

CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 50-784 / SE1-004

Drug Name: Zithromax[®] (azithromycin tablets and azithromycin for oral suspension)

Indication(s): Treatment of acute bacterial sinusitis

Applicant: Pfizer

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1. EXECUTIVE SUMMARY

1.1. CONCLUSIONS AND RECOMMENDATIONS

Azithromycin given for three days was statistically noninferior to amoxicillin/clavulanate given for ten day with respect to clinical response at the Test-of-Cure (TOC) assessment based on a 2-sided 97.5% confidence interval and a noninferiority margin of -10%. In addition, the number of patients with a baseline pathogen met the recommendations set forth in the draft guidance for the treatment of acute bacterial sinusitis: The recommended number of patients and the number of patients in the bacteriologic MITT population along with the bacteriologic response rates are the following: at least 25 patients with *Haemophilus influenzae* (32 bacteriologic MITT with a response rate of 78.1%), at least 25 patients with *Streptococcus pneumoniae* (25 bacteriologic MITT with a response rate of 80.8%) and at least 15 patients with *Moraxella catarrhalis* (15 bacteriologic MITT with a response rate of 92.9%).

Both clinical response at TOC in study A0661036 and bacteriologic response at TOC in study A0661057 did not differ by much in the three treatment groups with respect to gender. Similarly, for age, both response rates did not differ by much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine whether either clinical or bacteriologic response rates varied by ethnic group.

1.2. BRIEF OVERVIEW OF CLINICAL STUDIES

This submission contains two studies to demonstrate the efficacy and safety of oral Zithromax[®] (azithromycin) 500 mg/day for 3 days (1.5 g total) for the treatment of acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* in adults.

The first study, A0661036, is a randomized, double-blind, multicenter trial comparing azithromycin (tablets) 500 mg/day for 3 days (1.5 g total), azithromycin (tablets) 500 mg/day, for 6 days (3.0 g total), and oral Augmentin[®] (1500 mg amoxicillin/375 mg clavulanate) 500/125 mg TID for 10 days for the treatment of acute bacterial sinusitis. The primary endpoint in this study is the investigator assessment of the clinical outcome at the End of Study visit.

The second study, A0661057, is an open label, multicenter trial comparing azithromycin (tablets) 500 mg/day for 3 days (1.5 gm total) and azithromycin (tablets) 500 mg/day for 6 days (3.0 g total) for the treatment of acute bacterial sinusitis. Bacteriologic cultures were also taken at baseline. In addition, repeat cultures were recommended only for

clinical failures. The primary endpoint in this study was the sponsor's assessment of bacteriological response at the end of study visit for the bacteriological modified intent-to-treat (MITT) population.

1.3. STATISTICAL ISSUES AND FINDINGS

There were no major statistical issues; however, the only minor issue was that the Sponsor did not consider missing or unknown observations as failures for the MITT analyses for both studies. Because there were few such observations, the results did not change significantly and the revised findings have been provided in §2. In addition, in the double blind trial (A0661036), more patients discontinued from the study in the amoxicillin/clavulanate group than in either of the azithromycin groups. So the lower bound of the confidence interval was larger when missing or unknown observations were considered failures.

STUDY A0661036

For the co-primary endpoint, clinical response at the TOC visit for the MITT population, the response rate was 69.4% (213/307) for the azithromycin 3-day group, 71.2% (218/306) for the azithromycin 6-day group, and 67.1% (206/307) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-6.1% for azi 3-day vs. amox/clav and -4.2% for azi 6-day vs. amox/clav).

Similarly, for the other co-primary endpoint, clinical response at the TOC visit for the CE population, the response rate was 71.7% (195/272) for the azithromycin 3-day group, 71.3% (199/271) for the azithromycin 6-day group, and 71.3% (179/251) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-8.5% for azi 3-day vs. amox/clav and -6.7% for azi 6-day vs. amox/clav).

In the both the MITT and CE populations for the TOC assessment, clinical response did not differ by much in the three treatment groups with respect to gender. Similarly, for age, the clinical response rates did not differ by much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine if the clinical response rates varied by ethnic group.

STUDY A0661057

For the primary endpoint, bacteriologic response at the TOC visit for the bacteriologic MITT population, the response rate was 81.1% (60/74) for the azithromycin 3-day group and 83.7% (77/92) for the azithromycin 6-day group.

This study met the recommendations set forth in the draft guidance for acute bacterial sinusitis with respect to the number of patients with baseline pathogens. The recommended number of patients and the number of bacteriologic MITT patients along with the response rates for the primary endpoint in the azithromycin 3-day group were the following: at least 25 patients with *Haemophilus influenzae* (32 bacteriologic MITT with a response rate of 78.1%), at least 25 patients with *Streptococcus pneumoniae* (25 bacteriologic MITT with a response rate of 80.8%) and at least 15 patients with *Moraxella catarrhalis* (15 bacteriologic MITT with a response rate of 92.9%). In addition, the number of patients with *Staphylococcus aureus* (2 bacteriologic MITT with a response rate of 100.0%) was far less than the recommended 10-20 patients to establish the efficacy of azithromycin in the treatment of patients with acute sinusitis due to *Staphylococcus aureus*. Note that the Sponsor was not pursuing a claim for this pathogen. These results are presented in Table 17.

At the TOC assessment for the Bacteriologic MITT population, bacteriologic response did not differ by much in the three treatment groups with respect to gender. Similarly, for age, the clinical response rates did not differ by much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine if the bacteriologic response rates varied by ethnic group.

2. INTRODUCTION

2.1. OVERVIEW

2.1.1. CLASS AND INDICATION

Zithromax[®] (azithromycin), an azalide, is a member of the macrolide class of antibiotics. Macrolides are primarily bacteriostatic and bind to the 50S subunit of the ribosome, thus inhibiting bacterial 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 (AECB) in adults due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*;
- Community-acquired pneumonia (CAP) in adults and children due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*;

- Pharyngitis/tonsillitis in adults and children caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy;
- Uncomplicated skin and skin structure infections in adults due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*;
- Urethritis and cervicitis in adults due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*;
- Genital ulcer disease in adult men due to *Haemophilus ducreyi* (chancroid).

Zithromax® (azithromycin) 500 mg tablets was approved, under NDA 50-784, in 2002, for a 3-day dosing regimen (500 mg/day) to treat acute bacterial exacerbations of chronic obstructive pulmonary disease (AECB) in adults. This sNDA is intended to provide evidence for the addition of a new indication, acute bacterial sinusitis, using the same dosing regimen of 500 mg once-daily for 3 days in adults. The indicated pathogens for sinusitis, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* are identical to those approved in NDA 50-784 for the treatment of AECB.

In addition to the adult claim, Pfizer is also filing a labeling supplement to NDA 50-710 for use of a 3-day regimen of azithromycin for oral suspension in the treatment of pediatric patients 6 months and older with acute bacterial sinusitis at 10 mg/kg/day. This pediatric claim is based on the safety and efficacy that has been established in the present sNDA in adults with acute bacterial sinusitis and on the fact that comparable 3-day pediatric dosing has been shown to be safe and effective in treating acute otitis media (NDA 50-710/S-009 approved December 14, 2001). The microbiology of acute bacterial sinusitis in children is similar to that seen in adults, with the primary pathogens being *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*. The same pathogens are the most frequent cause of bacterial acute otitis media in children.

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2.2. DATA SOURCES

The studies included in this submission are described in Table 1.

Table 1: Studies included in submission

Study	Design	Sample Size	Electronic Archive
A0661036	<ul style="list-style-type: none"> • 3-arm trial <ul style="list-style-type: none"> ○ Azithromycin 500 mg for 3 days ○ Azithromycin 500 mg/day for 6 days ○ Amoxicillin/Clavulanate TID for 10 days • Multi-center 		\\cdsesub1\N50784\S_004\2003-03-17\clinstat\abs\0661036.pdf
A0661057	<ul style="list-style-type: none"> • Azithromycin 500 mg for 3 days vs. Azithromycin 500 mg/day for 6 days • Open label • Multi-center 		\\cdsesub1\N50784\S_004\2003-03-17\clinstat\abs\0661057.pdf

3. STATISTICAL EVALUATION

3.1. EVALUATION OF EFFICACY

3.1.1. STUDY DESIGN AND ENDPOINTS

STUDY A0661036

This study is a randomized, double-blind, multicenter trial comparing azithromycin (tablets) 500 mg/day for 3 days (1.5 g) (1.5 g total), azithromycin (tablets) 500 mg/day, for 6 days (3.0 g total), and oral Augmentin® (amoxicillin/clavulanate) 500/125 mg TID for 10 days for the treatment of acute bacterial sinusitis. Nine hundred forty-one patients, eighteen years of age or older, with clinically documented acute bacterial infection of the maxillary sinuses were randomized (316 azithromycin 3-day, 311 azithromycin 6-day, and 314 amoxicillin/clavulanate).

Primary Objective:

The primary objective of the study was to evaluate the clinical efficacy of oral azithromycin administered at 500 mg/day for 3 or 6 days with oral amoxicillin/clavulanate administered at 1500 mg amoxicillin/375 clavulanate per day for 10 days in the treatment of patients with acute bacterial sinusitis.

Secondary Objective

The secondary objectives of the study were to compare the safety and toleration of oral azithromycin administered at 500 mg/day for 3 or 6 days with oral amoxicillin/clavulanate administered at 1500 mg amoxicillin/375 clavulanate per day for 10 days.

Primary Efficacy Endpoint:

The primary efficacy endpoint was the clinical response based on the investigators' assessment of the clinical outcome (cure, failure, or unknown) at the End of Study (EOS) visit (Visit 4) in both the clinical MITT and clinically evaluable (CE) populations.

Secondary Efficacy Endpoint:

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

At baseline, the assessment of current signs and symptoms was graded as absent, mild, moderate, or severe. Patients were contacted via telephone on Day 4±1 (Visit 2) to assess their response. If necessary, study drug was discontinued and appropriate non-study antimicrobial therapy was started. These patients were told to return for the final clinical assessments.

Clinical efficacy assessments were done at the EOT visit (Visit 3, Day 10±2) and at the EOS visit (Visit 4, Day 28±4). Safety was also monitored throughout the study.

There were three analysis populations:

- 1) The safety population included all treated patients. Safety assessments included review of adverse events, clinical laboratory data, physical examinations, vital signs and collection of concomitant drug and non-drug treatment data.
- 2) A modified clinical intent-to-treat (MITT) population which included patients who had clinically documented acute bacterial infection of the maxillary sinuses at baseline including purulent nasal discharge and/or facial pain/pressure/tightness or pain that worsens with movement or percussion lasting longer than 7 days but less than 28 days. In addition, the subject received at least one dose of study medication
- 3) A clinically evaluable population which included all MITT patients unless any one or more of the following criteria applied:
 - a) did not meet all inclusion and exclusion criteria,
 - b) received less than 80% of required active study medication doses except if failed and discontinued,
 - c) received more than 120% of required active study medication doses.In addition, patients who met the following criteria were excluded from the clinical evaluable analyses at the relevant visit(s)
 - a) did not meet all inclusion and exclusion criteria
 - b) received less than 80% of required active study medication doses except if failed and discontinued

- c) received more than 120% of required active study medication doses
- d) received concomitant systemic antibiotic for intercurrent illness prior to the evaluation point,
- e) had no visit at an evaluation point unless the subject was previously designated as a treatment failure,
- f) had a visit date outside the visit window, unless the subject was previously designated as a treatment failure,
- g) had no radiology data at Visit 4 unless: 1) the subject was considered a clinical failure prior to Visit 4, or 2) the subject had an x-ray at Visit 3 and was a cure at both Visits 3 and 4.

STUDY A0661057

The second study, A0661057, is a randomized, open label, multicenter trial comparing azithromycin (tablets) 500 mg/day for 3 days (1.5 gm total) and azithromycin (tablets) 500 mg/day for 6 days (3.0 g total) for the treatment of acute bacterial sinusitis in adults. Five hundred thirty-nine patients were randomized to treatment (284 azi 3-day; 255 azi 6-day).

Although the patients were allocated randomly to treatment group, there were more patients enrolled in the azithromycin 3-day treatment group than in the azithromycin 6-day treatment group. This was because amendment 2 of the protocol allowed randomization to continue in only one treatment group after the required number of patients with target pathogens had been reached in the other treatment group.

Bacteriologic cultures were also taken at baseline. In addition, repeat cultures were recommended only for clinical failures. Clinical evaluations were done at the End of Therapy (EOT) visit (Visit 3, Day 7+2) and at the End of Study (EOS) visit (Visit 4, Day 28±4).

Primary Objective:

The primary objective of the study was to evaluate the bacteriologic efficacy of oral azithromycin administered at 500 mg/day for 3 or 6 days in the treatment of patients with acute bacterial sinusitis.

Secondary Objective

The secondary objectives of the study were to compare the clinical efficacy and safety and toleration of azithromycin dosed at 500 mg/day for 3 or 6 days.

Primary Efficacy Endpoint:

The Sponsor's assessment of bacteriological response at the end of study visit for the bacteriological MITT population. Bacteriological response will be categorized as Documented Eradication, Presumed Eradication, Documented Persistence, Presumed Persistence, Superinfection with the first two categories being classified as Successes and the remainder Failures.

Secondary Efficacy Endpoints:

- Investigator's assessment of clinical response (clinical MITT and clinical evaluable populations) at the EOT and EOS visits, the sponsor's assessment of bacteriological response (bacteriological MITT and bacteriological evaluable populations) at the EOT visit and at the EOS visit (bacteriological evaluable population).

Clinical response at the end of therapy and the end of study were summarized for both the clinically evaluable and clinical MITT populations. In addition, bacteriological eradication rates were summarized for the bacteriologic evaluable and bacteriological MITT populations. Safety was monitored throughout the study.

The bacteriological MITT population was defined as a subset of the patients in the clinical MITT population with a positive baseline culture for *H. influenzae*, *S. pneumoniae*, *M. catarrhalis* or *S. aureus* (when isolated in pure culture with a colony count of $>10^4$ CFU/mL).

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

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

3.1.2. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

STUDY A0661036

Nine hundred forty-one patients (316 azithromycin [azi] 3-day; 311 azi 6-day; 314 amoxicillin/clavulanate [amox/clav]) were randomized to treatment. Nine hundred thirty-six patients (312 azi 3-day; 311 azi 6-day; and 313 amox/clav) were treated with study drug. Of the 936 treated patients, 297 patients (95.2%) in the azi 3-day group, 292 patients (93.9%) in the azi 6-day group, and 282 patients (90.1%) in the amox/clav group completed treatment. Table 2 presents the number of patients evaluable for efficacy and safety analyses. In addition, Table 3 provides the reasons for exclusion for this study.

There were more patients who discontinued study in the amoxicillin/clavulanate treatment group (31 patients) than in either of the two azithromycin treatment groups (15 patients in the azi 3-day group and 19 patients in the azi 6-day group). The most common reason for discontinuation due to a treatment emergent adverse event was diarrhea and occurred at a higher rate in the amoxicillin/clavulanate group.

One of the forty-seven sites was considered ineligible by the FDA. This resulted in five azi 3-day, five azi 6-day, and six amox/clav patients being excluded from the efficacy analyses. This results in the difference between the Treated patients and the clinical MITT patients.

Table 2: Study Populations for Study A0661036

	Subject Evaluation Groups		
	Azi 3-Day	Azi 6-Day	Amox/clav
	N (%)	N (%)	N (%)
Randomized	316	311	314
Treated	312	311	313
Completed Study	297 (95.2)	292 (93.9)	282 (90.1)
Discontinued Study	15 (4.8)	19 (6.1)	31 (9.9)
Analyzed for Efficacy			
Clinical MITT	307 (98.4)	306 (98.4)	307 (98.1)
Evaluable at EOT	303	298	291
Evaluable at EOS	298	294	288
Clinical Evaluable			
EOT	269 (86.2)	271 (87.1)	259 (82.7)
EOS	272 (87.2)	271 (87.1)	251 (80.2)
Analyzed for Safety			
Adverse Events	312 (100.0)	311 (100.0)	313 (100.0)
Laboratory Data	308 (98.7)	300 (96.5)	296 (94.6)

Table 3: Reasons for Exclusions for Study A0661036

Exclusion Reason	Azi 3-day	Azi 6-day	Amox/Clav
Excluded From Clinical MITT Population	9	5	7
Subject was not randomized	0	0	0
Subject had incorrect diagnosis	0	0	0
Subject did not take study medication	4	0	1
Site considered ineligible by FDA	5	5	6
Excluded From Clinical Evaluable Population			
Visit 3	42	35	50
Subject is not in clinical MITT population	9	5	7
Subject did not meet all inclusion and exclusion criteria	23	17	24
Subject received less than 80% of required active study medication doses	1	3	16
Subject received more than 120% of required active study medication doses	0	0	2
Subject received concomitant systemic antibiotic for intercurrent illness	1	0	0
No clinical response at visit 3	4	8	16
Clinical response outside 8-15 days	12	11	5
Visit 4	40	35	59
Subject is not in clinical MITT population	9	5	7
Subject did not meet all inclusion and exclusion criteria	23	17	24
Subject received less than 80% of required active study medication doses	1	3	16
Subject received more than 120% of required active study medication doses	0	0	2
Subject received concomitant systemic antibiotic for intercurrent illness	2	2	3
No clinical response at visit 4	9	12	19
Clinical response outside 22-36 days	3	4	2
X-ray not done and not failure#	9	15	24

*: Patients may be excluded for more than one reason.

#: Subject not excluded from clinical evaluable population at visit 4 if x-ray done at visit 3 instead of visit 4 and investigator clinical response was cure at both visits.

STUDY A0661057

Five hundred thirty-nine patients were randomized to treatment (284 azi 3-day; and 255 azi 6-day). Five hundred thirty-six patients (281 azi 3-day and 255 azi 6-day) were treated with study drug and were evaluable for safety analyses. Three patients who were randomized to the azi 3-day treatment group did not receive study treatment and were not included in the efficacy and safety analyses. These patients did not receive study drug for the following reasons: Subject No. 001093—otolaryngologist refused to perform TAP; Subject No. 001641—had uncontrolled hyperglycemia; Subject No. 001124—sub-investigator disagreed with radiologist’s interpretation of baseline sinus radiograph. Of

the 536 treated patients, 273 patients (97.2%) in the azi 3-day group and 249 patients (97.6%) in the azi 6-day group completed the study. Table 4 presents the number of patients evaluable for efficacy and safety analyses. In addition, Table 5 provides the reasons for exclusion for this study.

There were more patients enrolled in the azithromycin 3-day treatment group than in the azithromycin 6-day treatment group. This was because amendment 2 of the protocol allowed randomization to continue in only one treatment group after the required number of patients with target pathogens had been reached in the other treatment group.

Table 4: Study Populations for Study A0661057

	Subject Evaluation Groups	
	Azi 3-Day	Azi 6-Day
	N (%)	N (%)
Randomized	284	255
Treated	281	255
Completed Study	273 (97.2)	249 (97.6)
Discontinued Study	8 (2.8)	6 (2.4)
Analyzed for Efficacy		
Clinical MITT	281 (100.0)	254 (99.6)
Clinical Evaluable		
Visit 3	257 (91.5)	233 (91.4)
Visit 4	254 (90.4)	232 (90.2)
Bacteriological MITT	74 (26.3)	92 (36.1)
Bacteriological Evaluable		
Visit 3	71 (25.3)	88 (34.5)
Visit 4	68 (24.2)	84 (32.9)
Analyzed for Safety		
Adverse Events	281 (100.0)	255 (100.0)
Laboratory Data	281 (100.0)	255 (100.0)

Table 5: Reasons for Exclusion

Exclusion Reason	Azi 3-day	Azi 6-day
Excluded From Clinical MITT Population	0	1
Subject had incomplete-diagnosis criteria	0	1
Excluded From Clinical Evaluable Population		
EOT	24	22
Subject is not in clinical MITT population	0	1
Subject did not meet all inclusion and exclusion criteria	13	12
Subject received less than 80% of required active study medication doses	2	2
Subject received more than 120% of required active study medication doses	0	0
Subject received concomitant systemic antibiotic	0	0
No clinical response at EOT	2	0
Clinical response outside 6-12 days	10	6
Antibiotic taken prior to baseline but exclusion #4=No	0	1
EOS	27	25
Subject is not in clinical MITT population	0	1
Subject did not meet all inclusion/exclusion criteria	13	12
Subject received < 80% of required study doses (unless failure)	2	2
Subject received > 120% of required study doses	0	0
No clinical response at visit 4	5	6
Subject received concomitant systemic antibiotic	1	0
Clinical response outside 22-36 days (unless failure)	6	4
Antibiotic taken prior to baseline, but exclusion #4 = No	0	1
Baseline X-ray negative, but inclusion #4 = Yes	1	0
Signs/Symptoms not present at baseline for >7 days, but inclusion #3 = Yes	0	1
X-ray not done and not failure#	7	9

*: Patients may be excluded for more than one reason.

#: Subject not excluded from clinical evaluable population at visit 4 if x-ray done at visit 3 instead of visit 4 and investigator clinical response was cure at both visits.

3.1.3. STATISTICAL METHODOLOGIES

STUDY A0661036

Clinical efficacy was analyzed for both the clinical MITT and clinically evaluable populations. This was accomplished using 97.5% confidence intervals comparing the proportion of patients with a clinical response of success (cure +improvement at EOT [Visit 3], cure at EOS [Visit 4]) for each of the two azithromycin treatment groups with the amoxicillin/clavulanate group. The confidence intervals on the differences in proportions were computed using the normal approximation to the binomial distribution.

The co-primary efficacy analysis was the 97.5% confidence interval of the difference in clinical response between each of the azithromycin treatment groups and the

amoxicillin/clavulanate group (i.e., azithromycin – amoxicillin/clavulanate) at the end of study (Visit 4) for the MITT and clinically evaluable population. The agreed upon noninferiority margin was –10%.

Secondary efficacy analyses include computation of the 97.5% confidence intervals on the difference in proportions of patients with a successful clinical response for the MITT population at the end of study (Visit 4) and for the MITT and clinically evaluable populations at the end of therapy (Visit 3). In addition, the distribution of completion of therapy based on number of days of active therapy was determined and each azithromycin treatment group was compared with amoxicillin/clavulanate using a Chi-square statistic. A subject was considered as having completed therapy if he or she received at least 3 days of azithromycin 3-Day, 6 days of azithromycin 6-Day or 10 days of amoxicillin/clavulanate.

STUDY A0661057

The number and percentage of patients classified as Success (cure + improvement at EOT [Visit 3], cure at EOS [Visit 4]) and Failure are displayed and a 95% confidence interval of the success rate was computed for each treatment group separately using the normal approximation to the binomial distribution. Bacteriological eradication rates (documented eradication + presumed eradication) and 95% confidence intervals were calculated by treatment group for all bacteriological MITT and evaluable populations. No statistical comparisons or inferences between the treatment groups were made. However, Dr. John Alexander, the clinical team leader, requested that the 95% confidence intervals be calculated for the difference in response rates between the azithromycin groups. The results are presented in §3.1.4.

3.1.4. RESULTS AND CONCLUSIONS

STUDY A0661036

The clinical reviewer, Dr. Nasim Moledina, was given a random sample of 93 patients (31 patients per treatment group) and agreed with the eligibility of patients and the classification of outcomes. Given this, the following results are those presented by the sponsor.

Nine hundred twenty patients (307 azi 3-day; 306 azi 6-day; 307 amox/clav) were included in the clinical MITT analyses. The lower bound of the 2-sided 97.5% confidence intervals for the difference between the clinical response rates for both of the azithromycin treatment groups (azi 3-day; azi 6-day) versus the amoxicillin/clavulanate was greater than the noninferiority margin of -10% for both the EOT (Visit 3) and EOS (Visit 4) assessment. The clinical response rates at the EOT (secondary endpoint) and EOS (primary endpoint) time points are shown in the following table.

Table 6: Clinical Response Rates (MITT patients classified as Unknown are excluded)

Analysis Population	Time	N (%)			97.5 % CI	
		Azi 3-Day	Azi 6-Day	A/C	Azi 3D – A/C	Azi 6D – A/C
MITT	EOT	268/303 (88.4)	265/298 (88.9)	248/291 (85.2)	(-3.0, 9.4)	(-2.5, 9.9)
	EOS	213/298 (71.5)	218/294 (74.1)	206/288 (71.5)	(-8.4, 8.3)	(-5.6, 10.9)
CE	EOT	239/269 (88.8)	242/271(89.3)	220/259(84.9)	(-2.7, 10.5)	(-2.2, 10.9)
	EOS	195/272(71.7)	199/271(73.4)	179/251(71.3)	(-8.5, 9.2)	(-6.7, 10.9)

EOT Success = Cure + Improvement; EOS Success = Cure

The above table was submitted by the sponsor. However, we have an issue with the entries for the MITT population. Patients who were classified as Unknowns were excluded from the calculation of response rates for that visit rather than including them as failures. We would prefer to use the results that the sponsor submitted as a sensitivity analysis where Unknowns or missing observations were classified as failures rather than excluding them for inference purposes. Treating missing or unknown observations as failures would adhere to the ITT principle and also follow the draft guidance for acute bacterial sinusitis. The effect of this change does not substantially change the results of the analyses. In fact, because the amoxicillin/clavulanate arm has more Unknowns than their either of the azithromycin arms, it's response rate is decreased more than the azithromycin arms so the lower bound of the confidence interval is farther away from the noninferiority margin. The revised results are presented below:

For the co-primary endpoint, clinical response at the EOS visit for the MITT population, the response rate was 69.4% (213/307) for the azithromycin 3-day group, 71.2% (218/306) for the azithromycin 6-day group, and 67.1% (206/307) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-6.1% for azi 3-day vs. amox/clav and -4.2% for azi 6-day vs. amox/clav).

Similarly, for the other co-primary endpoint, clinical response at the EOS visit for the CE population, the response rate was 71.7% (195/272) for the azithromycin 3-day group, 71.3% (199/271) for the azithromycin 6-day group, and 71.3% (179/251) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-8.5% for azi 3-day vs. amox/clav and -6.7% for azi 6-day vs. amox/clav).

For the secondary endpoint, clinical response at the EOT visit for the MITT population, the response rate was 87.3% (268/307) for the azithromycin 3-day group, 86.6% (265/306) for the azithromycin 6-day group, and 80.8% (248/307) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for

both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-0.1% for azi 3-day vs. amox/clav and -0.9% for azi 6-day vs. amox/clav).

Similarly, for the other secondary endpoint, clinical response at the EOT visit for the CE population, the response rate was 88.8 % (239/269) for the azithromycin 3-day group, 89.3% (242/271) for the azithromycin 6-day group, and 84.9% (220/259) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-2.7% for azi 3-day vs. amox/clav and -2.2% for azi 6-day vs. amox/clav).

Table 7: Revised Clinical Response Rates in the MITT Population

Time	#Patients w/o a clinical response or classified as Unknown			N (%)			97.5 % CI (%)	
	Azi 3-Day	Azi 6-Day	A/C	Azi 3-Day	Azi 6-Day	A/C	Azi 3D – A/C	Azi 6D – A/C
EOT	4	8	16	268/307 (87.3)	265/306 (86.6)	248/307 (80.8)	(-0.1, 13.2)	(-0.9, 12.6)
EOS	9	12	19	213/307 (69.4)	218/306 (71.2)	206/307 (67.1)	(-6.1, 10.7)	(-4.2, 12.5)

EOT Success = Cure + Improvement; EOS Success = Cure

STUDY A0661057

The clinical reviewer, Dr. Nasim Moledina, was given a random sample of 60 patients (30 patients per treatment group) and agreed with the eligibility of patients and the classification of outcomes. Given this, the following results are those presented by the sponsor.

DSI conducted an investigation at one of the sites and found some potential problems for twelve patients. However, the clinical reviewer checked the flagged patients and concluded that the discrepancies were minor and did not invalidate the results for these patients.

As in Study A0661036, we would prefer that missing or unknown observations be classified as failures for inference purposes in the ITT analyses rather than excluding them. Treating missing or unknown observations as failures would adhere to the ITT principle and also follow the draft guidance for acute bacterial sinusitis. The results in the following tables reflect this change however this revision does not substantially change the results of the analyses. In addition, I have also constructed 95% confidence intervals for the difference in response rates between the two treatment groups in Table 8 and Table 10 as requested by the Clinical Team Leader, Dr. John Alexander.

For the primary endpoint, bacteriologic response at the EOS visit for the bacteriologic MITT population, the response rate was 81.1% (60/74) for the azithromycin 3-day group and 83.7% (77/92) for the azithromycin 6-day group. The 95% confidence interval of the difference in response rates for the azithromycin groups (3-day – 6-day) was (-16.0%, 8.0%).

The following table presents the results from the primary endpoint, response at the EOS assessment, as well as the secondary endpoint, bacteriologic response at the EOT assessment for the bacteriologic MITT population.

Table 8: Overall Bacteriologic Response in the Bacteriologic MITT Population (Unknowns classified as Failures))

Time	N (%)		95 % CI (%)
	Azi 3-Day	Azi 6-Day	Azi 6-Day – Azi 3-Day
EOT	66/74 (89.2)	88/92 (95.7)	(-1.6, 16.1)
EOS	60/74 (81.1)	77/92 (83.7)	(-16.0, 8.0)

Note: Success = Documented Eradication + Presumed Eradication

In addition, by-pathogen analyses are also presented for the primary endpoint. This study had the recommended number of patients with baseline pathogens set for in the draft guidance for acute bacterial sinusitis that there be a sufficient number of patients with clinical and microbial outcomes: for the azithromycin 3-day group. The recommended number and the number of bacteriologic MITT patients along with the bacteriologic response rates follow: at least 25 patients with *Haemophilus influenzae* (32 bacteriologic MITT with an response rate of 78.1%), at least 25 patients with *Streptococcus pneumoniae* (25 bacteriologic MITT with a response rate of 80.8%) and at least 15 patients with *Moraxella catarrhalis* (15 bacteriologic MITT with a response rate of 92.9%). In addition, the number of patients with *Staphylococcus aureus* (2 bacteriologic MITT with a response rate of 100.0%) was far less than the recommended number of 10-20 to establish the efficacy of azithromycin in the treatment of patients with acute sinusitis due to *Staphylococcus aureus*. Note that the sponsor was not pursuing a claim for this pathogen. These results of bacteriologic response by baseline pathogen for the MITT population are presented in Table 9. Note that the exact 95% confidence intervals for the response rates are relatively wide because of the small sample sizes.

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Table 9: Bacteriologic response by Baseline Pathogen in the Bacteriologic MITT Population (Unknowns are Failures)

Baseline Pathogen	Bacteriologic Response					
	Azi 3-day			Azi 6-day		
	n/N	%	95% CI (%)	n/N	%	95% CI (%)
EOT						
<i>H. influenzae</i>	28/32	87.5	(76.0, 96.5)	27/28	96.4	(81.6, 99.9)
<i>S. pneumoniae</i>	23/26	88.5	(69.8, 97.6)	39/42	92.9	(80.5, 98.5)
<i>M. catarrhalis</i>	14/15	93.3	(68.0, 99.8)	19/19	100.0	(82.4, 100.0)
<i>S. aureus</i>	2/2	100.0	(15.8, 100.0)	6/6	100.0	(54.1, 100.0)
EOS						
<i>H. influenzae</i>	25/32	78.1	(60.0, 90.7)	24/28	85.7	(67.3, 96.0)
<i>S. pneumoniae</i>	21/26	80.8	(60.6, 93.4)	34/42	81.0	(65.9, 91.4)
<i>M. catarrhalis</i>	13/15	92.9	(59.5, 98.3)	15/19	79.0	(54.4, 94.0)
<i>S. aureus</i>	2/2	100.0	(15.8, 100.0)	6/6	100.0	(54.1, 100.0)

Success = Documented Eradication + Presumed Eradication

Because of the small sample sizes and success rates being close to the boundary, exact confidence intervals are reported

The results for the secondary endpoints are presented below in Table 10 - Table 13

Table 10: Clinical Response Rates (MITT Patients Classified as Unknowns are Failures)

Analysis Population	Time	N (%)		95 % CI (%)
		Azi 3-Day	Azi 6-Day	Azi 6-Day – Azi 3-Day
MITT	EOT	248/281 (88.3)	240/254 (94.5)	(1.5, 11.1)
	EOS	214/281 (76.2)	210/254 (82.7)	(-0.4, 13.3)
CE	EOT	228/257 (88.7)	220/233 (94.4)	(0.8, 10.8)
	EOS	195/254 (76.8)	193/230 (83.9)	(0.03, 14.2)

EOT Success = Cure + Improvement; EOS Success = Cure

Table 11: Clinical Response by Baseline Pathogen in Bacteriological MITT Population (Unknowns classified as Failures)

Baseline Pathogen	Clinical Response n/N (%)	
	Azi 3-Day	Azi 6-Day
EOT		
<i>H. influenzae</i>	28/32 (87.5)	27/28 (96.4)
<i>S. pneumoniae</i>	23/26 (88.5)	39/42 (92.9)
<i>M. catarrhalis</i>	14/15 (93.3)	19/19 (100.0)
<i>S. aureus</i>	2/2 (100.0)	6/6 (100.0)
EOS		
<i>H. influenzae</i>	24/32 (75.0)	24/28 (85.7)
<i>S. pneumoniae</i>	21/26 (80.8)	34/42 (81.0)
<i>M. catarrhalis</i>	13/15 (92.9)	15/19 (78.9)
<i>S. aureus</i>	2/2 (100.0)	6/6 (100.0)

EOT Success = Cure + Improvement; EOS Success = Cure

Table 12: Overall Bacteriological Response in the Bacteriologic Evaluable Population

Time	N (%)		95 % CI (%)
	Azi 3-Day	Azi 6-Day	Azi 6-Day – Azi 3-Day
EOT	63/71 (88.7)	84/88 (95.5)	(-1.6, 16.7)
EOS	56/68 (82.4)	69/84 (82.1)	(-12.4, 12.6)

Table 13: Bacteriologic response by Baseline Pathogen for Bacteriologic Evaluable Population

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

3.2. EVALUATION OF SAFETY

The Sponsor evaluated safety based on the occurrence of adverse events. No statistical analyses were performed

STUDY A0661036

The incidence of treatment emergent adverse events (TEAEs), irrespective of relationship to study drug, was higher in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups (51.0% azi 3-day patients, 53.7% azi 6-day patients, and 67.1% amox/clav patients). The incidences of both diarrhea (17.3% azi 3-day; 23.2% azi 6-day; 33.2% amox/clav) and nausea (7.7% azi 3-day; 9.3% azi 6-day; 12.8% amox/clav) were higher in the amoxicillin/clavulanate treatment group than in the azithromycin treatment groups.

Diarrhea was the most frequently occurring adverse event across all treatment groups and was the only TEAE that occurred at a 5% or higher difference in rate between the azithromycin treatment groups and the amoxicillin/clavulanate treatment group. The incidences of diarrhea, nausea, and abdominal pain were slightly higher in the azithromycin 6-day treatment group compared with the azithromycin 3-day treatment group.

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

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

STUDY A0661057

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

Six patients (3 azi 3-day and 3 azi 6-day) discontinued (study drug and/or study) due to adverse events. Of these 6 patients, 2 patients in the azi 3-day group and all 3 patients in the azi 6-day group discontinued study drug. Two patients (one subject in each treatment group) experienced serious adverse events. The first subject (azi 3-day) experienced suicidal ideation on Day 6. The second subject (azi 6-day) was hospitalized for

septicemia on Day 26. Both these events resolved and the investigator considered these events to be unrelated to study drug.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. GENDER, RACE, AND AGE

The sponsor did not submit any analyses that examined any gender, race or age differences in the primary endpoint. The reviewer has calculated the following results based on the sponsor's MITT population for Study A0661036 and the Bacteriological MITT for Study A0661057.

STUDY A0661036

In the both the MITT and CE populations for the EOS assessment, clinical response did not differ much in the three treatment groups with respect to gender. Similarly, for age, for the clinical response rates did not differ much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine if the clinical response rates varied by ethnic group.

Table 14: Clinical Response Rates for the MITT Population for the EOS Assessment

Subgroup	n/N (%)		
	Azi 3-Day	Azi 6-Day	A/C
Gender			
Female	128/186 (68.8)	128/187 (68.4)	124/179 (69.3)
Male	85/121 (70.25)	90/119 (75.6)	82/128 (64.1)
Age			
18-44	142/200 (71.0)	143/196 (73.0)	121/186 (65.0)
45-64	60/88 (68.2)	59/87 (67.8)	72/102 (70.6)
>=65	11/19 (57.9)	16/23 (69.6)	13/19 (68.4)
Ethnicity			
Asian	1/2 (50.0)	8/9 (88.9)	1/3 (33.3)
Black	8/15 (53.3)	10/16 (62.5)	10/14 (71.4)
Hispanic	9/13 (69.2)	14/21 (66.7)	7/7 (100.0)
Other	3/6 (50.0)	1/2 (50.0)	2/3 (66.7)
White	192/271 (70.8)	185/258 (71.7)	186/273 (68.1)

Table 15: Clinical Response Rates for the CE population at the EOS Assessment

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

STUDY A0661057

At the EOS assessment for the Bacteriologic MITT population, bacteriologic response did not differ by much in the three treatment groups with respect to gender. Similarly, for age, the bacteriologic response rates did not differ by much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine if the bacteriologic response rates varied by ethnic group.

Table 16: Subgroup analyses of the Overall Bacteriologic Response in the Bacteriologic MITT Population (Unknowns classified as Failures)

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

4.2. OTHER SPECIAL/SUBGROUP POPULATIONS

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1. STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

There were no major statistical issues; the only issue was that the sponsor did not consider missing or unknown observations as failure for the MITT analyses. Because there were few such observations, the results did not change significantly and the revised findings are provided.

STUDY A0661036

For the co-primary endpoint, clinical response at the EOS visit for the MITT population, the response rate was 69.4% (213/307) for the azithromycin 3-day group, 71.2% (218/306) for the azithromycin 6-day group, and 67.1% (206/307) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-6.1% for azi 3-day vs. amox/clav and -4.2% for azi 6-day vs. amox/clav).

Similarly, for the other co-primary endpoint, clinical response at the EOS visit for the CE population, the response rate was 71.7% (195/272) for the azithromycin 3-day group, 71.3% (199/271) for the azithromycin 6-day group, and 71.3% (179/251) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 95% confidence interval was larger than the agreed upon noninferiority margin of -10% (-8.5% for azi 3-day vs. amox/clav and -6.7% for azi 6-day vs. amox/clav).

For the secondary endpoint, clinical response at the EOT visit for the MITT population, the response rate was 87.3% (268/307) for the azithromycin 3-day group, 86.6% (265/306) for the azithromycin 6-day group, and 80.8% (248/307) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-0.1% for azi 3-day vs. amox/clav and -0.9% for azi 6-day vs. amox/clav).

Similarly, for the other secondary endpoint, clinical response at the EOT visit for the CE population, the response rate was 88.8% (239/269) for the azithromycin 3-day group, 89.3% (242/271) for the azithromycin 6-day group, and 84.9% (220/259) for the amoxicillin/clavulanate group. The lower bound of difference between response rates for both of the azithromycin groups compared to the amoxicillin/clavulanate group for the 2-sided 97.5% confidence interval was larger than the agreed upon noninferiority margin of -10% (-2.7% for azi 3-day vs. amox/clav and -2.2% for azi 6-day vs. amox/clav).

In the both the MITT and CE populations for the EOS assessment, clinical response did not differ by much in the three treatment groups with respect to gender. Similarly, for age, the clinical response rates did not differ by much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine if the clinical response rates varied by ethnic group.

STUDY A0661057

For the primary endpoint, bacteriologic response at the EOS visit for the bacteriologic MITT population, the response rate was 81.1% (60/74) for the azithromycin 3-day group and 83.7% (77/92) for the azithromycin 6-day group. The 95% confidence interval of the difference in response rates for the azithromycin groups (3-day – 6-day) was (-16.0%, 8.0%).

This study met the recommendations set forth in the draft guidance for acute bacterial sinusitis with respect to the number of patients with baseline pathogens. The per-pathogen response rates for the primary endpoint, bacteriologic response in the bacteriologic MITT population were all greater than 75%. The recommended number of patients and the number of bacteriologic MITT patients in the azithromycin 3-day group along with the bacteriologic response rates for the primary endpoint are as follows: at least 25 patients with *Haemophilus influenzae* (32 bacteriologic MITT with a response rate of 78.1%), at least 25 patients with *Streptococcus pneumoniae* (25 bacteriologic MITT with a response rate of 80.8%) and at least 15 patients with *Moraxella catarrhalis* (15 bacteriologic MITT with a response rate of 92.9%). Note that the number of patients with *Staphylococcus aureus* at baseline (2 bacteriologic MITT with a response rate of 100.0%) was far less than the recommended number of 10-20 patients to establish the efficacy of azithromycin in the treatment of patients with acute sinusitis due to *Staphylococcus aureus*. Note that the Sponsor was not pursuing a claim for this pathogen. These results, along with those for the azithromycin 6-day group are presented in Table 17. Note that the exact 95% confidence intervals for the response rates are relatively wide because of the small sample sizes.

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Table 17: Bacteriologic response by baseline pathogen in the bacteriologic MITT population

Baseline Pathogen	Bacteriologic Response					
	Azi 3-day			Azi 6-day		
	n/N	%	95% CI (%)	n/N	%	95% CI (%)
EOT						
<i>H. influenzae</i>	28/32	87.5	(76.0, 96.5)	27/28	96.4	(81.6, 99.9)
<i>S. pneumoniae</i>	23/26	88.5	(69.8, 97.6)	39/42	92.9	(80.5, 98.5)
<i>M. catarrhalis</i>	14/15	93.3	(68.0, 99.8)	19/19	100.0	(82.4, 100.0)
<i>S. aureus</i>	2/2	100.0	(15.8, 100.0)	6/6	100.0	(54.1, 100.0)
EOS						
<i>H. influenzae</i>	25/32	78.1	(60.0, 90.7)	24/28	85.7	(67.3, 96.0)
<i>S. pneumoniae</i>	21/26	80.8	(60.6, 93.4)	34/42	81.0	(65.9, 91.4)
<i>M. catarrhalis</i>	13/15	92.9	(59.5, 98.3)	15/19	79.0	(54.4, 94.0)
<i>S. aureus</i>	2/2	100.0	(15.8, 100.0)	6/6	100.0	(54.1, 100.0)

Exact 95% confidence intervals are presented

At the EOS assessment in the Bacteriologic MITT population, bacteriologic response did not differ by much in the three treatment groups with respect to gender. Similarly, for age, the bacteriologic response rates did not differ by much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine if the bacteriologic response rates varied by ethnic group.

5.2. CONCLUSIONS AND RECOMMENDATIONS

Azithromycin given for three days was statistically noninferior to amoxicillin/clavulanate given for ten day with respect to clinical response at EOS based on a noninferiority margin of -10%. In addition, the number of patients with a baseline pathogen met the recommendations set forth in the draft guidance for the treatment of acute bacterial sinusitis: The recommended number of patients and the number of bacteriologic MITT patients along with their response rates in the azithromycin 3-day group for each baseline pathogen are at follows: at least 25 patients with *Haemophilus influenzae* (32 bacteriologic MITT with a response rate of 78.1%), at least 25 patients with *Streptococcus pneumoniae* (25 bacteriologic MITT with a response rate of 80.8%) and at least 15 patients with *Moraxella catarrhalis* (15 bacteriologic MITT with a response rate of 92.9%). Note that the number of patients with *Staphylococcus aureus* (2 bacteriologic MITT with a response rate of 100.0%) was far less than the recommended number of 10-20 patients to establish the efficacy of azithromycin in the treatment of patients with acute sinusitis due to *Staphylococcus aureus*. Note that the Sponsor was not pursuing a claim for this pathogen.

Both clinical response at EOS in study A0661036 and bacteriologic response at EOS in study A0661057 did not differ by much in the three treatment groups with respect to gender. Similarly, for age, both response rates did not differ by much for the 18-44 and 45-64 groups. It was difficult to make a judgment about the 65+ group because there were very few patients in this group. Finally, because most of the patients were Caucasian, it was not possible to determine whether either clinical or bacteriologic response rates varied by ethnic group.

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