate of all-causality adverse events (36%) than subjects treated with levofloxacin (31%). The adverse events most frequently reported by azithromycin SR-treated subjects were diarrhea/loose stools (12%), nausea (4%), and abdominal pain (3%). Headache (4%), nausea (4%), and rhinitis (2%) were the events most frequently reported by levofloxacin-treated subjects.

Treatment Related Adverse Events: Treatment related adverse events were those considered by the investigator to be possibly, probably, or definitely related to study medication (or of unknown relation). Twenty-three percent of azithromycin SR-treated subjects experienced treatment-related adverse events, as compared with 15% of levofloxacin-treated subjects. Diarrhea/loose stools (11%), nausea (4%), and abdominal pain (3%) were the events most frequently associated with study therapy for azithromycin SR-treated subjects. The adverse events most frequently associated with levofloxacin therapy were nausea (3%), diarrhea/loose stools (2%), and dizziness (2%). A total of 27 azithromycin SR subjects (10%) had treatment related diarrhea; 16 cases were mild, 8 were moderate and 3 were severe. For 15 of the 27 subjects (56%), diarrhea was limited to Study Days 1 and/or 2.

3.4.2 Evaluation of Safety (Study A0661075)

All subjects who received at least one dose of study medication were included in the analysis of safety. Adverse events of all causalities and treatment related adverse events that occurred during therapy or up to 35 days after the last dose were summarized by the investigator's assessment of severity (mild, moderate, severe), and coded using COSTART. Adverse events with an unknown relationship to therapy were included with those judged to be treatment related.

Adverse Events: Adverse events (all causality) were reported by 116 of 247 (47%) azithromycin SR-treated subjects and 123 of 252 (49%) of clarithromycin ER-treated subjects. Overall, 26% of subjects in the azithromycin SR treatment group and 25% of subjects in the clarithromycin ER treatment group experienced adverse events considered by the investigator to be treatment related.

Discontinuations and Dose Reduction Due to Adverse Events: The number of study discontinuations due to adverse events was less than or equal to 4% in both treatment groups. Nine azithromycin SR-treated subjects (4%) and 8 clarithromycin ER-treated subjects (3%) discontinued due to adverse events. Worsening of pneumonia and the diagnosis of other pulmonary infections were the most frequently occurring adverse events that resulted in discontinuation from the study. Four of the 9 azithromycin SR-treated subjects and 2 of the 8 clarithromycin ER-treated subjects experienced adverse events of worsening of pneumonia that led to discontinuation. There were no temporary dose reductions due to adverse events in this study.

All-Causality Adverse Events: Azithromycin SR-treated subjects experienced a slightly lower incidence of adverse events than subjects treated with clarithromycin ER, 47% of azithromycin SR-treated subjects and 49% of clarithromycin ER-treated subject experienced adverse events. The adverse events most frequently reported by azithromycin SR-treated subjects were diarrhea/loose stools (14%), respiratory disorder (5%), abdominal pain (5%), and headache (5%). Diarrhea/loose stools (8%), respiratory disorder (5%), asthma (5%), headache (4%), and nausea (4%) were the events most frequently reported by clarithromycin ER-treated subjects. The incidence of digestive-related adverse events was higher in azithromycin SR-treated subjects; 22% of azithromycin SR-treated subjects experienced digestive system-related adverse events as compared to 18% clarithromycin ER-treated subjects. The most frequently experienced digestive-related adverse events were diarrhea/loose stools (14%), nausea (4%), and vomiting (2%) in azithromycin SR treated subjects. The incidence of nausea was similar in both treatment groups. A small percentage of azithromycin SR- and clarithromycin ER-treated subjects, approximately 6%, respectively, experienced severe adverse events.

Treatment Related Adverse Events: Treatment related adverse events were those considered by the investigator to be related (or to have an unknown relationship) to study medication. Twenty-six percent of the azithromycin SR-treated subjects experienced treatment-related adverse events, as compared with 25% of clarithromycin ER-treated subjects. Diarrhea/loose stools (12%), abdominal pain (4%), and nausea (4%) were the events most frequently associated with study therapy for azithromycin SR-treated subjects. The adverse events most frequently associated with clarithromycin ER therapy were diarrhea/loose stools (8%), taste perversion (4%), and nausea (3%). A total of 25 azithromycin SR subjects (10%) had treatment related

diarrhea; all of which were mild (16) or moderate (9) in severity. Thirteen of the 25 of subjects (52%) had diarrhea limited to Study Day 1 or the following day. Most treatment related adverse events in both treatment groups were mild to moderate in severity. A small percentage of azithromycin SR- and clarithromycin ER-treated subjects, approximately 1 and 2%, respectively, experienced severe adverse events. Severe treatment related events included: abdominal pain and respiratory disorder (azithromycin SR treatment group); and asthēnia, dry mouth, hyperventilation, taste perversion, and nausea (clarithromycin ER-treatment group).

3.4.3 Evaluation of Safety (Study A0661103)

All subjects who received at least one dose of study medication were included in the analysis of safety. Adverse events of all causalities and treatment related adverse events that occurred during therapy or up to 35 days after the last dose were summarized by the investigator's assessment of severity (mild, moderate, severe), and coded using COSTART. Adverse events with an unknown relationship to therapy were included with those judged to be treatment related.

Adverse Events: Adverse events (all causality) were reported by 84 of 211 (40%) azithromycin SR-treated subjects and 65 of 212 (31%) of levofloxacin-treated subjects. Overall, 20% of subjects in the azithromycin SR treatment group and 12% of subjects in the levofloxacin treatment group experienced adverse events considered by the investigator to be treatment related.

Discontinuations and Dose Reduction Due to Adverse Events: The number of study discontinuations due to adverse events was relatively low in both treatment groups. Three azithromycin SR-treated subjects (1%) and 5 levofloxacin-treated subjects (2%) discontinued from the study due to adverse events. Pneumonia (exacerbation of pneumonia) (1 azithromycin SR subject, 3 levofloxacin subjects) and respiratory disorder (1 azithromycin SR subject, 2 levofloxacin subjects) were the most frequent adverse events that led to discontinuation from the study. All but 2 of the adverse events that led to discontinuation were considered serious (1 azithromycin SR-treated subject, 1 levofloxacin-treated subject).

All-Causality Adverse Events: The number of azithromycin SR-treated subjects who experienced an adverse event was slightly higher than the number of subjects treated with levofloxacin; 40% of azithromycin SR-treated subjects and 31% of levofloxacin-treated subject experienced adverse events. The adverse events most frequently reported by azithromycin SR-treated subjects were diarrhea/loose stools (14%), headache (3%), and vomiting (3%). Diarrhea/loose stools (6%), headache (5%), respiratory disorder (3%), asthēnia (3%), and pneumonia (3%) were the events most frequently reported by levofloxacin-treated subjects. The incidence of digestive-related adverse events was higher in azithromycin SR-treated subjects; 20% of azithromycin SR-treated subjects experienced digestive system-related adverse events as compared to 9% of levofloxacin-treated subjects. The most frequently experienced digestive-related adverse events were diarrhea/loose stools (14%), vomiting (3%), and nausea (2%) in azithromycin SR treated subjects. The incidence of nausea was similar in

both treatment groups. Most adverse events were mild to moderate in severe across treatment groups. A small percentage of azithromycin SR- and levofloxacin-treated subjects, approximately 2% in each treatment group, experienced severe adverse events.

Treatment Related Adverse Events: Treatment related adverse events were those considered by the investigator to be related (or to have an unknown relationship) to study medication. Twenty percent of the azithromycin SR-treated subjects experienced treatment related adverse events, as compared with 12% of levofloxacin-treated subjects. Diarrhea/loose stools (13%), abdominal pain (2%), and vomiting (2%) were the events most frequently associated with study therapy for azithromycin SR-treated subjects. The adverse events most frequently associated with levofloxacin therapy were diarrhea/loose stools (5%), abdominal pain (1%), nausea (1%), and vomiting (4%). A total of 26 azithromycin SR subjects (12%) had treatment related diarrhea; all cases were mild (22) or moderate (4) in severity. Twenty-two of the 26 of subjects (85%) had diarrhea limited to Study Day 1 or 2. Most treatment related adverse events in both treatment groups were mild to moderate in severity.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Findings in Special/Subgroup Populations (Study A0661078 in ABS)

Table 20 Sponsor Assessment of Clinical Response at TOC by Gender, Age, Race and Region in MITT Population (Study A0661078)

	Number Cured / Number of Subjects (%)		
	Azithromycin SR N = 270	Levofloxacin N = 264	TOTAL N = 534
Gender			
MALE	118 / 126 (93.7)	85 / 98 (86.7)	203 / 224 (90.6)
FEMALE	128 / 144 (88.9)	150 / 166 (90.4)	278 / 310 (89.7)
Age (years)			
< 65	233 / 255 (91.4)	222 / 248 (89.5)	455 / 503 (90.5)
65 to 74	9 / 11 (81.8)	8 / 11 (72.7)	17 / 22 (77.3)
>= 75	4 / 4 (100.0)	5 / 5 (100.0)	9 / 9 (100.0)
Race			
WHITE	164 / 180 (91.1)	162 / 178 (91.0)	326 / 358 (91.1)
BLACK	7 / 9 (77.8)	4 / 5 (80.0)	11 / 14 (78.6)
ASIAN	35 / 37 (94.6)	34 / 37 (91.9)	69 / 74 (93.2)
HISPANIC	40 / 44 (90.9)	33 / 42 (78.6)	73 / 86 (84.9)
OTHER	0 / 0	2 / 2 (100.0)	2 / 2 (100.0)
Geographic Region			
North America	78 / 91 (85.7)	72 / 86 (83.7)	150 / 177 (84.7)
Latin America	72 / 80 (90.0)	71 / 79 (89.9)	143 / 159 (89.9)
Europe	61 / 62 (98.4)	59 / 63 (93.7)	120 / 125 (96.0)
India	35 / 37 (94.6)	33 / 36 (91.7)	68 / 73 (93.2)

*North America includes only US and Canada; Source: Sponsor's table

Statistical Reviewer Comments: Overall, in Study A0661078, there were no remarkable differences in clinical cure rates by gender, age, race or region in the MITT population (table 20). By gender, the MITT population cure rates were similar between azithromycin SR-treated subjects and levofloxacin-treated subjects. Azithromycin SR-treated subjects had higher cure rates in males than levofloxacin-treated subjects (93.7% vs. 86.7%). By age, in the MITT population, cure rates were also similar between azithromycin SR-treated subjects and levofloxacin-treated subjects. By race, cure rates for azithromycin SR-treated subjects were highest in the white population (89.5%) and lower in the black and Asian populations (61.5% and 85.3% respectively). In contrast, cure rates in levofloxacin-treated subjects were highest in the black and Asian populations (100.0% and 97.0% respectively) but lower in the white population (84.8%). By region, in the Clinical Per Protocol population Study A0661078, cure rates for azithromycin SR-treated subjects were highest in India (94.6%) and Europe (98.4%), but lower in Latin America (90.0%), and North America (85.7%). A similar trend by region was observed in levofloxacin-treated subjects where cure rates were higher in Europe (93.7%), but lower in Latin America (89.9%), and North America (83.7%). Comparable results were also observed in the Clinical Per Protocol and All Treated populations.

4.2 Findings in Special/Subgroup Populations (Study A0661075 in CAP)

Table 21 Sponsor Assessment of Clinical Response at TOC by Gender, Age, Race and Region in MITT Population (Study A0661075)

Characteristics	Number Cured / Number of Subjects (%)		
	Azithromycin SR N = 226	Clarithromycin ER N = 234	TOTAL N = 460
Gender			
MALE	89 / 102 (87.3)	109 / 126 (86.5)	198 / 228 (86.8)
FEMALE	108 / 124 (87.1)	96 / 108 (88.9)	204 / 232 (87.9)
Age (years)			
16 to 44	91 / 104 (87.5)	111 / 127 (87.4)	202 / 231 (87.4)
45 to 64	82 / 95 (86.3)	75 / 85 (88.2)	157 / 180 (87.2)
65 to 74	17 / 20 (85.0)	18 / 21 (85.7)	35 / 41 (85.4)
>= 75	7 / 7 (100.0)	1 / 1 (100.0)	8 / 8 (100.0)
Race			
WHITE	154 / 172 (89.5)	151 / 176 (85.8)	305 / 348 (87.6)
BLACK	8 / 13 (61.5)	14 / 14 (100.0)	22 / 27 (81.5)
ASIAN	29 / 34 (85.3)	32 / 33 (97.0)	61 / 67 (91.0)
HISPANIC	4 / 5 (80.0)	5 / 8 (62.5)	9 / 13 (69.2)
OTHER	2 / 2 (100.0)	3 / 3 (100.0)	5 / 5 (100.0)
Geographic Region			
North America	98 / 119 (82.4)	108 / 131 (82.4)	206 / 250 (82.4)
Latin America	31 / 32 (96.9)	32 / 33 (97.0)	63 / 65 (96.9)
Europe	41 / 43 (95.3)	36 / 40 (90.0)	77 / 83 (92.8)
India	27 / 32 (84.4)	29 / 30 (96.7)	56 / 62 (90.3)

*North America includes only US and Canada; Source: Sponsor's table

Statistical Reviewer Comments: Overall, in Study A0661075, there were no remarkable differences in clinical cure rates by gender, age, race or region in the MITT population (table 21). The MITT population cure rates, by gender and age, were similar between azithromycin SR-treated subjects and clarithromycin -treated subjects. By race, cure rates for azithromycin SR-treated subjects were highest in the white population (89.5%) and lower in the black and Asian populations (61.5% and 85.3% respectively). In contrast, cure rates in clarithromycin ER-treated subjects were highest in the black and Asian populations (100.0% and 97.0% respectively) but lower in the white population (84.8%). By race, clinical cure rates for azithromycin SR-treated subjects were highest in Latin America (96.9%) and Europe (95.3%), but lower in India (84.4%) and North America (82.4%). Clinical cure rates for clarithromycin-ER treated subjects were higher in India (96.7%).

Table 22 Sponsor Assessment of Clinical Response at TOC, Number (%) of Clinical Per Protocol Subjects, U.S vs. Non-U.S (Study A0661075)

	Azithromycin SR		Comparator		Difference (%)	95% CI
Study A0661075 (U.S*)						
Subjects at TOC, N (%)	98		111			
Cure	88	(89.8)	103	(92.8)	-3.0	(-11.5, 5.0)
Failure	10	(10.2)	8	(7.2)		
Study A0661075 (Non-U.S)						
Subjects at TOC, N (%)	104		98			
Cure	99	(95.2)	95	(96.9)	-1.7	(-8.2, 4.1)
Failure	5	(4.8)	3	(3.1)		

* Denotes U.S. and Canada. 95% exact confidence interval computed Source: FDA Table.

Statistical Reviewer Comments: At the request of the Medical Officer, Dr. Nasim Moledina, analyses were also performed to determine the influence of region (U.S. versus Non U.S.) on non-inferiority of azithromycin SR therapy to comparator therapy in the per-protocol population for both CAP studies. Table 22 shows that in Study A0661075 azithromycin SR therapy was less effective relative to comparator therapy for U.S. sites. A similar finding is also found in Table 24 for Study A0661103. However, this difference in efficacy between treatment therapies across U.S. and non-US sites was not large enough to unduly influence overall findings in the per-protocol population.

4.3 Findings in Special/Subgroup Populations (Study A0661103 in CAP)

Table 23 Sponsor Assessment of Clinical Response at TOC by Gender, Age, Race and Region in MITT Population (Study A0661103)

Number Cured / Number of Subjects (%)		
Azithromycin SR	Levofloxacin	TOTAL
N = 195	N = 199	N = 394

Gender			
MALE	94 / 114 (82.5)	91 / 101 (90.1)	185 / 215 (86.0)
FEMALE	71 / 81 (87.7)	88 / 98 (89.8)	159 / 179 (88.8)
Age (years)			
16 to 44	73 / 87 (83.9)	75 / 84 (89.3)	148 / 171 (86.5)
45 to 64	55 / 63 (87.3)	63 / 70 (90.0)	118 / 133 (88.7)
65 to 74	29 / 35 (82.9)	23 / 26 (88.5)	52 / 61 (85.2)
>= 75	8 / 10 (80.0)	18 / 19 (94.7)	26 / 29 (89.7)
Race			
WHITE	106 / 119 (89.1)	114 / 125 (91.2)	220 / 244 (90.2)
BLACK	4 / 4 (100.0)	1 / 3 (33.3)	5 / 7 (71.4)
ASIAN	31 / 46 (67.4)	40 / 45 (88.9)	71 / 91 (78.0)
HISPANIC	1 / 2 (50.0)	2 / 2 (100.0)	3 / 4 (75.0)
OTHER	23 / 24 (95.8)	22 / 24 (91.7)	45 / 48 (93.8)
Geographic Region			
North America	63 / 77 (81.8)	70 / 82 (85.4)	133 / 159 (83.6)
Latin America	37 / 37 (100.0)	34 / 35 (97.1)	71 / 72 (98.6)
Europe	35 / 38 (92.1)	36 / 38 (94.7)	71 / 76 (93.4)
India	30 / 43 (69.8)	39 / 44 (88.6)	69 / 87 (79.3)

*North America includes only US and Canada; Source: Sponsor's table

Statistical Reviewer Comments: Overall, in Study A0661103, there were no remarkable differences in clinical cure rates by gender, age, race or region in the MITT population. By gender, cure rates were lower in azithromycin SR-treated male subjects than in levofloxacin-treated male subjects, 82.5% (94/114) in azithromycin SR versus 90.1% (91/101) in levofloxacin.. By race, cure rates were largely similar between azithromycin SR-treated subjects and levofloxacin-treated subjects. However, cure rates were lower in azithromycin SR-treated Asian subjects than in levofloxacin-treated Asian subjects (67.4% (31/46) Azithromycin SR versus 88.9% (40/45) levofloxacin). By region, clinical cure rates for both azithromycin SR-treated and levofloxacin-treated subjects were lowest in India and North America. Clinical cure rates were lower in India for azithromycin SR-treated subjects than for levofloxacin-treated subjects (69.8% (30/43) Azithromycin SR versus 88.6% (39/45) Levofloxacin. Comparable results were also observed in the Clinical Per Protocol and All Treated populations.

Table 24 Sponsor Assessment of Clinical Response at TOC, Number (%) of Clinical Per Protocol Subjects, U.S vs. Non-U.S (Study A0661103)

	Azithromycin SR	Comparator	Difference (%)	95% CI
Study A0661103 (U.S)				
Subjects at TOC, N (%)	64	76		
Cure	55 (85.9)	69 (90.8)	-4.9	(-16.7, 6.5)
Failure	9 (14.1)	7 (9.2)		
Study A0661103 (Non-U.S)				
Subjects at TOC, N (%)	110	113		
Cure	101 (91.8)	108 (95.6)	-3.8	(-11.0, 3.0)
Failure	9 (8.2)	5 (4.4)		

* Denotes U.S. and Canada. 95% exact confidence interval computed Source: FDA Table.

Statistical Reviewer Comments: *At the request of the Medical Officer, Dr. Nasim Moledina, analyses were also performed to determine the influence of region (U.S. versus Non U.S.) on non-inferiority of azithromycin SR therapy to comparator therapy in the per-protocol population for both CAP studies. Table 24 shows that in Study A0661103 azithromycin SR therapy was less effective relative to comparator therapy for U.S. sites. (A similar finding is also found in Table 22 for Study A0661075). However, this difference in efficacy between treatment therapies across U.S. and non-US sites was not large enough to unduly influence overall findings in the per-protocol population.*

5. SUMMARY AND CONCLUSIONS

Study A0661078 (ABS)

Study A0661078 demonstrated the non-inferiority of azithromycin SR therapy to levofloxacin therapy in the treatment of acute, uncomplicated bacterial maxillary sinusitis (ABS). According to the FDA analysis, clinical per protocol population (co-primary endpoint) subjects had cure rates at TOC of 94.5% (azithromycin SR) versus 92.9% (levofloxacin), a 1.6% difference with 95% CI (-2.6% to 5.8%). In the clinical MITT population (co-primary endpoint), subjects had cure rates at TOC of 91.1% (azithromycin SR) versus 89.1% (levofloxacin), a 1.9% difference with 95% CI (-3.1%, 7.0%). Secondary analyses were also consistent with the primary analysis and show Azithromycin SR therapy to be noninferior to levofloxacin therapy in the bacteriologic per protocol, bacteriologic ITT, ITT and all treated analysis populations. Similar differences in cure rates between azithromycin SR and clarithromycin therapy were also observed in subjects with documented infections of key CAP pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*. Note that secondary analyses of Study A0661078 were not powered to demonstrate non-inferiority.

Studies A0661075 and A0661103 (CAP)

Study A0661075 demonstrated the non-inferiority of azithromycin SR therapy to clarithromycin therapy in the treatment of mild to moderate CAP. In the clinical per protocol population (co-primary endpoint), subjects had cure rates at TOC of 92.6% (azithromycin SR) versus 94.7% (clarithromycin ER), a -2.2% difference with 95% CI (-6.9% to 2.6%). In the clinical MITT population (co-primary endpoint), subjects had cure rates at TOC of 87.2% (azithromycin SR) versus 87.6% (clarithromycin ER), a -0.4% difference with 95% CI (-6.5% to 5.6%). Analyses of secondary endpoints were also consistent with the primary analysis and show Azithromycin SR therapy to be noninferior to clarithromycin therapy in the bacteriologic per protocol, bacteriologic ITT, ITT and all treated analysis populations. Note that secondary analyses of Study A0661075 were not powered to demonstrate non-inferiority.

Study A0661103 failed to demonstrate the non-inferiority of azithromycin SR therapy to levofloxacin therapy in the treatment of CAP since non-inferiority within a 10% margin could not be demonstrated in the MITT population. In the primary analysis, clinical per-protocol population (co-primary endpoint) subjects had cure rates at TOC of 89.7% (azithromycin SR)

versus 93.7% (levofloxacin), a -4.0% difference with 95% CI (-9.7% to 1.7%). In the MITT population (co-primary endpoint) subjects had cure rates at TOC of 84.6% (azithromycin SR) versus 89.9% (levofloxacin), a -5.3% difference with 95% CI (-11.9% to 1.2%). Analyses of secondary endpoints also failed to provide strong evidence of non-inferiority since the non-inferiority of azithromycin SR therapy could not be shown in the ITT, all treated, bacteriologic per-protocol and bacteriologic MITT populations. Note that secondary analyses of Study A0661103 were not powered to demonstrate non-inferiority.

Although Study A0661103 failed to demonstrate the non-inferiority of azithromycin SR therapy to levofloxacin therapy using a margin of -10% in the MITT population, it did show non-inferiority in the per-protocol population analysis. Additionally, the lower bounds of the 95% CIs for the treatment differences in clinical cure rates were close to -10% in the ITT (-10.3%) and all treated (-10.2%) analysis populations. Across both studies, similar differences in cure rates between azithromycin SR and comparator therapy were observed in subjects with documented infections of key CAP pathogens, such as *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.

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Date: 06/10/2005

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Biometrics Division Director: Dr. Huque

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/s/

Christopher Khedouri
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Scott Komo
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Signing for Dr. Thamban Valappil

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