

azithromycin ER, was assigned a cure as a result of spontaneous resolution of the subject's signs and symptoms of ABS.

Table 33: Number of Subjects Involved in Protocol Deviation and Reasons for Deviation

Protocol Category	Reason for Protocol Deviation	Azithromax ER	Levofloxacin
Inclusion Criteria	Lacked Cardinal S/S -Based Diagnosis of ABS	2	3
	No X-ray confirmation of clinical ABS	0	1
Exclusion Criteria	Antibiotics given within 7 days of randomization	1	0
Dosing Regimen	Patient received placebo instead of azithromycin	1	0
Visit Window	Visit 4 done outside of the visit window	2	2
	Subject missed visit 4 altogether	1	1
Protocol Criteria	Transantral Puncture not done	0	1
	Sinus X-ray >48 hours prior to randomization	2	0
	Visits 2-4 not compared to baseline	0	1
TOTAL		9	9

S/S = Signs and symptoms; ABS= Acute bacterial sinusitis

MO's Comments: *The reviewer considers the subject whose sinusitis self-resolved after receiving placebo as clinically and bacteriologically ineligible, lest study medication falsely receives the credit for cure. This subtraction should be reflected in the efficacy analysis. Nevertheless, the number of subjects who deviated from the protocol is relatively small by comparison to the much larger number of subjects in the study population. Although the numbers of subjects differ between the two groups within specific protocol deviation categories, the differences are small and the deviations occur only in 9 subjects per study group. The occurrence of equal numbers of deviations across study groups probably reduces the likelihood of observing any significant impact of protocol deviations on the overall difference across study arms in the final analyses of efficacy results.*

Subject Disposition

Evaluation group:

Of the 541 subjects who were randomized, 538 (99.4%) were treated. Two hundred and seventy of these treated subjects received azithromycin ER. Two hundred and sixty eight subjects received levofloxacin, the comparator drug. Of the 538 treated subjects, 507 (94.2%) were included in the Clinical Per Protocol population. One subject randomized to the azithromycin ER arm, and 2 to the levofloxacin arm, did not receive treatment and were excluded from the efficacy and safety analyses. Of these 3 subjects, one did not meet the entry criteria; the second was no longer willing to participate in the study. The third could not be given study medication. No reasons were given.

Demographics and Baseline Characteristics

As shown in tables 34 and 35, overall, the two treatment groups show similarity with respect to baseline demographic characteristics. However, 53.3% of treated subjects in the azithromycin ER group are female compared to 63.1% in the levofloxacin group. With respect to race, the proportions of the Caucasians, the majority in both arms, were similar, i.e. 66.7% in the azithromycin ER group compared to 67.5% in the levofloxacin group. Two hundred and fifty-five (94.4%) were less than 65 years of age in the azithromycin ER group compared to 252 (94.0%) in the levofloxacin group

Table 34: Modified Sponsor's Table of Subject Demographic Characteristics at Baseline [All Treated (ITT) subjects]

	Azithromycin ER			Levofloxacin		
	Male	Female	Total	Male	Female	Total
№ of Subjects →	126 (46.7)	144 (53.3%)	270	99 (36.9)	169 (63.1)	268
Age (years)	Number (%) of Subgroups			Number (%) of Subgroups		
< 65	123 (97.6)	132 (91.7)	255 (94.4)	95 (96.0)	157 (92.9)	252 (94.0)
≥ 65 to < 75	3 (2.4)	8 (5.6)	11 (4.1)	3 (3.0)	8 (4.7)	11 (4.1)
≥ 75	0	4 (2.8)	4 (1.5)	1 (1.0)	4 (2.4)	5 (1.9)
Mean	36.2	40.3	38.4	37.5	40.6	39.4
SD	12.8	15.5	14.4	13.4	14.5	14.1
Range	18-73	18-88	18-88	18-75	18-81	18-81
Race						
White	85 (67.5)	95 (66.0)	180 (66.7)	66 (66.7)	115 (68.0)	181 (67.5)
Black	2 (1.6)	7 (4.9)	9 (3.3)	1 (1.0)	4 (2.4)	5 (1.9)
Asian	24 (19.0)	13 (9.0)	37 (13.7)	16 (16.2)	21 (12.4)	37 (13.8)
Hispanic	15 (11.9)	29 (20.1)	44 (16.3)	16 (16.2)	27 (16.0)	43 (16.0)
Other	0	0	0	0	2 (1.2)	2 (0.7)
Weight (Kg)						
N	126(100.0)	144(100.0)	270(100.0)	99(100.0)	169(100.0)	268(100.0)
Mean	79.9	67.4	73.2	79.9	70.3	73.9
SD	19.4	17.0	19.2	15.2	17.9	17.6
Range	46.0-159.0	42.0-135.0	42.0-159.0	48.0-132.0	35.0-145.0	35.0-145.0
Height (cm)						
N	126	144	270	99	169	268
Mean	175.3	161.3	167.8	174.9	161.0	166.1
SD	8.8	7.7	10.8	9.9	8.0	11.0
Range	145.0-193.0	130.0-178.0	130.0-193.0	128.0-206.0	133.0-183.0	128.0-206.0

Table 6, pg 35 SD= Standard Deviation; Kg= Kilograms; cm= centimeter

MO's Comments: *The subjects' demographic features at baseline are evaluated to ensure absence of factors introduced during randomization that can inherently tilt the balance in favor of either of the 2 groups being compared in efficacy analyses. Overall, the two groups are fairly balanced. However, there is a disproportionate number of female subjects in the levofloxacin arm (63.1%) compared to the Azithromycin arm (53.3%) at baseline and at the TOC visit (Tables 34 and 35). Although the racial composition shows a larger proportion of whites than non-whites by a ratio of ≈ 2:1, the ratios are similar across the study groups.*

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

Table 35: Sponsor's Table of Subject Demographic Characteristics (Clinical Per Protocol subjects at TOC)

	Azithromycin ER			Levofloxacin		
	Male	Female	Total	Male	Female	Total
No of Subjects →	121	135	256	94	157	251
By Age (years)	Number (%) of Subgroups			Number (%) of Subgroups		
< 65	118 (97.5)	124 (91.9)	242 (94.5)	91 (96.8)	146 (93.0)	237 (94.4)
≥ 65 to < 75	3 (2.5)	7 (5.2)	10 (3.9)	2 (2.1)	7 (4.5)	9 (3.6)
≥ 75	0	4 (3.0)	4 (1.6)	1 (1.1)	4 (2.5)	5 (2.0)
Mean	35.9	40.2	38.2	37.2	40.3	39.2
SD	12.7	15.8	14.5	13.2	14.6	14.1
Range	18-73	18-88	18-88	18-75	18-81	18-81
Race						
White	81 (66.9)	93 (68.9)	174 (68.0)	65 (69.1)	107 (68.2)	172 (68.5)
Black	2 (1.7)	6 (4.4)	8 (3.1)	1 (1.1)	4 (2.5)	5 (2.0)
Asian	24 (19.8)	11 (8.1)	35 (13.7)	13 (13.8)	21 (13.4)	34 (13.5)
Hispanic	14 (11.6)	25 (18.5)	39(15.2)	15 (16.0)	23 (14.6)	38 (15.1)
Other	0	0	0	0	2 (1.3)	2 (0.8)
Weight (Kg)						
N	121(100.0)	135(100.0)	256(100.0)	94(100.0)	157(100.0)	251(100.0)
Mean	79.2	66.3	72.4	80.5	70.1	74.0
SD	19.0	15.1	18.2	14.3	17.8	17.3
Range	46.0-159.0	42.0-135.0	42.0-159.0	51.0-132.0	35.0-145.0	35.0-145.0
Height (cm)						
N	121 (100.0)	135 (100.0)	256(100.0)	94(100.0)	157 (100.0)	251(100.0)
Mean	175.0	161.3	167.8	175.4	161.0	166.4
SD	8.6	7.8	10.7	9.9	8.2	11.3
Range	145.0-193.0	130.0-178.0	130.0-193.0	128.0-206.0	133.0-183.0	128.0-206.0

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Table 36: Modified Sponsor's Table of Prognostic Factors and Other Baseline Characteristics (All Treated Subjects)

	Azithromycin ER			Levofloxacin		
	Male	Female	Total	Male	Female	Total
№ of Subjects →	126	144	270	99	169	268
History of Allergic Rhinitis	Number (%) of Subgroups			Number (%) of Subgroups		
Yes	45(35.7)	52(36.1)	97(35.9)	32(32.3)	58 (34.3)	90 (33.6)
No	81 (64.3)	92 (63.9)	173 (64.1)	67 (67.7)	111 (65.7)	178 (66.4)
№ of Sinusitis Episodes the Previous Year						
0	62 (49.2)	76 (52.8)	138 (51.1)	54 (54.5)	70 (41.4)	124 (46.3)
1	40 (31.7)	34 (23.6)	74 (27.4)	27 (27.3)	42 (24.9)	69 (25.7)
2	18 (14.3)	21 (14.6)	39 (14.4)	12 (12.1)	37 (21.9)	49 (18.3)
3	5 (4.0)	13 (9.0)	18 (6.7)	6 (6.1)	19 (11.2)	25 (9.3)
№ of Maxillary Sinuses Involved						
None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.4)
One	70 (55.6)	83 (57.6)	153 (56.7)	59 (59.6)	91 (53.8)	150 (56.0)
Both	56 (44.4)	61 (42.4)	117 (43.3)	40 (40.4)	77 (45.6)	117 (43.7)
Sinus X-ray Result**						
Air/Fluid Level Only	16 (12.7)	30 (20.8)	46 (17.0)	16 (16.2)	35 (20.7)	51 (19.0)
Opacification Only	90 (71.4)	82 (56.9)	172 (63.7)	59 (59.6)	101 (59.8)	160 (59.7)
Both	20 (15.9)	32 (22.2)	52 (19.3)	24 (24.2)	32 (18.9)	56 (20.9)
Current Smoking Status						
Never smoked	69 (54.8)	105 (72.9)	174 (64.4)	54 (54.5)	131 (77.5)	185 (69.0)
Ex-smoker	24 (19.0)	17 (11.8)	41 (15.2)	23 (23.2)	12 (7.1)	35 (13.1)
Smoker	33 (26.2)	22 (15.3)	55 (20.4)	22 (22.2)	26 (15.4)	48 (17.9)
Alcohol Use						
Yes	57 (45.2)	29 (20.1)	86 (31.9)	45 (45.5)	35 (20.7)	80 (29.9)
No	69 (54.8)	115 (79.9)	184 (68.1)	54 (54.5)	134 (79.3)	188 (70.1)

**Radiologist interpretation prevails over Investigator's interpretation whenever both are present

Source: Table 6.1, Page 131 of Sponsor's submission

These prognostic factors and other baseline characteristics were similar across both treatment groups (table 36). Ninety-seven (35.9%) had a history of allergic rhinitis compared to 90 (33.6%) in the levofloxacin group. One hundred and thirty-one (48.9%) had a history of previous episodes of sinusitis in the azithromycin group compared to 143 (53.7%) in the levofloxacin group. Number of smokers among the subjects were 55 (20.4%) in the azithromycin group compared to 48 (17.9%) in the levofloxacin group.

MO's comments: *Although more subjects had a history of allergic rhinitis in the Azithromycin ER arm compared to the levofloxacin arm [97(35.9%) vs. 90(33.6%)] the difference is probably not clinically significant. This difference between the arms is not large enough to warrant separate analysis of the allergic rhinitis subset of subjects.*

Populations Analyzed

Table 37 shows the sponsor's tabulation of the following population groups analyzed:

- All Randomized Subjects: All subjects who received a randomization number from the central randomization system.

- All Treated Subjects: All Randomized Subjects who received at least one dose of study medication.
- Clinically Eligible Subjects: All Treated Subjects with an appropriate, protocol-defined diagnosis.

Clinical Per Protocol population includes the following subjects:

- Treatment success who has received at least 80% of study medication (active drug or placebo)
- Treatment failure who has received at least 3 days of dosing (active or/and placebo).
- Received no concomitant systemic antibiotic with activity against typical Acute Bacterial Sinusitis pathogens.
- Received an assessment in the appropriate visit window.

Table 37: Sponsor's Overall Subject Evaluation Groups, Number (%) ^a of Subjects

Evaluation Group	Azithromycin ER	Levofloxacin	Total All
Randomized	271 (100.0)	270 (100.0)	541 (100.0)
All Treated	270 (99.6)	268 (99.3)	538 ^d (99.4)
Clinically Eligible	270 (100.0)	264 (98.5)	534 (99.3)
Excluded	0 (0.0)	4 (1.5)	4 (0.7)
Reason ^b			
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	14 (5.2)	17 (6.3)	31 (5.8)
Reason ^b			
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 in the All Randomized and All Treated populations based on All Randomized; otherwise, percentages are based on the All Treated 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 (see Section 6.1). TOC = Test of Cure.

Subject Discontinuation from Study and Dose Reductions Due to Adverse Events

Five azithromycin ER-treated subjects (2%) and 3 levofloxacin-treated subjects (1%) discontinued the study due to adverse events (Table 38). Worsening of acute sinusitis, and sinus

pain were the most frequently occurring adverse event that resulted in discontinuation from the study. All adverse events that led to discontinuation in levofloxacin-treated subjects were drug-related. Only 1 azithromycin ER-treated subject had a study drug-related adverse event that led to discontinuation.

Table 38: Reasons for discontinuation from evaluation – Patient Profile

Azithromycin ER Group		
Center-Patient ID	Azithromycin ER	Action
1. 01007-01020	Insufficient Clinical response Persistence of sinus pain	Withdrawn
2. 01010-01007	Adverse Event Abdominal Pain/ Stomach cramps	Withdrawn
3. 01019-01006	Adverse Events 1. Chest Pain/ burning (4 th day) 2. Epistaxis 3. Lower Respiratory Tract Infection	Withdrawn
4. 01046-01017	Insufficient Clinical response 1. Persistence/worsening of sinusitis 2. Vomiting	Withdrawn
5. 01050-01006	Insufficient Clinical response 1. Persistence/worsening of sinusitis (Moderate - Study drug related)	Withdrawn
Levofloxacin Group		
Center/Patient ID	Levofloxacin	Action
1. 01049-01021	Cutaneous Rash (Study Drug related - Mild)	Withdraw from study on Day-11 (EOT) due to an AE of RASH
2. 01050-01011	Insufficient Clinical response Persistence/worsening of sinusitis	Withdrawn
3. 01081-01011	Adverse Events Allergic reaction – unspecified	Withdrawn

Statistical Methods

Sample Size

A requirement for 402 Clinical Per Protocol population subjects (201 subjects per arm) was stipulated based on the following assumptions:

- 80% power to show non-inferiority based on a 2-sided 95% CI;
- A 95% CI for the difference in cure rates using the normal approximation to the binomial distribution was used to determine if Azithromycin ER was considered noninferior to

levofloxacin; if so, the lower boundary of the 95% CI for the difference in cure rates (azithromycin ER minus levofloxacin) would be greater than -10%.

- An assumed clinical cure rate of 85% in both treatment groups.
- To account for an estimated 20% non-evaluable subjects, a total of 504 subjects were targeted for enrollment.

Out of a total of 541 subjects enrolled in the study, 507 (93.7%) Clinical Per Protocol subjects were evaluated at the TOC visit; thus, a higher evaluability than projected was achieved.

Efficacy Results

Sponsor's and the Investigator's Assessments of Primary Clinical Efficacy Response

The results of the sponsor's and the investigator's primary efficacy rate assessments of clinical response for the Clinical Per Protocol population at the TOC visit are presented in tables 39 and 40 respectively. According to the sponsor's assessment, subjects in the Clinical Per Protocol population treated with azithromycin ER had a clinical cure rate of 94.5% compared with 92.8% for subjects treated with levofloxacin. The 95% CI for the difference in cure rates was reported to be -2.5% to 5.9%. The lower limit of this CI was greater than -10%, the chosen delta prior to the study. This indicates that azithromycin ER therapy was non-inferior to levofloxacin therapy in the treatment of acute, uncomplicated bacterial maxillary sinusitis. The Investigator's assessment was similar to that of the sponsor.

Primary Efficacy Outcome in Clinical Per Protocol Subjects

Table 39: Sponsor's Assessment [Number (%)] of Clinical Response (Clinical Per Protocol Subjects) at TOC visit

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

- CI* = Confidence Interval (for the difference in cure rates between treatment groups)
- Non-inferiority = lower limit of > -10 %
- From Sponsor's Table 15

Table 40: Investigator's Assessment of Clinical Response (Clinical Per Protocol Subjects) at TOC Visit

Characteristics	Azithromycin ER	Levofloxacin	Difference	95% CI*
No (%) of Subjects @ TOC	256	251		
Cure	242 (94.5)	233 (92.8)		
Failure			1.7	-2.4, 5.8
Signs/ Symptoms worse or persisted	12 (4.7)	15 (6.0)		
New Signs/ Symptoms	1 (0.4)	2 (0.8)		
Missing	1(0.4)	1(0.4)		
Total	14 (5.5)	18 (7.2)		

* Confidence Interval for the difference in cure rates between treatment groups

MO's Comment: Per the sponsor's analysis, subjects in the Clinical Per Protocol population treated with azithromycin ER had a clinical cure rate of 94.5% compared with 92.8% for subjects treated with levofloxacin. The 95% CI for the difference in the cure rates -2.6% to 5.8%. The lower limit of this CI is greater than -10%, the delta value chosen prior to the study. This indicates that a single dose of 2 gm of Azithromycin ER slurry was non-inferior to 500 mg of levofloxacin, given once daily for 10 days, in the treatment of acute, uncomplicated bacterial maxillary sinusitis. Overall, the reviewer agrees with this assessment. However, there are a few individual subjects whose assessments by the sponsor are different from the reviewer's assessment. For example, the patient who received placebo and was counted by the sponsor as a cure and imputed to the Azithromycin ER arm was considered by the reviewer as ineligible. Two cured patients in the levofloxacin group were added to the evaluable failure population because their purulent discharge was seen only in the posterior pharynx rather than in the nasal cavities. The two patients were re-classified among the cured group by the reviewer. The number of subjects involved is small, the changes are minor, and as shown in tables 41 and 42 below, the data modification was not large enough to make any significant impact on the final efficacy results.

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Table 41: Listing of Re-Classified Patients in the Reviewer's Analysis

Characteristics	SID	Azithromycin ER	Levofloxacin	Inv. Response	Reviewer's Response
Sponsor's All Treated		270	268	-	-
Received Placebo by error	10551001	1	0	Clinical Cure	Ineligible
Lacked S/S of ABS; no purulent drainage in nasal cavity; drainage in posterior pharynx; cured	10621006 10621010	0	2	Excluded (Unevaluable)	Cured (Evaluable)
Transcription Error (X-ray (+); s. tap done)	10501018	-	1	Ineligible	Cured (Evaluable)

CPPP= Clinical Per Protocol Population; ITT= Intent-To-Treat population; LTFU= Lost to follow up
 I = indeterminate; Rx = Treatment

Table 42: Reviewer's Assessment [Number (%)] of Clinical Response (Clinical Per Protocol Subjects) at the TOC visit

Characteristics	Azithromycin ER	Levofloxacin	Difference	95% CI*
No. of Subjects @ TOC	255	254	Difference = 1.6	95% CI = - 2.6, 5.8
Cure	241 (94.5)	236 (92.9)		
Failure	14 (5.5)	18 (7.1)		

- CI = Confidence Interval (for the difference in cure rates between treatment groups)
- Non-inferiority = lower limit > -10 %

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Influence of demographic and regional factors on efficacy analysis

No significant differences were noted in clinical cure rates by gender, age, or race in the Clinical Per Protocol population. By region, clinical cure rates for azithromycin ER-treated subjects were highest in India (100%). Other regions included Europe (98.4%), Latin America (94.7%) and North America (89.3%). A similar trend by region was observed in levofloxacin-treated subjects.

Other factors

For subjects with a previous history of allergic rhinitis, clinical cure rates were 93.4% in the azithromycin ER group and 89.3% in the levofloxacin group. Subjects with no previous history of allergic rhinitis at baseline had success rates of 95.2% in the azithromycin ER group and 94.6% in the levofloxacin group. The overall cure rate for smokers in both groups (95.8%) was similar to that of non-smokers or ex-smokers (93.2% and 93.2%, respectively). Subjects with 3 episodes of sinusitis in the previous one year had lower cure rates (88.2% azithromycin ER; 78.3% levofloxacin) as compared with subjects who had no episodes (93.3% azithromycin ER; 94% levofloxacin), 1 episode (98.6% azithromycin ER; 98.4% levofloxacin) or 2 episodes (94.3% azithromycin ER; 89.6% levofloxacin) within the previous year. Comparable results were observed in the All Treated and Clinically Eligible populations. For cure rate result analyses in gender, race and age subgroups, see table 43 (sponsor's table) below.

Table 43: Clinical Cure Rates at the TOC visit by Baseline Characteristics (Clinical Per Protocol Subjects)

Characteristics	Number Cured / Number of Subjects (%)		
	Azithromycin ER N = 256	Levofloxacin N = 251	TOTAL N = 507
Gender			
MALE	117 /121 (96.7)	85 /94 (90.4)	202 / 215 (94.0)
FEMALE	125 /135 (92.6)	148 / 157 (94.3)	273 / 292 (93.5)
Age (years)			
< 65	229/ 242 (94.6)	221 / 237 (93.2)	450 / 479 (93.9)
65 to 74	9 /10 (90.0)	7 /9 (77.8)	16 /19 (84.2)
>= 75	4 /4 (100.0)	5 /5 (100.0)	9 /9 (100.0)
Race			
WHITE	163 /174 (93.7)	160 / 172 (93.0)	323 / 346 (93.4)
BLACK	6 /8 (75.0)	4 /5 (80.0)	10 /13 (76.9)
ASIAN	35 /35 (100.0)	34 /34 (100.0)	69 /69 (100.0)
HISPANIC	38 /39 (97.4)	33 /38 (86.8)	71 /77 (92.2)
OTHER	0 /0	2 /2 (100.0)	2 /2 (100.0)
Geographic Region			
North America	75 /84 (89.3)	71 /83 (85.5)	146 / 167 (87.4)
Latin America	71 /75 (94.7)	71 /75 (94.7)	142 / 150 (94.7)
Europe	61 /62 (98.4)	58 /60 (96.7)	119 / 122 (97.5)
India	35 /35 (100.0)	33 /33 (100.0)	68 /68 (100.0)

TOC = Test of Cure; Clinical Cure is sponsor assessed.

N = Number of Clinical Per Protocol subjects at TOC for each treatment group.

Missing values for clinical response are imputed as failures; Per Protocol populations, by definition, do not have missing values.

ITT Population.

In the intent-to-treat population (ITT), the clinical cure rate was determined by the sponsor to be 91.1% for azithromycin ER-treated subjects and 89.0% for levofloxacin-treated subjects in the study. The differences between treatment groups with respect to clinical cure rates were comparable in the All Randomized, All Treated subjects.

Table 44: Sponsor’s Primary Efficacy Outcome in Clinical ITT Population

	Azithromycin	Levofloxacin	Difference	= 1.9
All Treated Subjects	270	268		
Cure	246 (91.1)	239 (89.2)	95% CI	= -3.1, 6.9
Failure	24 (8.9)	29 (10.8)		

MO’s comments: The clinical cure rate in the intent-to-treat population in the Azithromycin ER group was 91.1% compared to 89.2% in the Levofloxacin group in the sponsor’s report (Table 44). The confidence interval is -3.1 to 6.9. The figures are similar to the reviewer’s analyses (Table 45).

Table 45: Reviewer’s Primary Efficacy Outcome in Clinical ITT Population

	Azithromycin	Levofloxacin	Difference	1.5
All Subjects	269	268		
Cure	245 (91.1)	239 (89.2)	95% CI	-3.1, 6.9
Failure	24 (8.9)	29 (10.8)		

6.2.5 Clinical Microbiology

Bacteriologic Efficacy

The reviewer’s table 46 below shows the proportion of study subjects from whom baseline pathogens were isolated as contained in the sponsor’s tables on pages 173-(table 2.7)-and 487 (Table 5.5.1) of their study report. Accordingly, of the 270 subjects who were azithromycin ER-treated, 108 (40.0 %) grew 120 pathogens from their sinus aspirates cultures at baseline. Similarly, of the 268 subjects who were levofloxacin-treated, 120 (44.7%) grew 139 pathogens from their sinus aspirate cultures at baseline. The table 46 also shows the relative proportions of subjects with single and multiple pathogens at baseline in the ITT population; the number of subjects and baseline pathogens in the Bacteriologic Per Protocol subjects as well as the proportion of subjects with no growth from their maxillary sinus cultures.

Table 46: Overall Growth of Baseline Pathogens

ITT population	Azithromycin N=270	Levofloxacin N=268	Total N=538
Total number (%) of Subjects with baseline pathogens	108 (40.0)	120 (44.7)	228 (42.3)
Total (%) with a single pathogen	97 (35.9)	103 (38.4)	200 (37.1)
Total (%) with multiple pathogens	11 (4.0)	17 (6.3)	28 (5.2)
Total number of pathogens	120	139	259
Total number (%) of Subjects with no baseline pathogens	162 (60.0)	148 (55.3)	310 (57.7)
Bacteriologic Per Protocol Population			
Total number (%) of Subjects that grew pathogens	102 (37.8)	111(41.4)	213 (39.6)
Total number of pathogens	114	129	243

MO's Comments: Only 40% of azithromycin ER-treated subjects grew pathogens from their sinus aspirates at baseline compared to 60% azithromycin ER-treated subjects that grew no pathogens at baseline. Similarly, 44.7% of levofloxacin-treated subjects grew pathogens from their sinus aspirate cultures at baseline compared to 55.3% subjects who had no growth of pathogens from their sinus cultures at baseline. The proportions of subjects with baseline growth of pathogens across study arms in the ITT population (40% versus 44%) or in the Bacteriologic Per Protocol Population (37.8% versus 41.4%) are comparable. The corollary proportions in the ITT population shown on the same table (6.3.14a) are also comparable. The proportionate representation of individual pathogens important in the causation of ABS is further analyzed below.

Bacteriologic Eradication by Baseline Pathogen

As shown in the sponsor's summary (Table 47), the overall bacteriologic eradication rate, as reported by the sponsor, was 98.2% and 93% among the azithromycin ER-treated subjects and levofloxacin-treated subjects respectively at the TOC visit. The difference in cure rates between the 2 groups was 5.2% and an exact 95% CI of - 2.1% to 10.2%.

Combined Clinical and Bacteriologic Assessments: Clinical Cure by Baseline Pathogen

Tables 47 and 48 show the results of the secondary efficacy analyses of sponsor's assessment of clinical response by baseline pathogen for the Bacteriologic Per Protocol population at the TOC visit. The bacteriologic eradication rate at the TOC visit was 100% each for *S. pneumoniae* and *M. catarrhalis* in azithromycin ER-treated subjects and 92.3% and 90.9% in levofloxacin-treated subjects respectively. The eradication rate is 96.3 % for *H. influenzae* in azithromycin-treated subjects and 100% in levofloxacin-treated subjects in clinical cure rates by baseline pathogen for the Bacteriologic Per Protocol population at the TOC visit. These rates were similar across treatment groups for subjects with *S. pneumoniae* isolates, *H. influenzae* (including beta-lactamase positive and negative isolates), and *M. catarrhalis*.

Table 47: Sponsor's Summary of Bacteriologic Eradication Rates of All Baseline Pathogens at the TOC visit in Bacteriologic Per protocol Subjects

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

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

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

Table 48: Bacteriologic Eradication Rate (%) By Pathogen at TOC (Bacteriologic per Protocol Subjects)

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

OC= Test of Cure; n= number of pathogens eradicated or presumed eradicated (within the pathogen category) at post Baseline visit. N = Number of pathogens isolated at Baseline.

^b A subject may have more than one pathogen isolated at Baseline

^c In some cases, isolates of *M. catarrhalis* were not tested for the presence of beta-lactamase at the central lab. Therefore the number of isolates classified as either beta-lactamase positive or negative may not add up to the total number of isolates for this pathogen.

MO's Comments: Table 39 provides the rates of eradication (or presumed eradication) for the three pathogens that the sponsor has included in the proposed indication for acute bacterial sinusitis. The number of total pathogens exceeds the number of patients with one of the three key pathogens. Some subjects had multiple pathogens. Many other microorganisms (including various Gram-negative rods) were added by the sponsor as pathogens to their analysis. The number of subjects (8) used to determine the clinical response of *M. catarrhalis* in the Bacteriologic Per Protocol population should be put in context. The FDA's Draft Guidance and Points to Consider documents recommend at least 15 subjects on the study drug arm

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

Table 49 shows the cure rate in the Bacteriologic ITT population at the TOC visit.

Table 49: * Summary of Bacteriologic Eradication Rates of overall Baseline Pathogens in the Bacteriologic ITT Population at the TOC visit.

	Azithromycin ER	Levofloxacin	Difference	95% CI
	n (%)	N (%)		
ITT Subjects	N=120	N=139		
Eradication	114 (95.0)	120 (88.5)	6.5	-0.4, 13.6
Persistence	6 (1.8)	16 (7.0)		

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

* Table provided by the Agency's Statistician

Comparison of Clinical and Bacteriologic Response

Follow-up sinus taps were not required in this study. Two hundred and twenty nine of the 232 eradicated pathogens were assigned a bacteriologic response of presumed eradication. The use of clinical outcome as an indication of bacteriologic response is shown on table 50 on the 3 key pathogens.

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Table 50: Clinical Response versus Bacteriologic Response at the TOC visit in the Bacteriologic Per Protocol Subjects (Sponsor Assessment)

Pathogens ↓	Azithromycin ER					Levofloxacin				
	Number of pathogens					Number of pathogens				
	No of subjects	E	PE	P	PP	No of subjects	E	PE	P	PP
<i>S. pneumoniae</i>										
Cure	36	0	36	0	0	36	0	36	0	0
Failure	1	1	0	0	0	3	0	0	0	3
Total	37	1	36	0	0	39	0	36	0	3
<i>H. influenzae</i>										
Cure	26	0	26	0	0	30	0	30	0	0
Failure	1	0	0	0	1	0	0	0	0	0
Total	27	0	26	0	1	30	0	30	0	0
<i>M. catarrhalis</i>										
Cure	8	0	8	0	0	10	0	10	0	0
Failure	0	0	0	0	0	1	0	0	0	1
Total	8	0	8	0	0	11	0	10	0	1

Bacteriologic Response: E= Eradication; PE = Presumed Eradication; P = Persistence; PP = Presumed Persistence;

Modified from sponsor's Table 2.3, Section 13, Page 481

Repeated Sinus Taps

Only 3 subjects had their sinuses re-tapped for clinical failure at TOC. One subject (10251002) who received azithromycin ER and completed the study, had *S. pneumoniae* isolated at Baseline, was considered a clinical Failure due to persistence of signs and symptoms of ABS. Aspirate from repeat sinus tap grew *E. coli*. There was no growth of *S. pneumoniae* (i.e. eradicated). Following TOC assessment, the subject subsequently received moxifloxacin. The other 2 subjects who had their sinuses re-tapped (10511026 and 10641002) were in the levofloxacin group.

MO's Comment: The results of the main secondary efficacy parameter, i.e. bacterial eradication in the Bacteriologic per Protocol Population, particularly the key pathogens, based on clinical responses of cure or improvement at the TOC visit are similar in both the Azithromycin-treated and Levofloxacin-treated groups. The microbiologic response was presumed, i.e. corresponding with clinical response, in all but 3 cases, as sinus cultures at post-therapy or follow-up visits were not typically obtained. It is noteworthy, as reported above, that one of these 3 cases had *S. pneumoniae* isolated at Baseline, had persistence of signs and symptoms of ABS, and was considered a clinical Failure. Aspirate from repeat sinus tap, however, grew *E. coli*; there was no growth of *S. pneumoniae* (i.e., eradicated). The microbiological outcome was driven by the clinical outcome for the vast majority of patients.

Susceptibility versus Bacteriologic Response

Table 51 represents susceptibility versus bacteriologic response for key baseline pathogens in the Bacteriologic Per Protocol population. Most organisms were susceptible to study therapy. Although 5 of 37 *S. pneumoniae* isolates in the azithromycin ER group were categorized as azithromycin-resistant, the bacteriologic eradication rate for these *S. pneumoniae* isolates was 100%. One of the 5 isolates had an MIC >256, but was eradicated upon repeat sinus aspiration, even though patient was a clinical failure (patient 10251002 mentioned above). The remaining four baseline isolates had MICs of 4 (2 isolates), > 4 (1 isolate) and 8 (1 isolate). Each of these patients was assigned a response of presumed eradicated.

Table 51: Susceptibility of baseline pathogens versus Sponsor-Assessed Bacteriologic Response [Number of Pathogens = Bacteriologic Per Protocol Subjects]

Baseline Pathogen At TOC ↓	Azithromycin ER Subjects				Levofloxacin Subjects			
	Susceptibility to azithromycin				Susceptibility to Levofloxacin			
	S	I	R	Not Tested	S	I	R	Not Tested
<i>S. pneumoniae</i>								
Eradication	0	0	1	0	0	0	0	0
Presumed Eradication	32	0	4	0	36	0	0	0
Presumed Persistence	0	0	0	0	3	0	0	0
Total	32	0	5	0	39	0	0	0
<i>H. influenzae</i>								
Presumed Eradication	26	0	0	0	30	0	0	0
Presumed Persistence	1	0	0	0	0	0	0	0
Total	27	0	0	0	30	0	0	0
<i>M. catarrhalis</i>								
Presumed Eradication	1	0	0	7	0	0	0	10
Presumed Persistence	0	0	0	0	0	0	0	1
Total	1	0	0	7	0	0	0	11

S= Susceptible; I= Intermediate; R= Resistant ;
 Results based on MIC and /or Disk diffusion (DD) testing. DD used when MIC result missing. Not Tested = Pathogens with no established breakpoint criteria by NCCLS

Modification of sponsor's table 5.6.4, Page 531 of sponsor's application

Overall Bacteriologic Susceptibility

Most isolates were susceptible to both azithromycin and levofloxacin (Table 52) across geographic regions (North America, Latin America, India, and Europe). Twelve of the 81 *S. pneumoniae* isolates (15%) were resistant to azithromycin. None of the *S. pneumoniae* isolates was resistant to levofloxacin. By region, the 12 resistant *S. pneumoniae* isolates were identified in the following regions: United States (3 isolates), Europe (3 isolates: 1 each from Poland, Germany, and Lithuania), and Latin America (6 isolates: 5 from Chile and 1 from Costa Rica). None of the *H. influenzae* isolates were resistant to either azithromycin or levofloxacin.

Table 52: Susceptibility of Baseline Pathogens, Number of Pathogens (All Randomized Subjects Without Regard to Treatment Group)

Baseline Pathogens ↓	Azithromycin ER Subjects					Levofloxacin Subjects				
	Susceptibility ^a to azithromycin					Susceptibility ^a to Levofloxacin				
	Total	S	I	R	Not Tested ^b	Total	S	I	R	Not Tested ^b
<i>S. pneumoniae</i>	81	69	0	12	0	81	81	0	0	0
<i>H. influenzae</i>	60	60	0	0	0	60	60	0	0	0
<i>M. catarrhalis</i> *	21	1	0	0	20	21	1	0	0	20

S = Susceptible, I = Intermediate, R = Resistant; susceptibility based upon current breakpoints per organism for azithromycin and levofloxacin. Pathogens were tested for susceptibility to both azithromycin and levofloxacin.

^a Susceptibility results based on MIC and/ or disk diffusion testing; disk result used only if MIC result was missing.

^b Not tested includes pathogens for which no NCCLS breakpoint criteria have been established.

*Categorization of susceptibility for *M. catarrhalis* was identified after database lock as an error. No NCCLS breakpoints have been established for this pathogen; therefore, all isolates should be noted as Not Tested.

Susceptibility versus Clinical Response

A comparison of clinical response and susceptibility of Baseline pathogens for the Bacteriologic Per Protocol population is presented in Table 53. While 4 of the 5 azithromycin ER-treated subjects with azithromycin-resistant *S. pneumoniae* were assessed as cures, one azithromycin ER-treated subject with azithromycin-susceptible *H. influenzae* was assessed as a clinical failure. Three levofloxacin-treated subjects with levofloxacin-susceptible *S. pneumoniae* were assessed as failures.

Table 53: Sponsor-Assessed Susceptibility of baseline pathogens versus Clinical Response

Pathogens At TOC ↓	Azithromycin ER Subjects				Levofloxacin Subjects			
	Susceptibility to azithromycin				Susceptibility to Levofloxacin			
	S	I	R	Not Tested	S	I	R	Not Tested
<i>S. pneumoniae</i>								
Cure	32	0	4	0	36	0	0	0
Failure	0	0	1	0	3	0	0	0
Total	32	0	5	0	39	0	0	0
<i>H. influenzae</i>								
Cure	26	0	0	0	30	0	0	0
Failure	1	0	0	0	0	0	0	0
Total	27	0	0	0	30	0	0	0
<i>M. catarrhalis</i>								
Cure	1	0	0	7	0	0	0	10
Failure	0	0	0	0	0	0	0	1
Total	1	0	0	7	0	0	0	11

S= Susceptible; I= Intermediate; R= Resistant ;
 Results based on MIC and /or Disk diffusion (DD) testing. DD used when MIC result missing. Not Tested = Pathogens with no established breakpoint criteria by NCCLS

MO's Comments: *The in-vitro resistance of S. pneumoniae to azithromycin ER in 4 of the 5 subjects did not automatically translate into clinical ineffectiveness, even where S. pneumoniae was the only organism isolated. This non-correlation between the in vitro resistance of S. pneumoniae to azithromycin ER and the clinical course of the patient may be related, at least in part, to the tendency of ABS, like acute otitis media, to self-resolve. The apparent clinical paradox can be accounted for by the individual's immune system which probably plays a greater role than the antibiotic contribution to pathogen eradication. In a case of mixed bacterial and viral co-infection, the subject's symptomatology may persist as the viral contribution to the disease process may outlast that of the bacteria. The disease may therefore continue until the underlying viral disease runs its full course. This explanation is supported by the experience of the patient from whom H. influenzae was cultured but the patient was a clinical failure, even though the organism was susceptible to azithromycin ER. The number of these patients was very-small by comparison to the majority in the study. Even though no S. pneumoniae isolate was resistant to levofloxacin, the overall results of bacterial eradication, as judged by the corresponding clinical presumed eradication, were similar across study arms.*

Efficacy for Study Drug Resistant *S. pneumoniae*

Overall, 12 azithromycin non-susceptible *S. pneumoniae* isolates were identified at baseline. Ten of these were tested for the presence of erythromycin ribosomal methylase (erm) and macrolide efflux pump (mef). Five of these isolates were from azithromycin ER-treated subjects in the Bacteriologic Per Protocol population. Of these 5 isolates, 1 was categorized as having the erm gene and another as having the mef gene; both subjects were considered clinical cures. One resistant *S. pneumoniae* isolate (MIC >256, from Subject 10251002) was documented as eradicated upon repeat sinus aspiration (discussed previously). It was categorized as having both mef and erm-TR genes; the patient was considered to be a clinical failure. The remaining 2 isolates were not viable upon arrival from Dublin at the central genotyping laboratory; genotyping was not performed on these isolates. All 5 isolates were considered eradicated (or presumed eradicated) at the TOC visit.

6.2.6 Efficacy Conclusions

The MO has reviewed the data submitted by the sponsor and derived from Study 1078, a pivotal multi-center, international, randomized, double-blind, double-dummy, Phase 3 clinical trial in which subjects were assigned to receive either a single dose of 2 gm of azithromycin ER, given orally, or levofloxacin, 500 mg daily orally for 10 days. By this study, the sponsor's objective was to show that this single dose of 2.0 gm of azithromycin ER, given orally, is clinically non-inferior to levofloxacin 500 mg once daily for 10 days, in the treatment subjects, 18 years or older, with uncomplicated acute bacterial maxillary sinusitis (ABS).

Based on the analyses of the data and the other accompanying information submitted by the sponsor, the Medical Reviewer is able to make the following efficacy conclusions:

1. The clinical cure rate of 94.5% in the Clinical Per Protocol subjects who received azithromycin ER is similar to the clinical cure rate of 92.8% in subjects in the comparator group who received levofloxacin treatment. The lower limit of the 95% CI of -2.5 is greater than the pre-specified delta of -10%. Thus, the results analyzed showed that a single dose of 2 gm of the study drug, azithromycin ER, was non-inferior to levofloxacin, 500 mg daily for 10 days, in the treatment of acute bacterial maxillary sinusitis.
2. The clinical cure rate in the clinical intent-to-treat population in the azithromycin ER-treated group was 91.1%, also similar to the rate of 89.2% in the levofloxacin-treated group.
3. Clinical cure rates were similar across treatment groups for subjects with *H. influenzae* (including beta-lactamase positive and negative isolates), *M. catarrhalis*, and *S. pneumoniae* isolates. The number of subjects whose sinus aspirates were positive for *M. catarrhalis* at baseline was only 8, less than the 15 recommended in the FDA **Draft Guidance** document for Acute Bacterial Sinusitis studies.
4. In the Bacteriologic Per Protocol population, the overall bacteriologic eradication rates were 98.2% for azithromycin ER-treated arm and 93% for levofloxacin-treated arm at the TOC visit. The exact 95% CI was -2.1% to 15.4%.
5. By pathogen, the eradication rate for *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* isolates were, 100%, 100%, and 96% respectively in azithromycin ER-treated subjects. The bacteriologic assessment of pathogen eradication was typically derived from an assignment of presumed eradication, based upon clinical response of cure.
6. The bacteriologic eradication rate (eradicated and presumed eradicated) at the TOC visit was 100% for the 5 azithromycin-resistant *S. pneumoniae* isolates identified in azithromycin ER-treated Bacteriologic Per Protocol subjects. Eighty percent (4 of 5 subjects with these isolates) were considered clinical cures.
7. There were no significant differences in cure rates between treatment groups in different demographic subgroups by gender, age, or race in the Clinical Per Protocol population.
8. By region, the reported clinical cure rates for azithromycin ER-treated subjects were as follows: India (100%), Europe (98.4%), Latin America (94.7%), and North America (89.3%).

Limitations of the available data

This was an active control non-inferiority trial comparing azithromycin ER to levofloxacin in the treatment of ABS. One of the limitations of such trials is that enrollment of patients with a high likelihood of viral infection or spontaneous resolution of their bacterial infection would make the two treatments appear similar. The sponsor has used adequate inclusion and exclusion criteria and performed sinus baseline punctures in order to limit enrollment of such subjects. As a non-inferiority trial, the ability of this trial to provide substantial

evidence of efficacy depends on the historical information on the treatment effect of antibiotics in the treatment of ABS. To the extent that this trial differs from older studies demonstrating treatment effects, then our ability to conclude that this non-inferiority study provides substantial evidence of efficacy may be reduced.

This particular study had a few minor flaws. For example, there were instances of discrepancies between the stipulations of the protocol and the application of those stipulations in clinical assessments of a few subjects. A few examples of the areas where the medical reviewer was in disagreement with the sponsor included the following: 1.) the attribution (in effect) of the self-resolution of a patient's signs and symptoms of ABS to azithromycin ER following the receipt of only placebo, 2.) the exclusion from the study of 3 patients who were in the levofloxacin arm who had purulent drainage in the posterior pharynx because the drainage was not in the nasal cavity, and 3.) the inclusion of a patient who was on doxycycline during the study in the Clinical Per Protocol population in the sponsor's analyses. There were some instances of transcription errors.

Nevertheless, the sum of these events was insignificant relative to the larger number of instances in which the rules of the studies were followed according to the protocol and according to expectation. And therefore, the overall efficacy results were not adversely affected.

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7 INTEGRATED REVIEW OF SAFETY

Azithromycin ER is not currently marketed anywhere in the world. Thus, all safety data reported for azithromycin ER in this dossier is from the 5 Phase 3 and 14 Phase 1 studies. All of these studies had completed the clinical phase as of the cutoff date, and therefore safety data is included for all treated subjects.

The five adult Phase 3 studies included 1292 subjects who received azithromycin ER (single dose, 2.0 grams) and 1304 subjects who received a comparator. Among the 1304 subjects who received comparators, 252 received clarithromycin, 754 received levofloxacin, and 298 received azithromycin 3-day. Among the comparator subjects who received levofloxacin, 486 were assigned to receive a 7-day regimen and 268 were assigned to receive a 10-day regimen.

There were 6 adult Phase 1 studies which investigated the to-be-marketed formulation of azithromycin ER at the proposed dose. These studies included 545 treated subjects. Of these 545 subjects, 437 received at least one 2.0 g dose of Azithromycin ER. The other 108 subjects received 2.0 g of a commercial azithromycin immediate release formulation. The remaining 8 Phase 1 studies included one pediatric study, and seven studies investigating varying formulations.

7.1 Methods and Findings

The following is a brief description of the methods of recording and summarizing safety data for the clinical studies.

Premature Discontinuation

Discontinuation from study was assessed for all treated subjects in the studies.

Reporting and Evaluation of Adverse Events

Adverse events were monitored during the course of the studies. Subjects were observed and questioned in a nonspecific fashion for any new or continuing symptoms, or adverse events, since the previous visit. Adverse events were recorded during clinic visits and evaluated by the investigator for intensity and relationship to study drug. Only those events that were treatment emergent (began or increased in intensity or frequency during the study) were collected. In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, ECG) were recorded as adverse events. Investigator terms were mapped to a modified COSTART dictionary and converted to preferred terms. Adverse events and laboratory abnormalities reported up to 35 days following the end of treatment are included in all summary tables.

This Summary of Clinical Safety also presents analyses of selected adverse events by onset day, and by onset day and duration.

With the exception of the analyses of adverse events by onset day and by onset day and duration,

a subject with multiple adverse events was counted only once in the total for number of subjects with adverse events. A subject with multiple events within a body system was counted only once in the total for number of subjects with adverse events within that body system. An adverse event that occurred more than once for the same subject was counted only once in the total for that adverse event and in the total for number of adverse events. For assessment of severity in the case of multiple experiences of the same adverse event, the subject was counted once at the worst severity.

While the conventional presentation of adverse events provides a reasonable indication of the safety profile of a drug, it may underestimate the actual extent of morbidity associated with these events. For a medication that can be delivered in one dose, especially where the adverse events generally occur around the time of dosing, the extent of reduction in morbidity afforded by a single dose option can be lost if the events are described simply as an incidence rate. As a result, to better describe the relative impact of adverse events for Azithromycin ER and its comparators, adverse event data are also presented as 'adverse event burden'. Adverse event burden (adverse events per person year) was calculated for all-cause and treatment-related adverse events (including headache, rash, dizziness, and taste perversion) and for subsets of gastrointestinal related adverse events (diarrhea, vomiting, dyspepsia, loose stools, abdominal pain, nausea, and gastritis).

Serious adverse events

Serious adverse events judged to be reportable were filed according to regulatory requirements. Serious adverse events were listed by subject with information on gender, age, race, weight, dosing, time of onset of the event, any action taken, the investigator's assessment of causality, and the outcome of the event. These tables were derived from a separate Adverse Reaction Information System – Global (ARISg) database using the MedDRA adverse event dictionary, which is based upon rapidly communicated reports (usually made by telephone) from the investigator to the sponsor. Consequently, there may be occasional discrepancies between data in this database and that contained in the project database, which is based upon data from the case report forms.

A serious adverse event was defined as any adverse drug experience occurring at any dose that:

- Resulted in death
- Was life threatening
- Resulted in inpatient hospitalization or prolongation of existing hospitalization
- Resulted in a persistent or significant disability/incapacity, or
- Resulted in congenital anomaly/birth defect

Reporting and Evaluation of Clinical Laboratory Analyses

In the CAP [REDACTED] studies, clinical assessments (blood chemistry, hematology) were performed as specified by the protocol, and additional laboratory tests could be performed if deemed necessary by the investigator. In the other phase 3 studies (ABS and pharyngitis), there were no protocol-specified laboratory tests other than baseline pregnancy testing. Laboratory tests in these studies were conducted as deemed necessary by the investigator.

Laboratory abnormalities are summarized and listings, by subject and by test, are provided.

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

Baseline was defined as the last value prior to treatment. All incidences are rounded to the nearest whole percent. Median changes in laboratory data from Baseline to last observation (up to 35 days after the last dose of study drug) are tabulated. The percent of subjects with a laboratory abnormality was based on only those subjects undergoing that test.

Vital Signs, Physical Exams and Other Safety Measurements

Vital signs (sitting blood pressure, pulse, respiration, and temperature) were summarized as the median change from Baseline to last observation. Physical examination results were recorded only for the Baseline visit.

Analysis of Safety Data by Extrinsic and Intrinsic Factors

Selected data from the Phase 3 studies (adverse events and laboratory test abnormalities) were also analyzed by region (U.S. and non-U.S.) and demographic subsets, including gender, age and race.

Narrative Summaries of Studies Not Included in the Clinical Summary of Efficacy

One of the five Phase 3 adult studies is not included in the Summary of Clinical Efficacy. Study A0661119 was an adult study of azithromycin ER versus azithromycin 3-day in the treatment of GABHS pharyngitis. The safety data from this study is combined with other Phase 3 adult studies for analysis in this Summary of Clinical Safety.

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SUMMARY OF CLINICAL SAFETY -- PHASE 3 STUDIES

Five Phase 3 studies investigated the use of a single 2.0 g dose of azithromycin ER in the treatment of adults with [REDACTED] CAP, ABS, and GABHS pharyngitis. All 5 studies are included in this summary. The safety database from these studies includes 1292 subjects treated with azithromycin ER and 1304 subjects treated with comparators.

Each of the five adult Phase 3 studies was a randomized, double-blind, double-dummy, multicenter, international trial comparing the efficacy and safety of azithromycin ER to a standard comparator. Table 59 summarizes the indications, comparators, and enrollment of these five azithromycin ER studies.

Table 59: Phase 3 Azithromycin ER Studies

Protocol	Indication	Comparator	Number of Patients Treated	
			Azi ER	Comparator
[REDACTED]	[REDACTED]	Levofloxacin, 500 mg daily, 7 days	268	274
A0661075	CAP	Clarithromycin ER, 1 g daily, 7 days	247	252
A0661103	CAP	Levofloxacin, 500mg daily, 7 days	211	212
A0661078	ABS	Levofloxacin, 500mg daily, 10 days	270	268
A0661119	GABHS	Azithromycin, 500 mg daily, 3 days	296	298
TOTAL			1292	1304

Abbreviations: [REDACTED] ABS = acute bacterial sinusitis; CAP = community-acquired pneumonia; GABHS = Group A beta-hemolytic *Streptococcus* Note: All studies were randomized, active-controlled, double-blind studies of a 2.0g single dose of Azithromycin ER

7.1.1 Deaths

There were 10 deaths in the five azithromycin Phase 3 studies, none of which were considered related to study drug. Only one death occurred among subjects receiving azithromycin. Subject 10041001 in Study A0661103, a 68-year-old man who received azithromycin ER, died of heart failure on Day 12.

Of the remaining 9 deaths, 5 occurred among subjects receiving clarithromycin, and 4 occurred among subjects receiving levofloxacin. The most common causes of death were pulmonary disease or cardiovascular events. The reason for discontinuation from study was "Subject died" for only 1 subject who received clarithromycin, and 2 subjects who received levofloxacin. The reason for these discrepancies in the clarithromycin group is that 3 subjects died after they completed the study and the investigator learned of the death of one additional subject only after the end of the study. Subject 10271007 in Study A0661075 did not return for study visits, and the investigator learned after the study database had locked that the subject had died on Study Day 7.

The reasons for these discrepancies in the levofloxacin group is that 2 levofloxacin-treated subjects died after they either withdrew from or completed the study. Eight (8) of the 10 deaths occurred within 35 days of study drug treatment.

7.1.2 Other Serious Adverse Events

The following table shows the number of serious adverse events among adults in the Phase 3 clinical program.

Table 60: Summary of Serious Adverse Event Cases in Adult Phase 3 Studies, Including Deaths

	Number of Cases				
	Azithromycin ER (N=1292)	Comparators			
		All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azith 3 Day (N=298)
All Cases Reported	25	30	11	19	0
Cases Related to Study Drug	0	0	0	0	0
<i>Number of Subjects with Frequent Events:</i>					
Pneumonia*	5	6	1	5	0
COPD**	3	4	0	4	0
Heart failure	2	2	2	0	0
Multi organ failure/multi event	0	4	3	1	0

Source: Applicant's data - Appendix II, Table 1
 * Includes event terms: Worsening pneumonia, progression of community-acquired pneumonia, right lower lobe pneumonia, pneumonia aggravated, bilateral pneumonia, exacerbation of pneumonia, non-responsive Pneumonia; ** Includes event terms: Acute exacerbation of chronic obstructive pulmonary disease, COPD exacerbation for bronchial constriction, acute exacerbation of chronic bronchitis, infective exacerbation of chronic obstructive airways disease, worsening of bronchitis, recurrence of acute exacerbation of chronic bronchitis

Other serious adverse events in the azithromycin ER group included nephrotic syndrome, hypotension, metastatic lung carcinoma, stroke, congestive heart failure, duodenal ulcer, atrial fibrillation, pulmonary emboli, acute myocardial infarction, diabetic ketoacidosis, and valley fever.

Medical Officer's Comments:

According to the investigator's report, none of the serious adverse events were due to azithromycin.

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7.1.3 Dropouts and Other Significant Adverse Events

Table 61: Number of Subjects with Adverse Events Resulting in Discontinuation From Treatment in Phase 3 Studies

	Number (%) of Subjects	
	All Causality	Treatment-Related
By Treatment		
Azithromycin ER	24/1292 (1.9)	3/1292 (0.2)
All Comparators	30/1304 (2.3)	6/1304 (0.5)
Azithromycin 3-day	5/298 (1.7)	0/298 (0)
Levofloxacin	17/754 (2.3)	5/754 (0.7)
Clarithromycin ER	8/252 (3.2)	1/252 (0.4)
Azithromycin-Treated Subjects		
CAP	12/458 (2.6)	1/458 (0.2)
Pharyngitis	4/268 (1.5)	1/268 (0.4)
Sinusitis	5/270 (1.9)	1/270 (0.4)
Pharyngitis		
Azithromycin ER	3/296 (1.0)	0/296 (0)
Azithromycin 3-day	5/298 (1.7)	0/298 (0)

Medical Officer's Comments:

Overall rates of discontinuation from study were similar between the pooled azithromycin ER (8.9%, 115 of 1292) and comparator (8.2%, 107 of 1304) groups. CAP subjects had the highest overall rate of discontinuation from study. Treatment-related discontinuations from study (due to either adverse events or lack of efficacy) were comparable between the pooled azithromycin ER (2.9%, 37 of 1292) and comparator (3.0%, 39 of 1304) groups.

In an analysis of discontinuations from treatment due to all-cause adverse events, the rates were 1.9% (24 of 1292) for azithromycin ER and 2.3% (30 of 1304) for pooled comparators. Discontinuation rates due to treatment-related adverse events were very low: 0.2% (3 of 1292) and 0.5% (6 of 1304), respectively.

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Overall profile of dropouts

**Table 62: Discontinuations from Study - All Phase 3 Clinical Studies - All Adult Subjects
 All Treated Subjects**

Number (%) of Subjects	Azithromycin ER 1292	Comparators 1304
Discontinuations		
Subject Died	1 (0.1)	3 (0.2)
Related to Study Drug	37 (2.9)	39 (3.0)
Adverse event	3 (0.2)	4 (0.3)
Lack of efficacy	34 (2.6)	35 (2.7)
Not Related to Study Drug	77 (6.0)	65 (5.0)
Adverse event	12 (0.9)	23 (1.8)
Other	12 (0.9)	7 (0.5)
Subject defaulted	53 (4.1)	35 (2.7)
Total	115 (8.9)	107 (8.2)

Comparators included: Levofloxacin (Studies [REDACTED], A0661103, and A0661078), Clarithromycin (Study A0661075), Azithromycin 3-day (Study A0661119)

Subject defaulted includes subjects who discontinued due to the following reasons: Lost to Follow-up or Subject no longer willing to participate in study; Other includes subjects who discontinued due to the following reasons: Other, Did not meet entrance criteria, or Protocol violation.

Relationship to Study Drug is derived as Related if reason for discontinuation is Insufficient Clinical Response, or due to a treatment related adverse event; otherwise, Relationship is derived as Not Related.

Includes Protocols: A0661075, A0661078, [REDACTED], A0661103, A0661119

7.1.3.1 Adverse events associated with dropouts

There were 2 subjects who had their dose temporarily discontinued due to adverse events. Both of these subjects received azithromycin ER and had temporary dose discontinuation after Day 1; therefore, both subjects in fact received their full course of active treatment. The details on these two patients is as follows:

- Patient A0661103/10701009 was a 25 year old asian male who developed gastritis on Day 3 of treatment. Treatment was temporarily stopped and resumed on day 5.
- Patient A0661078/10511075 was a 20 year old Hispanic male who developed diarrhea of day 5 of therapy, but by day 7 had resolution of diarrhea and continued with treatment.

7.1.3.2 Other significant adverse events

N/A

7.1.4 Other Search Strategies

N/A

7.1.5 Common Adverse Events

A summary of the most common adverse events (all causality) by treatment group is presented in Table 63. This table includes any event that occurred at a rate of >1% in the azithromycin ER treatment group, the all comparators treatment group, or for any individual comparator.

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Table 63: Summary of Common (>1%) Adverse Events (All Causality) in Phase 3 Studies by Treatment Group

	Number (%) of Subjects				
	Azithromycin ER (N=1292)	Comparators			
		All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azi 3 Day (N=298)
At least one AE	526 (40.7)	518 (39.7)	123 (48.8)	271 (35.9)	124 (41.6)
Discontinued due to AEs	24 (1.9)	30 (2.3)	8 (3.2)	17 (2.3)	5 (1.7)
Body System					
Event (preferred term)					
Body as a Whole	183 (14.2)	171 (13.1)	44 (17.5)	95 (12.6)	32 (10.7)
Abdominal pain	44 (3.4)	37 (2.8)	5 (2.0)	16 (2.1)	16 (5.4)
Accidental injury	9 (0.7)	11 (0.8)	3 (1.2)	6 (0.8)	2 (0.7)
Asthenia	17 (1.3)	20 (1.5)	6 (2.4)	12 (1.6)	2 (0.7)
Back pain	13 (1.0)	10 (0.8)	5 (2.0)	4 (0.5)	1 (0.3)
Chest pain	9 (0.7)	7 (0.5)	3 (1.2)	4 (0.5)	0 (0)
Fever	13 (1.0)	7 (0.5)	2 (0.8)	5 (0.7)	0 (0)
Headache	48 (3.7)	52 (4.0)	11 (4.4)	33 (4.4)	8 (2.7)
Infection (fungal)	4 (0.3)	4 (0.3)	3 (1.2)	1 (0.1)	0 (0)
Neoplasm	0 (0)	4 (0.3)	3 (1.2)	1 (0.1)	0 (0)
Pain	11 (0.9)	14 (1.1)	5 (2.0)	8 (1.1)	1 (0.3)
Digestive	267 (20.7)	176 (13.5)	46 (18.3)	81 (10.7)	49 (16.4)
Anorexia	4 (0.3)	9 (0.7)	3 (1.2)	6 (0.8)	0 (0)
Constipation	4 (0.3)	9 (0.7)	1 (0.4)	8 (1.1)	0 (0)
Diarrhea	156 (12.1)	69 (5.3)	19 (7.5)	22 (2.9)	28 (9.4)
Dyspepsia	9 (0.7)	12 (0.9)	3 (1.2)	5 (0.7)	4 (1.3)
Nausea	56 (4.3)	39 (3.0)	10 (4.0)	23 (3.1)	6 (2.0)
Stools (loose)	12 (0.9)	8 (0.6)	2 (0.8)	2 (0.3)	4 (1.3)
Vomiting	25 (1.9)	24 (1.8)	9 (3.6)	8 (1.1)	7 (2.3)
Musculoskeletal	13 (1.0)	25 (1.9)	7 (2.8)	12 (1.6)	6 (2.0)
Myalgia	5 (0.4)	9 (0.7)	4 (1.6)	4 (0.5)	1 (0.3)
Nervous	30 (2.3)	55 (4.2)	10 (4.0)	36 (4.8)	9 (3.0)
Dizziness	14 (1.1)	26 (2.0)	4 (1.6)	17 (2.3)	5 (1.7)
Insomnia	5 (0.4)	13 (1.0)	5 (2.0)	8 (1.1)	0 (0)
Respiratory	173 (13.4)	197 (15.1)	55 (21.8)	100 (13.3)	42 (14.1)
Asthma	12 (0.9)	25 (1.9)	12 (4.8)	13 (1.7)	0 (0)
Bronchitis	6 (0.5)	11 (0.8)	0 (0)	11 (1.5)	0 (0)
Cough Increased	22 (1.7)	24 (1.8)	8 (3.2)	10 (1.3)	6 (2.0)
Dyspnea	18 (1.4)	15 (1.2)	4 (1.6)	11 (1.5)	0 (0)
Hemoptysis	3 (0.2)	4 (0.3)	3 (1.2)	1 (0.1)	0 (0)
Hyperventilation	3 (0.2)	5 (0.4)	4 (1.6)	1 (0.1)	0 (0)
Pharyngitis	22 (1.7)	19 (1.5)	4 (1.6)	4 (0.5)	11 (3.7)
Pleural Disorder	2 (0.2)	6 (0.5)	4 (1.6)	2 (0.3)	0 (0)
Pneumonia	13 (1.0)	15 (1.2)	5 (2.0)	10 (1.3)	0 (0.0)
Respiratory Disorder	27 (2.1)	33 (2.5)	13 (5.2)	19 (2.5)	1 (0.3)

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 NDA 50-797
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Respiratory Tract Inf.	25 (1.9)	29 (2.2)	8 (3.2)	7 (0.9)	14 (4.7)
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	Number (%) of Subjects				
	Comparators				
	Azithromycin ER (N=1292)	All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azi 3 Day (N=298)
Rhinitis	31 (2.4)	32 (2.5)	8 (3.2)	15 (2.0)	9 (3.0)
Sinusitis	9 (0.7)	12 (0.9)	2 (0.8)	7 (0.9)	3 (1.0)
Sputum Increased	11 (0.9)	12 (0.9)	3 (1.2)	9 (1.2)	0 (0)
Skin and Appendages	34 (2.6)	39 (3.0)	11 (4.4)	15 (2.0)	13 (4.4)
Maculopapular rash	0 (0)	5 (0.4)	2 (0.8)	0 (0)	3 (1.0)
Rash	13 (1.0)	13 (1.0)	1 (0.4)	5 (0.7)	7 (2.3)
Special Senses	22 (1.7)	34 (2.6)	12 (4.8)	18 (2.4)	4 (1.3)
Taste Perversion	4 (0.3)	13 (1.0)	9 (3.6)	4 (0.5)	0 (0)
Urogenital	18 (1.4)	19 (1.5)	6 (2.4)	7 (0.9)	6 (2.0)
Menstrual disorder*	0 (0)	2 (0.3)	0 (0)	0 (0)	2 (1.1)
Prostatic Disorder+	0 (0)	3 (0.5)	2 (1.5)	1 (0.2)	0 (0)

Source: Applicant's data tables
 Studies included: ██████████ A0661103, A0661075, A0661119, A0661078
 Comparators included: Levofloxacin (Studies ██████████ A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119) *Incidence in female subjects; +Incidence in male subjects

With the exception of diarrhea, which was reported more frequently among azithromycin ER subjects, the incidence of individual adverse events (all causality) was comparable for the azithromycin ER and all comparators groups.

A summary of the most common adverse events (all causality) for azithromycin ER-treated subjects, by indication, are presented in Table 64.

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Table 64: Summary of Common (>1%) Adverse Events (All Causality) in Azithromycin ER-Treated Subjects by Indication

	Number (%) of Subjects			
	Azithromycin ER			
	CAP (N=458)	 (N=268)	Sinusitis (N=270)	Pharyngitis (N=296)
At least one AE	200 (43.7)	115 (42.9)	96 (35.6)	115 (38.9)
Discontinued due to AEs	12 (2.6)	4 (1.5)	5 (1.9)	3 (1.0)
Body System				
Event (preferred term)				
Body as a Whole	67 (14.6)	45 (16.8)	33 (12.2)	38 (12.8)
Accidental injury	4 (0.9)	2 (0.7)	0 (0)	3 (1.0)
Abdominal pain	16 (3.5)	8 (3.0)	9 (3.3)	11 (3.7)
Asthenia	7 (1.5)	5 (1.9)	3 (1.1)	2 (0.7)
Back pain	3 (0.7)	6 (2.2)	1 (0.4)	3 (1.0)
Chest pain	5 (1.1)	2 (0.7)	2 (0.7)	0 (0)
Fever	9 (2.0)	1 (0.4)	3 (1.1)	0 (0)
Headache	18 (3.9)	12 (4.5)	8 (3.0)	10 (3.4)
Infection (bacterial)	2 (0.4)	1 (0.4)	0 (0)	3 (1.0)
Pain	4 (0.9)	4 (1.5)	2 (0.7)	1 (0.3)
Cardiovascular	5 (1.1)	5 (1.9)	5 (1.9)	1 (0.3)
Migraine	0 (0)	0 (0)	3 (1.1)	0 (0)
Digestive	97 (21.2)	61 (22.8)	49 (18.1)	60 (20.3)
Diarrhea	58 (12.7)	36 (13.4)	28 (10.4)	34 (11.5)
Dyspepsia	4 (0.9)	3 (1.1)	1 (0.4)	1 (0.3)
Dysphagia	0 (0)	0 (0)	0 (0)	5 (1.7)
Gastritis	5 (1.1)	0 (0)	4 (1.5)	1 (0.3)
Flatulence	1 (0.2)	7 (2.6)	2 (0.7)	0 (0)
Nausea	15 (3.3)	15 (5.6)	12 (4.4)	14 (4.7)
Stools (loose)	7 (1.5)	2 (0.7)	3 (1.1)	0 (0.0)
Vomiting	12 (2.6)	2 (0.7)	2 (0.7)	9 (3.0)
Hemic and Lymphatic	4 (0.9)	1 (0.4)	0 (0)	3 (1.0)
Lymphadenopathy	0 (0)	0 (0)	0 (0)	3 (1.0)
Musculoskeletal	8 (1.7)	3 (1.1)	1 (0.4)	1 (0.3)
Myalgia	2 (0.4)	3 (1.1)	0 (0)	0 (0)
Nervous	16 (3.5)	5 (1.9)	4 (1.5)	5 (1.7)
Dizziness	7 (1.5)	3 (1.1)	2 (0.7)	2 (0.7)
Respiratory	76 (16.6)	44 (16.4)	26 (9.6)	27 (9.1)
Asthma	7 (1.5)	5 (1.9)	0 (0)	0 (0)
Bronchitis	2 (0.4)	3 (1.1)	1 (0.4)	0 (0)
Cough Increased	11 (2.4)	7 (2.6)	4 (1.5)	0 (0)
Dyspnea	8 (1.7)	10 (3.7)	0 (0)	0 (0)
Epistaxis	2 (0.4)	0 (0)	7 (2.6)	0 (0)
Pharyngitis	7 (1.5)	2 (0.7)	4 (1.5)	9 (3.0)
Pneumonia	9 (2.0)	4 (1.5)	0 (0)	0 (0)
Respiratory Disorder	17 (3.7)	6 (2.2)	1 (0.4)	3 (1.0)

	Number (%) of Subjects			
	Azithromycin ER			
	CAP (N=458)	(N=268)	Sinusitis (N=270)	Pharyngitis (N=296)
Respiratory Tract Inf.	8 (1.7)	6 (2.2)	2 (0.7)	9 (3.0)
Rhinitis	8 (1.7)	8 (3.0)	8 (3.0)	7 (2.4)
Sputum Increased	7 (1.5)	4 (1.5)	0 (0)	0 (0)
Sinusitis	4 (0.9)	1 (0.4)	3 (1.1)	1 (0.3)
Skin and Appendages	13 (2.8)	7 (2.6)	5 (1.9)	9 (3.0)
Maculopapular rash	0 (0)	0 (0)	0 (0)	0 (0)
Rash	4 (0.9)	2 (0.7)	2 (0.7)	5 (1.7)
Special Senses	13 (2.8)	2 (0.7)	5 (1.9)	2 (0.7)
Ear pain	2 (0.4)	1 (0.4)	3 (1.1)	1 (0.3)
Urogenital	5 (1.1)	2 (0.7)	1 (0.4)	10 (3.4)
Menstrual disorder*	0 (0)	0 (0)	0 (0)	0 (0)
Vaginitis*	1 (0.4)	1 (1.1)	0 (0)	3 (1.6)

Source: Applicant's data
 Studies included: A0661103, A0661075 (CAP); (b) (4) A0661119(GABHS Pharyngitis);
 A0661078(Sinusitis)
 Comparators included: Levofloxacin (Studies (b) (4) A0661103, A0661078), Clarithromycin ER (Study
 A0661075)Azithromycin 3-day (Study A0661119)
 *Incidence in female subjects

Medical Officer's comments:

The overall frequency of adverse events (all causality) was comparable for the azithromycin treated subjects across the various indications. The digestive system had the highest incidence of adverse events, and the most frequently reported individual adverse event was diarrhea. Many of the adverse event terms were reported at a rate of >1% in only one of the four indications, and are related to that specific disease.

A summary by treatment group of the most common treatment-related adverse events by treatment group is presented in Table 65.

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Table 65: Summary of Common (>1%) Treatment-Related Adverse Events in Phase 3 Studies by Treatment Group

	Number (%) of Subjects				
	Azithromycin ER (N=1292)	Comparators			
		All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azith 3 Day (N=298)
At least one AE	295 (22.8)	229 (17.6)	62 (24.6)	109 (14.5)	58 (19.5)
Discontinued due to AEs	3 (0.2)	6 (0.5)	1 (0.4)	5 (0.7)	0 (0.0)
Body System					
Event (preferred term)					
Body as a Whole	78 (6.0)	61 (4.7)	17 (6.7)	28 (3.7)	16 (5.4)
Abdominal pain	35 (2.7)	27 (2.1)	3 (1.2)	10 (1.3)	14 (4.7)
Headache	17 (1.3)	8 (0.6)	3 (1.2)	4 (0.5)	1 (0.3)
Digestive	222 (17.2)	127 (9.7)	32 (12.7)	55 (7.3)	40 (13.4)
Diarrhea	141 (10.9)	63 (4.8)	17 (6.7)	18 (2.4)	28 (9.4)
Dyspepsia	8 (0.6)	8 (0.6)	1 (0.4)	3 (0.4)	4 (1.3)
Nausea	51 (3.9)	28 (2.1)	8 (3.2)	16 (2.1)	4 (1.3)
Loose Stools	10 (0.8)	8 (0.6)	2 (0.8)	2 (0.3)	4 (1.3)
Vomiting	14 (1.1)	9 (0.7)	2 (0.8)	5 (0.7)	2 (0.7)
Nervous	10 (0.8)	21 (1.6)	3 (1.2)	15 (2.0)	3 (1.0)
Dizziness	6 (0.5)	13 (1.0)	2 (0.8)	8 (1.1)	3 (1.0)
Special Senses	5 (0.4)	17 (1.3)	9 (3.6)	8 (1.1)	0 (0.0)
Taste Perversion	4 (0.3)	13 (1.0)	9 (3.6)	4 (0.5)	0 (0.0)
Source: Applicant's data - Studies included: A0661103, A0661075, A0661119, A0661078 Comparators included: Levofloxacin (Studies A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)					

The overall incidence of treatment-related adverse events was comparable in the azithromycin ER and all comparators groups. Digestive system adverse events, in particular diarrhea, were more common among azithromycin ER subjects than all comparator-treated subjects combined, but the gastrointestinal adverse event profile of azithromycin ER was comparable to that of the azithromycin 3-day regimen.

Among the 1292 subjects who received azithromycin ER in the adult Phase 3 studies, 141 had treatment-related diarrhea (10.9%), and 10 had treatment-related loose stools (0.8%). One subject had both diarrhea and loose stools, so the incidence of treatment-related diarrhea and/or loose stools (diarrhea/loose stools) in the Phase 3 studies was 150/1292, or 11.6%.

A summary of the most common treatment-related adverse events for azithromycin ER-treated subjects, by indication, are presented in Table 66.

Table 66: Summary of Common (>1%) Treatment-Related Adverse Events in Phase 3 Studies for Azithromycin ER-Treated Subjects by Indication

	Number (%) of Subjects			
	Azithromycin ER			
	CAP (N=458)	 (N=268)	Sinusitis (N=270)	Pharyngitis (N=296)
At least one AE	107 (23.4)	65 (24.3)	63 (23.3)	60 (20.3)
Discontinued due to AEs	1 (0.2)	1 (0.4)	1 (0.4)	0 (0.0)
Body System				
Event (preferred term)				
Body as a Whole	23 (5.0)	19 (7.1)	14 (5.2)	22 (7.4)
Abdominal pain	13 (2.8)	6 (2.2)	7 (2.6)	9 (3.0)
Headache	3 (0.7)	7 (2.6)	1 (0.4)	6 (2.0)
Digestive	78 (17.0)	51 (19.0)	47 (17.4)	46 (15.5)
Diarrhea	51 (11.1)	32 (11.9)	27 (10.0)	31 (10.5)
Dyspepsia	3 (0.7)	3 (1.1)	1 (0.4)	1 (0.3)
Flatulence	1 (0.2)	6 (2.2)	2 (0.7)	0 (0)
Gastritis	4 (0.9)	0 (0)	4 (1.5)	0 (0)
Nausea	12 (2.6)	14 (5.2)	12 (4.4)	13 (4.4)
Stools (loose)	6 (1.3)	1 (0.4)	3 (1.1)	0 (0)
Vomiting	6 (1.3)	1 (0.4)	2 (0.7)	5 (1.7)
Nervous	5 (1.1)	2 (0.7)	2 (0.7)	1 (0.3)
Dizziness	2 (0.4)	1 (0.4)	2 (0.7)	1 (0.3)
Respiratory	9 (2.0)	4 (1.5)	4 (1.5)	0 (0)
Respiratory Disorder	5 (1.1)	0 (0)	0 (0)	0 (0)
Skin and Appendages	7 (1.5)	5 (1.9)	4 (1.5)	3 (1.0)
Rash	4 (0.9)	2 (0.7)	2 (0.7)	2 (0.7)
Urogenital	2 (0.4)	2 (0.7)	0 (0)	4 (1.4)
Vaginitis*	1 (0.4)	1 (1.1)	0 (0)	2 (1.1)
Source: Applicant's data				
Studies included: A0661103, A0661075 (CAP), GABHS Pharyngitis (A0661119), and Sinusitis (A0661078). *Incidence in female subjects				

The overall incidence of treatment-related adverse events was comparable across the various indications. Again, the digestive system had the highest incidence of adverse events, with diarrhea being the most frequently reported individual event. The rates of diarrhea were comparable across the four indications.

7.1.5.1 Eliciting adverse events data in the development program

Refer to Section 7.1 methods.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Refer to Section 7.1.

7.1.5.3 Incidence of common adverse events

Refer to section 7.1.5.

7.1.5.4 Common adverse event tables

Refer to section 7.1.5.

7.1.5.5 Identifying common and drug-related adverse events

Refer to section 7.1.5.

7.1.5.6 Additional analyses and explorations

Analysis of GI AEs by Onset Day and by Duration

Given the single-dose nature of azithromycin ER and the multi-day dosing regimens of the comparators in the Phase 3 studies, an analysis of AEs by onset and duration was performed. Table 67 shows, for each treatment group, the day of onset and duration of treatment-related, treatment emergent gastrointestinal adverse events that occurred in each of the treatment groups at an incidence of $\geq 1\%$ (GI AEs $\geq 1\%$).

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Table 67: Number of Treatment-Emergent, Treatment-Related GI AEs with >1% Incidence in Phase 3 Studies by Treatment Group

Duration	Number (%) of Events -				
	Onset Day				
	Total	Day 1	Day 2	Day 3-7	>7 Days
Azithromycin ER (Number of Subjects = 1292)					
Any GI AE >1%	244 (100.0)	164 (67.2)	43 (17.6)	30 (12.3)	7 (2.9)
1 day	129 (52.9)	96 (39.3)	16 (6.6)	15 (6.1)	2 (0.8)
2 days	65 (26.6)	47 (19.3)	15 (6.1)	2 (0.8)	1 (0.4)
3-7 days	39 (16.0)	18 (7.4)	9 (3.7)	9 (3.7)	3 (1.2)
>7 days	11 (4.5)	3 (1.2)	3 (1.2)	4 (1.6)	1 (0.4)
All Comparators (Number of Subjects = 1304)					
Any GI AE >1%	130 (100.0)	56 (43.1)	34 (26.2)	31 (23.8)	9 (6.9)
1 day	60 (46.2)	21 (16.2)	15 (11.5)	18 (13.8)	6 (4.6)
2 days	22 (16.9)	8 (6.2)	9 (6.9)	5 (3.8)	0 (0)
3-7 days	37 (28.5)	22 (16.9)	7 (5.4)	6 (4.6)	2 (1.5)
>7 days	11 (8.5)	5 (3.8)	3 (2.3)	2 (1.5)	1 (0.8)
Azithromycin 3-day (Number of Subjects = 298)					
Any GI AE >1%	56 (100.0)	34 (60.7)	10 (17.9)	11 (19.6)	1 (1.8)
1 day	25 (44.6)	12 (21.4)	4 (7.1)	8 (14.3)	1 (1.8)
2 days	8 (14.3)	3 (5.4)	2 (3.6)	3 (5.4)	0 (0)
3-7 days	21 (37.5)	19 (33.9)	2 (3.6)	0 (0)	0 (0)
>7 days	2 (3.6)	0 (0)	2 (3.6)	0 (0)	0 (0)
Source: Applicant's data					
Studies included: ██████████ A0661103, A0661075, A0661119, A0661078					
Comparators included: Levofloxacin (Studies ██████████ A0661103, A0661078), Clarithromycin ER (Study A0661075)					
Azithromycin 3-day (Study A0661119)					
Note: Gastrointestinal adverse events are defined as any event in the digestive body system, plus abdominal pain (which is included in the system "body as a whole"). The GI AE >1% for azithromycin ER and all comparators were diarrhea, nausea and vomiting. For azithromycin 3-day (data from Study A0661119), they were diarrhea, nausea, vomiting and Dyspepsia.					

The analysis by onset day and duration was also done for the number of subjects with treatment related GI AEs >1%. Although gastrointestinal adverse events occurred more often in subjects receiving azithromycin ER, they were more likely to occur on the single day of treatment and resolve within 1-2 days than gastrointestinal events occurring in comparator-treated subjects. The majority of the azithromycin ER-treated subjects who had treatment-related diarrhea, nausea, abdominal pain and/or vomiting had these resolve within 2 days of commencing therapy (137/203; 67.5%), compared to 39 of 109 comparator treated subjects (35.8%). The majority of the azithromycin ER-treated subjects with treatment related diarrhea had their episodes resolve within 2 days of commencing therapy (94/141; 66.7%), compared to 23 of 63 comparator-treated subjects (36.5%).

Vomiting

Azithromycin ER is administered as a single dose. If a subject vomits within a short time after dosing, it is therefore possible that he or she may not have received an effective dose, and may

need to be re-dosed. If, however, the subject has in fact absorbed a significant proportion of the first dose, re-dosing may result in the subject receiving more than the intended dose, which could result in an increased risk of adverse events.

In the azithromycin ER study protocols, study personnel were instructed to re-administer the full dose to any subject that vomited within 5 minutes of dosing. Subjects who could not tolerate oral drug or had medical conditions that might interfere with absorption of drug were excluded from the studies.

Table 68 presents a summary of the incidence of treatment-related vomiting.

Table 68: Summary of Treatment-Related Vomiting in Phase 3 studies

	Azithromycin ER	Comparator
Total Number of Subjects	N=1292	N=1304
Subjects (%) Who Vomited at Any Time*	14 (1.1)	9 (0.7)
Subjects (%) Who Vomited on Day 1*	8 (0.6)	3 (0.2)
Vomiting Adverse Event Burden	0.178	0.083
Source: Applicant's data		
*Subjects who vomit more than one time are counted only once in each subset.		
Vomiting Adverse Event Burden = Days of Vomiting per Patient Year = (Number of Days of Treatment-Related Vomiting/Total Number of Observation Days for All Treated Subjects) x 365.25		

The incidence of treatment-related vomiting, both overall and on study Day 1, was slightly higher in the azithromycin ER arm than the all comparators arm.

In the azithromycin ER study protocols, study personnel were instructed to re-administer the full dose to any subject who vomited within 5 minutes of dosing. The protocol specified that blood samples were to be taken from any subject who vomited within 30 minutes of dosing in order to investigate how much drug is absorbed under these circumstances. Also, the clinical outcomes for subjects who vomited within 30 minutes were analyzed separately to assess whether the efficacy of azithromycin ER was affected by vomiting.

There were no subjects in any of the five Phase 3 studies who vomited within 5 minutes. There were only 2 subjects who vomited while under observation, both in Study A0661075. Neither of these subjects vomited within 30 minutes of dosing and neither was re-dosed. One of these subjects, who vomited at 45 minutes, had a blood sample drawn. The serum azithromycin concentration of that sample is not available.

Diarrhea

For subjects receiving azithromycin ER in the Phase 3 studies, the most frequent adverse event was diarrhea; this event was reported more frequently than for subjects who received comparators. The adverse events of diarrhea for the two treatment groups are summarized in Table 69.

Table 69: Summary of Diarrhea (All Causality and Treatment-Related) in Phase 3 Studies

	All-Causality		Treatment-Related	
	Azithromycin ER	Comparator	Azithromycin ER	Comparator
All Treated Subjects				
Number of Subjects	N=1292	N=1304	N=1292	N=1304
Diarrhea	156 (12.1)	69 (5.3)	141 (10.9)	63 (4.8)
Severe Diarrhea	5 (0.4)	3 (0.2)	5 (0.4)	3 (0.2)
Adverse Event Burden				
Total Observation Days	38886	39496	38886	39496
Adverse Event Burden of Diarrhea	3.5	1.9	2.7	1.7
Source: Applicant's data				
Adverse Event Burden = Adverse Event Days per Patient Year = (Number of Days of Treatment-Related Adverse Events/Total Number of Observation Days for All Treated Subjects) x 365.25 days				

Most of the events of diarrhea (all-causality) for Azithromycin ER-treated subjects in the Phase 3 studies did not require treatment (142/157, or 90.4%). Few subjects reported severe diarrhea. All severe diarrhea was considered treatment related, but there were no subjects who discontinued from the study due to diarrhea. Diarrhea was not reported as an SAE for any subject, and there were no reports of *Clostridium difficile* colitis or pseudomembranous colitis.

7.1.6 Less Common Adverse Events

Refer to section 7.1.5.

7.1.7 Laboratory Findings

Subjects who had at least one laboratory assessment at baseline and at least one post-baseline laboratory evaluation were evaluable for laboratory abnormalities. Table 70 presents the overall rates of clinically significant laboratory abnormalities by treatment group.

Table 70: Overall Incidence of Clinically Significant Abnormalities in Phase 3 Studies

	Number (%) of Subjects				
	Azithromycin ER	Comparators	Clarithromycin ER	Levofloxacin	Azith 3 Day
Number of Subjects	(N=1292)	(N=1304)	(N=252)	(N=754)	(N=298)
Evaluable for Laboratory Abnormalities	689 (53.3)	696 (53.4)	234 (92.9)	462 (61.3)	0 (0)
With Laboratory Test Abnormalities					
Regardless of Baseline Abnormality	176/689 (26)	212/696 (30)	75/234 (32)	137/462 (30)	NA
Considering Baseline Abnormality*					
Normal Baseline	105/689 (15)	123/696 (18)	41/234 (18)	82/462 (18)	NA
Abnormal Baseline	26/551 (5)	44/559 (8)	17/199 (9)	27/360 (8)	NA
Source: Applicant's data					
*Note: An individual subject with normal baseline for some parameters and abnormal baseline for others is included in the overall totals for both the "Normal Baseline" and "Abnormal Baseline" analyses					
N/A = Not Applicable for this study, which had no protocol specified safety laboratory tests.					

The azithromycin 3-day and levofloxacin arms have fewer evaluable subjects because Study A0661119 (the only one with azithromycin 3-day as a comparator) and Study A0661078 (one of the 3 levofloxacin studies) had no protocol-specified safety laboratory tests other than baseline pregnancy testing.

The overall rates of laboratory abnormalities for the five Phase 3 studies were similar between the azithromycin ER and all comparators groups. Among comparator-treated subjects, the overall incidence of laboratory abnormalities was similar for the clarithromycin and levofloxacin treatment groups.

The clinically significant laboratory test abnormalities (defined by criteria shown in the table) occurring in $\geq 1\%$ of subjects in either the azithromycin ER or all comparators groups are summarized in Table 71.

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Table 71: Incidence of Clinically Significant Abnormalities (Without Regard to Baseline Abnormality) in Phase 3 studies – Incidence of >1% in Azithromycin ER or Comparator Treatment Group

Parameter	Number (%) of Subjects with Laboratory Test Abnormalities	
	Azithromycin ER (N=1292)	All Comparators (N=1304)
	Number with Abnormality/Number Evaluable (%)	
Overall	176/689 (25.5)	212/696 (30.5)
Hematological		
WBC Count		
Increased: >17.5 $10^3/\text{mm}^3$	1/669 (0.1)	11/666 (1.7)
Lymphocytes (Abs) $10^3/\text{mm}^3$		
Decreased: <0.8 x LLN	20/160 (12.6)	20/170 (11.8)
Increased: >1.2 x ULN +	2/160 (1.3)	3/170 (1.8)
Lymphocytes (%)		
Decreased: <0.8 x LLN	35/508 (6.9)	40/500 (8.0)
Increased: >1.2 x ULN +	3/508 (0.6)	5/500 (1.0)
Neutrophils (Abs) $10^3/\text{mm}^3$		
Decreased: <0.8 x LLN	0/160 (0)	2/171 (1.2)
Increased: >1.2 x ULN	9/160 (5.7)	14/171 (8.2)
Basophils (%)		
Increased >1.2 x ULN	29/500 (5.8)	31/489 (6.3)
Eosinophils (Abs) $10^3/\text{mm}^3$		
Increased >1.2 x ULN	6/159 (3.8)	14/170 (8.2)
Eosinophils (%)		
Increased >1.2 x ULN	24/507 (4.7)	24/500 (4.8)
Monocytes (Abs) $10^3/\text{mm}^3$		
Increased >1.2 x ULN	5/159 (3.1)	3/169 (1.8)
Monocytes (%)		
Increased >1.2 x ULN +	8/507 (1.6)	14/501 (2.7)
Liver Function		
AST (SGOT) IU/L		
Increased >3.0 x ULN *	8/678 (1.2)	3/685 (0.4)
ALT (SGPT) IU/L		
Increased >3.0 x ULN *	10/674 (1.5)	4/677 (0.6)
Renal function		
BUN mg/dL		
Increased >1.3 x ULN	6/682 (0.9)	21/692 (3.0)
Creatinine mg/dL		
Increased >1.3 x ULN*	9/682 (1.3)	11/692 (1.6)
Electrolytes		
Bicarbonate mEq/L		
Decreased <0.9 x LLN	9/616 (1.5)	5/620 (4.0)
Increased >1.1 x ULN*,+	15/616 (2.4)	17/620 (2.7)
Other		
Glucose (random) mg/dL		
>1.5 x ULN	6/366 (1.6)	11/361 (3.0)

Source: Applicant's data. Notes: Any test with <30 evaluable subjects was not included in this table. * This test did not have a rate of abnormality >1% in the analysis of subjects with normal baseline.
+ This test did not have a rate of abnormality >1% in the analysis of subjects with abnormal baseline. Additional tests had a rate of abnormality >1% in the analysis of subjects with abnormal baseline: Decreased platelets ($<75 \times 10^3/\text{mm}^3$) for comparator (2/71; 2.8%); Increased platelets ($>700 \times 10^3/\text{mm}^3$) for Azithromycin ER (1/73; 1.4%) and comparator (1/71; 1.4%); Hemoglobin ($<0.8 \times$ baseline) for comparators (22/136; 1.5%).

The overall rates of laboratory abnormalities were similar for the azithromycin ER and comparator treatment groups, and there were few apparent differences in the rates for individual tests. No subject discontinued the study prematurely, nor had any temporary discontinuations or dose reductions due to laboratory abnormalities.

Among azithromycin ER-treated subjects, 1 subject had increased ALT and 2 subjects had increased ALT and increased AST, all had resolved by the end of study. One subject (Subject 10671003 in Study A0661075) had increased ALT, AST, and alkaline phosphatase reported as treatment-related adverse events; the outcome was noted as "unknown" but AST and ALT levels had declined and alkaline phosphatase levels had returned to normal at the time of the last assessment during the study, on Day 29. AST and ALT levels were normal at a follow up assessment after the study (64 days after dosing). An additional subject (Subject 10941005 in Study A0661103) had hepatic enzymes (transaminases) and alkaline phosphatase increases considered to be due to concomitant medication (diclofenac and dipyrrone); the outcome was noted as "unknown". An adverse event of hypoglycemia (not considered related to treatment) was reported for one subject.

Not all of the subjects who had elevations of ALT and AST had these increases reported as adverse events. In addition to the subjects with ALT, AST, and/or alkaline phosphatase increases noted as an adverse event, 9 other azithromycin ER-treated subjects had elevations of AST and ALT. The ALT and AST levels for 7 of these 9 subjects were decreasing by the time of the final laboratory assessment. Of the two remaining subjects, one had AST and ALT results only for Day 1 and Day 4. The other subject, who had abnormal levels at baseline, was still abnormal at the final assessment on Day 15.

Laboratory test results were analyzed for severity using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale from Grade 0 (least severe) to Grade 4 (most severe). There were only a few azithromycin ER-treated subjects with laboratory abnormalities of Grade 3, and none with abnormalities of Grade 4. The following abnormalities were Grade 3 for azithromycin ER-treated subjects: SGOT, 4 subjects; SGPT, 5 subjects; WBCs, 3 subjects; hemoglobin, lymphocytes, hyponatremia, and hyperglycemia, 2 subjects each; neutrophils, hypernatremia, and hypochloremia 1 subject each.

Clinically significant laboratory abnormalities were analyzed by age, race, and gender, using the same categories as for the adverse events. The overall rates of abnormalities are shown in Table 72.

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Table 72: Clinically Significant Laboratory Abnormalities by Demographic Characteristics in Phase 3 studies For Subjects with Normal Baseline

	Number of subjects with any abnormality/Number of subjects evaluable	
	Azithromycin ER (N=1292)	All Comparators (N=1304)
Overall	105/689 (15.2)	123/696 (17.7)
Age (yr)		
<16	0/0 (0)	0/0 (0)
16-44	31/210 (14.8)	39/221 (17.6)
45-64	46/295 (15.6)	46/312 (14.7)
> 65	28/184 (15.2)	38/163 (23.3)
Subjects > 75	5/49 (10.2)	12/51 (23.5)
Race (%)		
White	65/466 (13.9)	73/459 (15.9)
Black	6/47 (12.8)	6/45 (13.3)
Asian	27/118 (22.9)	35/127 (27.6)
Hispanic	6/28 (21.4)	7/36 (19.4)
Other	1/30 (3.3)	2/29 (6.9)
Gender (%)		
Males	59/390 (15.1)	76/409 (18.6)
Females	46/299 (15.4)	47/287 (16.4)
Geographic Region(%)		
U.S./Canada	41/306 (13.4)	32/313 (10.2)
Outside U.S./Canada	64/383 (16.7)	91/383 (23.8)
Source: Applicant's data		
Studies included: ██████████, A0661103, A0661075, A0661119, A0661078		
Comparators included: Levofloxacin (Studies ██████████, A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)		

In both treatment groups, males and females had similar rates of clinically significant laboratory abnormalities. While the incidence of laboratory abnormalities was similar across all age groups of azithromycin ER-treated subjects, they were less common than in subjects >65 years of age in the comparator-treated group. Asian and Hispanic subjects had the highest rates of laboratory abnormalities. Very few subjects in the race category of Other had laboratory abnormalities. The overall rate of clinically significant abnormalities for comparator-treated subjects was considerably higher for subjects outside the U.S. and Canada than for subjects within the U.S. and Canada, but the same effect was not seen for azithromycin ER-treated subjects.

7.1.7.1 Overview of laboratory testing in the development program

Reporting and Evaluation of Clinical Laboratory Analyses

In the CAP ██████████ studies, clinical assessments (blood chemistry, hematology) were performed as specified by the protocol, and additional laboratory tests could be performed if deemed necessary by the investigator. In the other phase 3 studies (ABS and pharyngitis), there were no protocol-specified laboratory tests other than baseline pregnancy testing. Laboratory

tests in these studies were conducted as deemed necessary by the investigator. Laboratory abnormalities are summarized and listings, by subject and by test, are provided. Baseline was defined as the last value prior to treatment. All incidences are rounded to the nearest whole percent. Median changes in laboratory data from baseline to last observation (up to 35 days after the last dose of study drug) are tabulated. The percent of subjects with a laboratory abnormality was based on only those subjects undergoing that test.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Refer to Section 7.1.7

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

7.1.7.3.3 *Marked outliers and dropouts for laboratory abnormalities*

Refer to Section 7.1.7

7.1.7.4 Additional analyses and explorations

Analysis of Safety Data by Extrinsic and Intrinsic Factors

Selected data from the Phase 3 studies (adverse events and laboratory test abnormalities) were also analyzed by region (U.S. and non-U.S.) and demographic subsets, including gender, age and race. (Refer to Table 72)

7.1.7.5 Special assessments

Intrinsic Factors

Gender

The five azithromycin ER Phase 3 studies enrolled nearly equal numbers of male and female subjects in the azithromycin ER and all comparators treatment groups.

Table 73 presents, by gender, the overall frequency of adverse events (all causality), and the overall frequency of discontinuation due to adverse events (all causality), and the most commonly reported adverse events of all causality (>3% in either treatment group).

Table 73: Summary of Adverse Events (All Causality) in Phase 3 Studies by Gender

	Number (%) of Subjects			
	Azithromycin ER		Comparator	
	Males (N=644)	Females (N=648)	Males (N=653)	Females (N=651)
At least one AE	249 (38.7)	277 (42.7)	232 (35.5)	286 (43.9)
Discontinued due to AEs	11(1.7)	13 (2.0)	16 (2.5)	14 (2.2)
Most common AEs				
Diarrhea	74 (11.5)	82 (12.7)	27 (4.1)	42 (6.5)
Headache	25 (3.9)	23 (3.5)	24 (3.7)	28 (4.3)
Nausea	16 (2.5)	40 (6.2)	12 (1.8)	27 (4.1)
Abdominal pain	20 (3.1)	24 (3.7)	10 (1.5)	27 (4.1)
AE = adverse event				
Source: Applicant's data				

Medical Officer's Comments:

In both treatment groups, the overall incidence of all causality adverse events was slightly higher in females.

The incidence of the most commonly reported adverse events was generally similar for males and females within the azithromycin ER and comparator groups. Two exceptions were the higher incidence of nausea reported by females in both treatment groups, and the higher incidence of abdominal pain reported by females in the comparator group.

Age

The majority of evaluable subjects in both treatment groups (82% azithromycin ER and 83% comparators) were between 16 and 64 years of age. There were 49 subjects <16 years old (19 azithromycin ER and 30 comparators) and 118 subjects (59 azithromycin ER and 59 comparators) ≥75 years old.

Table 74 presents, by age, the overall frequency of adverse events (all causality), and the overall frequency of discontinuation due to adverse events (all causality), and the most commonly reported adverse events of all causality (>3% in either treatment group).

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Table 74: Summary of Adverse Events (All Causality) for Subjects ≥16 Years of Age in Phase 3 Studies by Age

	Number (%) of Subjects					
	Azithromycin ER			Comparators		
	16-44 years (N=652)	45-64 years (N=407)	> 65 years (N=214)	16-44 years (N=657)	45-64 years (N=423)	> 65 years (N=194)
At least one AE	259 (39.7)	175 (43.0)	85 (39.7)	261 (39.7)	171 (40.4)	74 (38.1)
Discontinued due to AEs	10 (1.5)	9 (2.2)	3 (1.4)	11 (1.7)	11 (2.6)	8 (4.1)
Diarrhea	89 (13.7)	38 (9.3)	27 (12.6)	42 (6.4)	22 (5.2)	2 (1.0)
Headache	21 (3.2)	20 (4.9)	6 (2.6)	28 (4.3)	20 (4.7)	4 (2.1)
Nausea	30 (4.6)	18 (4.4)	7 (3.3)	19 (2.9)	12 (2.8)	6 (3.1)
Abdominal pain	26 (4.0)	13 (3.2)	5 (2.3)	22 (3.3)	10 (2.4)	5 (2.6)

AE = adverse event
 Source: Applicant's data

For subjects in the azithromycin ER group, age did not appear to have an effect on either the incidence of adverse events or discontinuations due to adverse events; however, in the comparator group, discontinuations due to adverse events were more frequent and diarrhea was less frequent in the subjects >65 years of age.

Vomiting decreased with increasing age in both the azithromycin ER and the comparator groups. The vomiting rate for azithromycin ER treated subjects was 15/652 (2.3%) for subjects 16-44 years of age, 7/407 (1.7%) for subjects 45-64 years of age, and 2/214 (0.9%) for subjects >65 years of age. The vomiting rate for comparator treated subjects was 15/657 (2.3%) for subjects 16-44 years of age, 6/423 (1.4%) for subjects 45-64 years of age, and 2/194 (1.0%) for subjects >65 years of age.

Study A0661119 allowed enrollment of subjects 13 years of age or older. Thus, the five Phase 3 studies designed as adult studies include some pediatric subjects, all of whom received either azithromycin ER or azithromycin 3-day for the treatment of pharyngitis. Of the 1292 subjects in the azithromycin ER group, 19 (1.5%) were less than 16 years of age; of the 1304 comparator treated subjects, 30 (2.3%) were less than 16 years of age.

Table 75 presents the overall frequency of adverse events (all causality), the overall frequency of discontinuation due to adverse events (all causality), and the most commonly reported adverse events of all causality for subjects 13-16 years of age.

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Table 75: Summary of Adverse Events (All Causality) for Subjects 13-16 Years of Age in Phase 3 Studies

	Number (%) of Subjects	
	Azithromycin ER (N=19)	Comparator* (N=30)
At least one AE	7 (36.8)	12 (40.0)
Discontinued due to AEs	2 (10.5)	0 (0.0)
Most common AEs		
Diarrhea	2 (10.5)	3 (10.0)
Dysphagia	3 (15.8)	0 (0.0)
Nausea	1 (5.3)	2 (6.7)
Pharyngitis	1 (5.3)	2 (6.7)
Respiratory tract infection	1 (5.3)	2 (6.7)
Vomiting	1 (5.3)	1 (3.3)
AE = adverse event		
*All subjects <16 years of age in adult Phase 3 studies received 3-day azithromycin		
Source: Applicant's data		

Medical Officer's Comments:

The adverse event profile for subjects 13-16 years of age is comparable that for subjects ≥16 years of age.

Race

The majority of evaluable subjects in both treatment groups were white. Because there were very few subjects (70) subjects evaluable for adverse events that were in the race category of 'Other', the comparisons in this section are among subjects in the White, Black, Asian and Hispanic groups.

Table 76 presents, by race, the overall frequency of adverse events (all causality), and the overall frequency of discontinuation due to adverse events (all causality), and the most commonly reported adverse events of all causality (>3% in either treatment group).

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Table 76: Summary of Adverse Events (All Causality) in Phase 3 Studies by Race

	Number (%) of Subjects							
	Azithromycin ER				Comparators			
	White (N=931)	Black (N=66)	Asian (N=183)	Hispanic (N=79)	White (N=928)	Black (N=57)	Asian (N=192)	Hispanic (N=90)
At least one AE	384 (41.2)	38 (57.6)	58 (31.7)	38 (48.1)	382 (41.2)	28 (49.1)	48 (25.0)	51 (56.7)
Discontinued due to AEs	17 (1.8)	2 (3.0)	3 (1.6)	1 (1.3)	25 (2.7)	0 (0.0)	3 (1.6)	2 (2.2)
Most common AEs								
Diarrhea	119 (12.8)	12 (18.2)	8 (4.4)	12 (15.2)	58 (6.3)	3 (5.3)	2 (1.0)	5 (5.6)
Headache	37 (4.0)	8 (12.1)	0 (0)	3 (3.8)	38 (4.1)	6 (10.5)	1 (0.5)	5 (5.6)
Nausea	39 (4.2)	7 (10.6)	3 (1.6)	6 (7.6)	25 (2.7)	2 (3.5)	3 (1.6)	9 (10.0)
Abdominal pain	33 (3.5)	6 (9.1)	2 (1.1)	3 (3.8)	30 (3.2)	1 (1.8)	1 (0.5)	5 (5.6)

AE = adverse event
 Source: Applicant's data
 Note: This table does not include results for subjects of racial group = Other, which included less than 3% of the study population (70 subjects)

Medical Officer's Comments:

The rates of discontinuation due to adverse events (all causality) were low and similar across all racial groups for both azithromycin ER and comparator populations.

The majority of subjects in the Phase 3 studies were white, so the overall adverse event rate and the rates of the most commonly reported all causality adverse events for white subjects were similar to the overall rates. The overall adverse event rate and the rates of the most commonly reported all causality adverse events were consistently lower among asian subjects. The overall adverse event rate for black and hispanic subjects was higher than for white subjects in both treatment groups, but these comparisons are based on a small number of subjects.

Extrinsic Factors

Just under half (1188/2596, 46%) of the subjects enrolled in the Phase 3 studies were from the U.S. and Canada. Table 77 presents, by geographic region, the overall frequency of adverse events (all causality), the overall frequency of discontinuations due to adverse events (all causality) and the most commonly reported adverse events of all causality.

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Table 77: Summary of Adverse Events (All Causality) in Phase 3 Studies by Geographic Region

	Number (%) of Subjects			
	Azithromycin ER		Comparators	
	US and Canada (N=589)	Outside U.S. and Canada (N=703)	US and Canada (N=599)	Outside U.S. and Canada (N=705)
At least one AE	316 (53.7)	210 (29.9)	316 (52.8)	202 (28.7)
Discontinued due to AEs	17 (2.9)	7 (1.0)	17 (2.8)	13 (1.8)
Most Common AEs				
Diarrhea	98 (16.6)	58 (8.3)	57 (9.5)	12 (1.7)
Headache	38 (6.5)	10 (1.4)	36 (16.0)	16 (2.3)
Nausea	37 (6.3)	19 (2.7)	25 (4.2)	14 (2.0)
Abdominal pain	33 (5.6)	11 (1.6)	19 (3.2)	18 (2.6)

AE = adverse event
 Source: Applicant's data

Medical Officer's Comments:

In both treatment groups, the overall frequency of adverse events, the rate of discontinuation due to adverse events, and the rates of the most common adverse events were all higher among subjects from the U.S. and Canada.

7.1.8 Vital Signs

In the 2 upper respiratory tract infection studies (ABS and pharyngitis), the protocol specified that vital signs were recorded at baseline and only as deemed necessary by the investigator at subsequent visits. In the 3 studies of lower respiratory infections (A0661075 and A0661103, CAP, [REDACTED], vital signs were assessed at baseline and at the On Treatment (Day 3-5) and TOC (Day 14-21) visits. There were no clinically significant median changes in vital signs in any of the studies.

Subject 10061006 in Study A0661075, who discontinued from the study due to adverse events, had an adverse event of hypotension that was considered an SAE and resulted in discontinuation. The event was considered to be a vagal response to a spinal tap and not related to treatment.

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (sitting blood pressure, pulse, respiration, and temperature) were summarized as the

median change from baseline to last observation. Physical examination results were recorded only for the baseline visit.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

Refer to section 7.1.8.

7.1.8.3.1 *Analyses focused on measures of central tendencies*

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

7.1.8.4 Additional analyses and explorations

N/A

7.1.9 Electrocardiograms (ECGs)

The current labeling for azithromycin products states that:

“Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.”

Medical Officer's Comments:

Azithromycin ER is not a new molecular entity but a new formulation of an already approved antimicrobial; thus, the sponsor was not required to perform additional studies to evaluate the QT interval.

7.1.10 Immunogenicity

N/A

7.1.11 Human Carcinogenicity

Refer to the current label for other azithromycin products.

7.1.12 Special Safety Studies

There were no special safety studies for azithromycin ER.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Azithromycin does not have the potential to be a drug of abuse.

7.1.14 Human Reproduction and Pregnancy Data

Pregnant or lactating women were excluded from enrolling in the Phase 3 studies, and women of child-bearing potential were required to use an effective method of contraception during the study. There was one unintended pregnancy reported as an adverse event in the Phase 3 studies. Subject 10691002 in Study A0661119, an azithromycin ER-treated subject, had a positive pregnancy test on Day 22, after the completion of study drug treatment. Therefore, the azithromycin ER studies provided little additional information concerning use of azithromycin in pregnant or lactating women, and the proposed label is based on information from currently marketed azithromycin products.

7.1.15 Assessment of Effect on Growth

N/A

7.1.16 Overdose Experience

In the Phase 3 studies, subjects received their single active dose of Azithromycin ER during the study visit. Subjects were re-dosed only if they vomited within 5 minutes of receiving azithromycin ER or the matching placebo. There were no subjects who received more than the intended dose of azithromycin ER. No subject vomited within 5 minutes and no subject was redosed.

7.1.17 Postmarketing Experience

Azithromycin ER has not been approved for marketing in any country as of the time of this submission; therefore, no postmarketing data for this product is available. Relevant information obtained from previous postmarketing experience with other azithromycin formulations is reflected in the proposed label for the new formulation.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Enrollment in the Phase 3 studies, including the number treated, the number completing the

study, and the number evaluable for safety (adverse events and laboratory abnormalities) is shown by treatment group in Table 78 and for azithromycin ER-treated subjects by indication in Table 79.

Table 78: Subject Evaluation Groups in Phase 3 Studies by Treatment Group

	Comparators				
	Azithromycin ER	All	Clarithromycin ER	Levofloxacin	Azithromycin 3 Day
Number of Subjects					
Treated	1292	1304	252	754	298
Completed	1177 (91.1)	1197 (91.8)	223 (88.5)	702 (93.1)	272 (91.3)
Discontinued	115 (8.9)	107 (8.2)	29 (11.5)	52 (6.9)	26 (8.7)
Analyzed for Safety					
Adverse Events	1292 (100.0)	1304 (100.0)	252 (100.0)	754 (100.0)	298 (100.0)
Laboratory Data	689 (53.3)	696 (53.4)	234 (92.9)	462 (61.3)	0 (0.0)
Source: Applicant's data					
Studies included: ██████████ A0661103, A0661075, A0661119, A0661078					
Comparators included: Levofloxacin (Studies ██████████ A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)					

Table 79: Subject Evaluation Groups in Phase 3 Studies for Azithromycin ER-Treated Subjects by Indication

	Azithromycin ER			
	CAP	██████████	Sinusitis	Pharyngitis
Number of Subjects				
Treated	458	268	270	296
Completed	394 (86.0)	249 (92.9)	263 (97.4)	271 (91.6)
Discontinued	64 (14.0)	19 (7.1)	7 (2.6)	25 (8.4)
Analyzed for Safety				
Adverse Events	458 (100.0)	268 (100.0)	270(100.0)	296 (100.0)
Laboratory Data	427 (93.2)	258 (96.3)	3 (1.1)	1 (0.3)
Source: Applicant's data				
Studies included: ██████████ A0661103, A0661075, A0661119, A0661078				
Comparators included: Levofloxacin (Studies ██████████ A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)				
Note: Two studies (A0661078 for sinusitis, and A0661119 for pharyngitis) had no protocol-specified safety laboratory tests other than baseline pregnancy testing.				

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

A summary of demographic characteristics by treatment group is presented in Table 80.

Table 80: Demographic Characteristics in Phase 3 Studies by Treatment Group

	Azithromycin ER (N=1292)	Comparators			
		All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azith 3 Day (N=298)
Age (yr)					
<16	19 (1.5)	30 (2.3)	0 (0)	0 (0)	30 (10.1)
16-64	1059 (82.0)	1080 (82.8)	226 (89.7)	588 (78.0)	266 (89.3)
> 65	214 (16.6)	194 (14.9)	26 (10.3)	166 (22.0)	2 (0.7)
Subjects >75	59 (4.6)	59 (4.5)	4 (1.6)	55 (7.3)	0 (0)
Mean	44.5	44.3	43.6	50.2	30.0
Range	13-95	13-87	16-77	18-87	13-73
Race (%)					
White	931 (72.1)	928 (71.2)	191 (75.8)	476 (63.1)	261 (87.6)
Black	66 (5.1)	57 (4.4)	15 (6.0)	36 (4.8)	6 (2.0)
Asian	183 (14.2)	192 (14.7)	34 (13.5)	138 (18.3)	20 (6.7)
Hispanic	79 (6.1)	90 (6.9)	9 (3.6)	73 (9.7)	8 (2.7)
Other	33 (2.6)	37 (2.8)	3 (1.2)	31 (4.1)	3 (1.0)
Gender (%)					
Males	644 (49.8)	653 (50.1)	134 (53.2)	404 (53.6)	115 (38.6)
Females	648 (50.2)	651 (49.9)	118 (46.8)	350 (46.4)	183 (61.4)
Source: Applicant's data. Studies included: ██████████ A0661103, A0661075, A0661119, A0661078 Comparators included: Levofloxacin (Studies ██████████ A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)					

A summary of demographic characteristics by indication, for azithromycin ER-treated subjects only, in Table 81.

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Table 81: Demographic Characteristics in Phase 3 Studies for Azithromycin ER-Treated Subjects by Indication

	Azithromycin ER			
	CAP (N=458)	(N=268)	Sinusitis (N=270)	Pharyngitis (N=296)
Age (yr)				
<16	0 (0)	0 (0)	0 (0)	19(6.4)
16-64	377 (82.3)	151 (56.3)	255 (94.4)	276 (93.2)
> 65	81 (17.7)	117 (43.7)	15 (5.6)	1 (0.3)
Subjects > 75	23 (5.0)	32 (11.9)	4 (1.5)	0 (0)
Mean	46.8	62.3	38.4	30.3
Range	17-95	38-94	18-88	13-67
Race (%)				
White	322 (70.3)	164 (61.2)	180 (66.7)	265 (89.5)
Black	19 (4.1)	32 (11.9)	9 (3.3)	6 (2.0)
Asian	82 (17.9)	46 (17.2)	37 (13.7)	18 (6.1)
Hispanic	8 (1.7)	22 (8.2)	44 (16.3)	5 (1.7)
Other	27 (5.9)	4 (1.5)	0	2 (0.7)
Gender (%)				
Males	233 (50.9)	177 (66.0)	126 (46.7)	108 (36.5)
Females	225 (49.1)	91 (34.0)	144 (53.3)	188 (63.5)
Source: Applicant's data				
Studies included: A0661103, A0661075, A0661119, A0661078				
Comparators included: Levofloxacin (Studies A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)				

Medical Officer's Comments:

Overall, the azithromycin ER and comparator groups had nearly identical numbers of male and female subjects. The pharyngitis study had a higher proportion of female subjects and the study had a higher proportion of male subjects.

Most of the subjects were white. The study enrolled the highest proportion of black subjects and the sinusitis study enrolled the largest proportion of hispanic subjects. The pharyngitis study, which was the only study with an azithromycin 3-day comparator, enrolled a smaller proportion of asian subjects than studies for other indications.

For all treatment groups and indications, the majority of subjects were between 16 and 64 years of age. Of the five studies, only one allowed the participation of subjects less than 16 years of age. The pharyngitis study, which had a lower age limit of 13, enrolled a total of 49 subjects less than 16 years of age. These subjects are included in all analyses of the adult safety database. The levofloxacin treatment group had a higher proportion of subjects 65 or older than other comparators; most of these subjects were enrolled in the study, which was amended early in the enrollment period to exclude subjects less than 50 years of age.

7.2.1.3 Extent of exposure (dose/duration)

The duration of active treatment for each treatment group is shown in Table 82.

Table 82: Duration of Active Treatment in Phase 3 Studies by Treatment Group

Duration of Treatment (days)	Number (%) of Subjects				
	Azithromycin ER (N=1292)	Comparators			
		All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azith 3 Day (N=298)
<1	1292 (100)	10 (0.8)	6 (2.4)	4 (0.5)	0
2-7	0	1025 (78.9)	245 (97.2)	482 (63.9)	298 (100)
8-14	0	269 (20.6)	1 (0.4)	268 (35.5)	0
15-28	0	0	0	0	0
29-60	0	0	0	0	0
61-90	0	0	0	0	0
>91	0	0	0	0	0
Median Duration	1.0	7.0	7.0	7.0	3.0
Range	1-1	1-10	1-8	1-10	1-4

Source: Applicant's data
 Studies included: ██████████ A0661103, A0661075, A0661119, A0661078
 Comparators included: Levofloxacin (Studies ██████████ A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)

The number of active doses taken by the subjects is shown in Table 83.

Table 83: Number of Active Doses in Phase 3 Studies by Treatment Group

Number of Active Doses	Azithromycin ER (N=1292)	Comparators			
		All (N=1304)	Clarithromycin ER (N=252)	Levofloxacin (N=754)	Azith 3 Day (N=298)
1	1292 (100)	10 (0.8)	6 (2.4)	4 (0.5)	0
2	0	5 (0.4)	1 (0.4)	3 (0.4)	1 (0.3)
3	0	301 (23.1)	1 (0.4)	4 (0.5)	296 (99.3)
4	0	7 (0.5)	2 (0.8)	4 (0.5)	1 (0.3)
5	0	3 (0.2)	0	3 (0.4)	0
6	0	2 (0.2)	1 (0.4)	1 (0.1)	0
7	0	707 (54.2)	240 (95.2)	467 (61.9)	0
8	0	6 (0.5)	1 (0.4)	5 (0.7)	0
9	0	0	0	0	0
10	0	263 (20.2)	0	263 (34.9)	0
Median	1	7	7	7	3
Range	1-1	1-10	1-8	1-10	2-4

Source: Applicant's data
 Studies included: ██████████ A0661103, A0661075, A0661119, A0661078
 Comparators included: Levofloxacin (Studies ██████████ A0661103, A0661078), Clarithromycin ER (Study A0661075) Azithromycin 3-day (Study A0661119)

Medical Officer's Comments:

All subjects in the azithromycin ER group received their full course of active treatment, while the majority of comparator-treated subjects received the full course of active treatment specified by the protocol. The levofloxacin treatment group included subjects receiving both 7- and 10-day regimens; had the 754 treated subjects received exactly the number of active doses prescribed, 486/754 subjects (64.4%) would have received 7 days of treatment and 268/754 (35.5%) would have received 10 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

N/A.

7.2.2.1 Other studies

N/A

7.2.2.2 Postmarketing experience

Azithromycin ER has not been approved for marketing in any country as of the time of this submission; therefore, no postmarketing data for this product is available.

7.2.2.3 Literature

N/A

7.2.3 Adequacy of Overall Clinical Experience

The data from five adult Phase 3 studies included 1292 subjects who received azithromycin ER (single dose, 2.0 grams) and 1304 subjects who received a comparator.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Reference is made to NDA 50,670.

7.2.5 Adequacy of Routine Clinical Testing

Reference is made to clinical review section 6.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Refer to Biopharmaceutics review by Dr. Charles Bonapace.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

N/A

7.2.8 Assessment of Quality and Completeness of Data

Refer to detailed review by DSI, and summary in section 4.4.

7.2.9 Additional Submissions, Including Safety Update

No additional safety data has been submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Refer to section 7 for details.

7.4 General Methodology

Refer to NDA 50,670. No new information has been filed to this NDA.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

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

8.2 Drug-Drug Interactions

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

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

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all

patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

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

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin—elevated digoxin concentrations.

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

Cyclosporine, hexobarbital and phenytoin concentrations.

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

8.3 Special Populations

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

Renal Insufficiency

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

Geriatric Use:

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

Hepatic Insufficiency

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

Gender

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

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

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

Special Populations

Renal Insufficiency:

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

Hepatic Insufficiency:

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

8.4 Pediatrics

The sponsor is in the process of completing the analysis of the pediatric clinical studies and anticipates submission of a supplemental NDA for recurrent/persistent acute otitis media (protocol A0661073) by approximately October 2005.

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

The proposed label for Zmax under the CLINICAL PHARMACOLOGY section is as follows:

Pediatric Patients

Zmax is not approved for pediatric patients.

8.5 Advisory Committee Meeting

There are no plans for an Advisory Committee.

8.6 Literature Review

Refer to the Reference section of this review.

8.7 Postmarketing Risk Management Plan

None

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Based on the safety and efficacy data submitted for the two CAP studies, a single, 2.0 g dose of azithromycin ER is clinically non-inferior to 7 days of clarithromycin ER (1.0 g QD for 7 days) and 7 days of levofloxacin (500 mg QD for 7 days) in the treatment of mild to moderate CAP. For subjects who had documented infections with key CAP pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, clinical cure rates were comparable in the two treatment groups.

The safety and efficacy data for ABS indication supports that the single dose of 2.0 gm of azithromycin ER, given orally, is clinically non-inferior to levofloxacin 500 mg once daily for 10 days, in the treatment of subjects, 18 years or older, with uncomplicated acute bacterial maxillary sinusitis (ABS) caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *M. catarrhalis*.

9.2 Recommendation on Regulatory Action

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

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

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

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

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

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

9.3.2 Required Phase 4 Commitments

No clinical Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

None requested.

9.4 Labeling Review

Acute Bacterial Maxillary Sinusitis - Reviewed by Dr. Menfo Imoisili.

The sponsor proposes the following labeling:

3 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Medical Officer's Comments:

All other sections of the proposed label are reviewed in detail in section 10.2.

9.5 Comments to Applicant

The following recommendations made by the clinical reviewers should be sent to the sponsor in a letter:

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

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

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

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10 APPENDICES

Study A0661075 - INDICATION: CAP

PROTOCOL SUMMARY:

Title:

A Multicenter, Randomized, Double-Blind, Double-Dummy Comparative Trial Of Azithromycin ER Versus Clarithromycin Extended Release For The Treatment Of Mild To Moderate Community-Acquired Pneumonia In Adults.

Rationale:

Community-acquired pneumonia (CAP), an infection of the pulmonary parenchyma acquired outside a hospital or long-term care facility, annually affects 2–3 million Americans. Azithromycin, as a five-day regimen, is approved for the treatment of CAP in the United States. The potential advantages of a single dose therapeutic regimen led to the development of an extended release formulation that will be evaluated in this study.

Objectives:

The primary objective is to confirm the hypothesis that a single, oral, 2.0 g dose of azithromycin ER is clinically non-inferior to 7 days of clarithromycin extended release, 1.0 g orally once daily for the treatment of mild to moderate community-acquired pneumonia.

The secondary objectives include assessments of bacteriologic efficacy and of safety for both treatment regimens.

Number of Subjects/Sites:

Approximately five hundred and four (504) subjects/90-100 sites

Study Country Locations:

United States and other international sites.

Study Population:

Adult outpatients greater than 16 years of age with clinical signs and symptoms compatible with mild to moderate Modified Fine Risk score of less than or equal to 70 (Fine Class I & II) community-acquired pneumonia.

Study Design:

Phase III, multicenter, multinational, double-blind, double-dummy study in which subjects will be randomized to one of two active treatment arms. Duration of dosing is seven days. Clinical and bacteriologic efficacy, the latter in subjects with a baseline pathogen, will be assessed at the Test of Cure visit, 14-21 days after starting study drug.

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

Outcomes Research questionnaire(s) will be administered at visits 1-5 to all subjects enrolled in the United States. All subjects who receive at least one dose of study medication will be assessed for safety.

Treatments:

Azithromycin ER, 2.0 g PO X1; clarithromycin extended release 1.0 g PO QD X7 days.

Endpoints:

Primary efficacy endpoint: Sponsor assessment of clinical response (clinical cure rate) at the TOC visit (Clinical Per Protocol subjects). Secondary efficacy endpoint: Bacteriological response (eradication rate) at the TOC visit. Additional secondary efficacy endpoints included: Investigator assessment of clinical response at the TOC visit, sponsor assessment of clinical response by baseline pathogen at the TOC visit, and sponsor assessment of clinical response in the non-primary populations.

Safety Measurement/Parameters:

Safety will be assessed by spontaneous reports, physical examination and laboratory test results in all subjects who received at least one dose of study medication.

Statistical Methods:

The primary efficacy analysis will compare the sponsor assessment of clinical cure rates of the azithromycin ER and clarithromycin extended release regimens at the Test of Cure visit (Day 14 - 21) in the Clinical Per Protocol population. Azithromycin ER will be considered non-inferior to clarithromycin extended release if the lower boundary of the 95% confidence interval for the difference in cure rates (azithromycin ER – clarithromycin extended release) is greater than -10%.

Other efficacy analyses will include comparisons of the clinical cure rates by pathogen and the bacteriologic eradication rates in the Bacteriologic Per Protocol population.

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

Study Schedule/Flowchart:

Visit Number	1	2	3	4	5
Study Day	Day 1 Baseline ^a	Day 3-5 On Treatment Visit	Day 8-11 End of Treatment Contact ^{b,d}	Day 14-21 Test Of Cure Visit	Day 28-35 Long Term Follow-up Visit
Informed Consent ^c	X	--	--	--	--
Medical History	X	--	--	--	--
Physical Exam	X	--	--	--	--
Focused (chest) Physical Exam	--	X	--	X	X ^e
Vital Signs	X	X	--	X	--
Clinical Signs and Symptoms	X	X	X ^e	X	X
Laboratory Tests ^g	X	--	--	X	--
Fingerstick Glucose	X	--	--	--	--
Urine for <i>S. pneumoniae</i> antigen	X	--	--	--	--
Blood cultures	X ^f	X ^f	--	--	--
Serum for Azithromycin Level Determination	X ^j	--	--	--	--
Pulse Oximetry	X	X ⁱ	--	--	--
Sputum Gram stain	X	X ^h	--	X ^g	X ^e
Sputum Culture and Susceptibility Testing	X	X ^h	--	X ^h	X ^h
Serology for <i>M. pneumoniae</i> and <i>C. pneumoniae</i>	X	--	--	--	X ^e
Oropharyngeal swab for PCR and culture of atypical pathogens	X	--	--	--	--
PA and Lateral Chest X-ray	X	X ⁱ	--	X	--
Pregnancy Test ⁱ	X	--	--	--	--
Administer Outcomes Research Questionnaire(s) ^m	X	X	X	X	X
Randomize and Dispense Study Medication	X ^e	--	--	--	--
Investigator Assessment of Clinical Response	--	--	--	X	--
Assess Adverse Events		X	X	X	X
Assess Adherence to Study Therapy	Directly observed	X	X	X	--
Assess Prior and Concomitant Treatments	X	X	X	X	X
^{a.} Azithromycin ER/placebo should be administered at least 1 hour before or 2 hours after a meal ^{b.} Entry procedures may be obtained no more than 48 hours prior to randomization. ^{c.} Telephone contact with office visit scheduled if worsening or new symptoms of pneumonia. ^{d.} Informed consent should be considered an ongoing dialogue between the Subject and Investigator and not limited to the first visit only. ^{e.} If not clinically improved, subject to be seen in office & procedures should be performed. ^{f.} Symptoms only. If clinically indicated.		^{g.} If sputum production persists. ^{h.} If sputum specimen has less than 10 epithelial cells/low power field. ^{i.} For women of child bearing potential as defined in Section 3.2.1 ^{j.} To be collected if subject vomits within 30 minutes of administration of azithromycin ER/placebo. ^{k.} To be collected from those patients with a positive <i>S. pneumoniae</i> urine antigen test. ^{l.} If blood cultures drawn at baseline were positive. ^{m.} For US sites only ^{n.} Must be done for all subjects discontinued early			

Inclusion Criteria

Subjects must meet the following criteria to be eligible for enrollment in the study:

1. Written informed consent of the subject or a legally authorized representative;
2. Males or females, 16 years of age or older, for whom oral therapy is indicated;
3. Cough productive of sputum (must be sent to the lab for culture and sensitivity);
4. Diagnosis of pneumonia as demonstrated by two or more of the following signs or symptoms:
 - a. Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, egophony);
 - b. Dyspnea or tachypnea;
 - c. 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;
 - d. An elevated total peripheral white blood cell count ($\text{WBC} > 10,000/\text{mm}^3$) or greater than 15% immature neutrophils (bands);
5. Chest radiograph, PA and lateral, revealing the presence of a new infiltrate or consolidation that cannot be attributed to a process other than pneumonia;
6. Modified Fine Risk score of ≤ 70 (Fine Class I & II);
7. Women of child-bearing potential (WOCBP) must have a negative urine pregnancy test within 48 hours prior to start of study medication.

NOTE: WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization or is not post-menopausal. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products (intrauterine devices; barrier methods) to prevent pregnancy, who are practicing abstinence, or who have a partner that is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

Exclusion Criteria

Subjects meeting any of the following criteria at the time of randomization are not eligible and are excluded from study participation:

1. Known or suspected hypersensitivity or intolerance to azithromycin, clarithromycin, or other macrolides;
 2. Previously diagnosed disease(s) of immune function, including:
 - a. Subjects with a baseline absolute neutrophil count $< 1000/\text{mm}^3$;
 - b. HIV positive subjects with a CD4 count < 200 ;
 - c. Any immunoglobulin or neutrophil disorder;
 3. Pregnant or lactating women;
 4. Treatment with any systemic antibiotic of greater than 1 dose or 1 combination dose (such as cephalosporin and macrolide) within the previous 7 days, or the likelihood of receiving other systemic antibiotics during participation in the study;
- NOTE: Subjects receiving a systemic antifungal or antiviral agent for prophylaxis or for treatment of a non-respiratory infection (e.g. for vaginal yeast infection or HSV) are eligible for study entry and may continue those medications.
5. Gastrointestinal disturbances that might affect drug absorption (e.g., malabsorption)

syndromes);

6. Any medical condition which, in the opinion of the Investigator, might interfere with the evaluation of the study drug and/or would make the subject unsuitable for enrollment;
7. Previously diagnosed conditions which tend to mimic or complicate the course and the evaluation of the infectious process (e.g., bronchiectasis, lung abscess or empyema, active TB, pulmonary malignancy, cystic fibrosis, postobstructive pneumonia);
8. Subjects receiving treatment with cisapride, pimozide, or terfenadine;
9. Known or suspected renal insufficiency with a calculated creatinine clearance of less than 10 mL/min;
10. Hospitalization in the previous 14 days or infection acquired in the hospital;
11. Residents of a long-term care facility;
12. Treatment with an investigational drug within 30 days prior to randomization;
13. Current evidence of hepatic disease (i.e. AST and/or ALT and/or total bilirubin \geq 3 times the upper limit of normal);
14. Inability or unwillingness to swallow pills or suspension;
15. Prior enrollment in either this study or any study utilizing Azithromycin ER.

Withdrawal Criteria

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

- An adverse event;
- Persistence or worsening of signs and symptoms of acute infection;
- Intercurrent illness;
- Subject's decision not to participate any further;
- In the Investigator's opinion, it is in the subject's best interest;
- The study is terminated by Pfizer;
- A female subject who becomes pregnant during study drug dosing must be discontinued immediately.

STUDY EVALUATIONS

Study Efficacy

Definition of Clinical Response

At the time of the Test of Cure visit (Day 14 - 21), or as noted before for subjects who discontinue prematurely, the Investigator will assess the subject's response to therapy according to the following criteria:

Cure:

- Signs and symptoms related to the acute infection have resolved, or clinical improvement is such that no additional antibiotics are deemed necessary, **AND** the CXR performed at the Test of Cure visit has either improved or not progressed.

Failure:

One or more of the following:

- Signs and symptoms related to the acute infection have persisted or worsened and additional antibiotics are necessary;
- New clinical signs and/or symptoms of pneumonia have appeared and additional antibiotics are necessary;
- Radiological evidence of pneumonia progression during treatment;
- Death due to pneumonia.

Definition of Bacteriologic Response

Each pathogen will be assigned a bacteriologic response. The bacteriologic response for respiratory pathogens isolated at baseline will be based upon Test of Cure culture results. If a sputum specimen cannot be produced at the Test of Cure visit, the bacteriologic response will be based on the clinical assessment at the Test of Cure visit. If more than one post-treatment sputum specimen is obtained for culture, the last culture taken prior to the start of another systemic antibiotic will be used to determine the bacteriologic response.

Eradication

The original pathogen is not identified in the sputum specimen obtained at the Test of Cure visit.

Presumed Eradication

The subject was not producing sputum at the Test of Cure visit and the clinical response was Cure.

Persistence

The original pathogen is still present in the sputum specimen obtained at the Test of Cure visit.

Presumed Persistence

The subject was not producing sputum at the Test of Cure visit and the clinical response was Failure.

Definition of Relapse

For those subjects with a clinical response of Cure at the Test of Cure visit, relapse at the time of the Long Term Follow-up visit (Days 28-35) will be determined. A subject will be considered to have relapsed if:

- Symptoms related to pneumonia return after initial resolution or improvement;
- New clinical signs or symptoms of pneumonia have appeared without documentation of a

new pathogen; or

- The subject received alternate antibiotic therapy for worsening signs or symptoms or reappearance of new signs and symptoms of pneumonia.

Additional Efficacy Assessments

Additional efficacy analyses included the following secondary endpoints, where sponsor assessment of clinical response is defined except for the assessment at the LTFU visit. Other efficacy assessments included:

- Sponsor assessment of clinical response at the TOC visit for the remaining study populations. Missing values were to be 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 TOC.
- Investigator assessment of clinical response for the Clinical Per Protocol population at the TOC visit;
 - Summary of baseline pathogen susceptibilities; and
 - Sponsor assessment of clinical response for the Clinical Per Protocol population at the LTFU visit (Days 28-35). Clinical outcome was classified as either Cure, Failure, or Relapse.

A subject with a sponsor-assessed clinical response of Cure was considered to have relapsed (Relapse) at LTFU if:

- Symptoms related to pneumonia returned after initial resolution or improvement;
- New clinical symptoms of pneumonia appeared without documentation of a new pathogen; or
- The subject received alternate antibiotic therapy for worsening signs or symptoms or reappearance of new signs and symptoms of pneumonia.

Failures at the TOC visit were to be carried forward as failures at LTFU.

Other Measurements

Azithromycin drug concentrations were to be determined for subjects who vomited within 30 minutes of receiving the first azithromycin ER/placebo dose.

Laboratory Tests

Clinical Laboratory Testing

The following laboratory tests will be performed within 48 hours prior to initiation of study therapy and at designated intervals.

Hematology

Hemoglobin

Hematocrit

WBC count with differential (automated)

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

Platelets
Serum Chemistry
Electrolytes (sodium, potassium, chloride, bicarbonate/CO₂)
Glucose
Urea nitrogen (BUN)
Creatinine
AST (SGOT)
ALT (SGPT)
Total bilirubin
Alkaline phosphatase

Oropharyngeal Swab
M. pneumoniae and *C. pneumoniae* PCR
M. pneumoniae culture

Urine Specimen
S. pneumoniae antigen testing

Serology
Paired serology *M. pneumoniae* and *C. pneumoniae* will be performed at the baseline visit and at the Long Term Follow-up visit (Day 28-35)

Pregnancy Test
Performed at baseline on women of childbearing potential.

Bacteriologic Laboratory Testing

It is critical that sputum specimens be appropriately obtained and tested.

Typical Pathogens

A Gram stain will be performed on all sputum specimens to determine acceptability of the specimen for culture. Only good quality sputum specimens (<10 epithelial cells per low power field) will be cultured. All pathogens will be tested according to procedures approved by the National Committee for Clinical Laboratory Standards (NCCLS) for susceptibility to azithromycin and clarithromycin (refer to Package Inserts for current breakpoints). Isolates of *S. pneumoniae* will be tested for susceptibility to penicillin. Testing for beta-lactamase will be performed when *Haemophilus influenzae*, _____ is isolated. Isolates of *Staphylococcus aureus* will be tested for susceptibility to methicillin.

Atypical Pathogens

The diagnosis of *M. pneumoniae* and *C. pneumoniae* will be based on the result of

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

oropharyngeal PCR/culture and serology according to the following:

- For *M. pneumoniae*:
 - A. A positive oropharyngeal PCR; or
 - B. A single IgM titer of $> 1:16$ by IFA; or
 - C. A single IgG titer of $> 1:32$ by IFA or
 - D. A four-fold increase or decrease in titer from baseline visit to the Long Term Follow-up visit;
 - E. A positive oropharyngeal culture.

- For *C. pneumoniae*:
 - A. A single micro-immunofluorescence IgM titer of $\geq 1:10$; or
 - B. A single micro-immunofluorescence IgG titer of $\geq 1:512$; or
 - C. A four-fold increase or decrease in titre from baseline to Test of Cure,
 - D. A positive oropharyngeal PCR.

Appears This Way
On Original

Study A0661103 - INDICATION: CAP

PROTOCOL SUMMARY:

Title:

A multicenter, randomized, double-blind, double-dummy comparative trial of azithromycin ER versus levofloxacin for the treatment of mild to moderate community acquired pneumonia in adults.

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

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

Evaluation Groups:

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

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

The Inclusion and Exclusion Criteria were similar to study A0661075 except the target population for this study was men or women ≥ 18 years of age who had clinical evidence of mild to moderate community-acquired pneumonia (CAP).

Withdrawal Criteria, Definition of Clinical Response, Definition of Bacteriologic Response, Definition of Relapse, Clinical Laboratory Testing, and Bacteriologic Laboratory Testing were similar to protocol A0661075.

10.1 Review of Individual Study Reports

The review of clinical and safety data can be found in sections 6 and 7.

10.2 Line-by-Line Labeling Review

Refer to the approval letter for a copy of the approved label.

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nasim Moledina
6/10/05 02:06:12 PM
MEDICAL OFFICER

Please review your section and sign off. Thanks

Charles Cooper
6/10/05 02:12:20 PM
MEDICAL OFFICER

Please sign

Menfo Imoisili
6/10/05 02:32:03 PM
MEDICAL OFFICER

I reviewed Acute Bacterial Sinusitis and recommended approval

John Alexander
6/10/05 02:56:45 PM
MEDICAL OFFICER

I concur with the review.

Janice Soreth
6/10/05 03:03:34 PM
MEDICAL OFFICER