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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
50-784

Statistical Review(s)

Statistical Review and Evaluation

NDA # 50784

Sponsor: Pfizer Inc.

Drug: Zithromax 500mg film coated tablet

Indication: Treatment for acute bacterial exacerbation of chronic bronchitis (AECB)

Documents Reviewed: Volumes 1- 3; November 13, 2001 Document; July 27, 2001 Electronic Submission; January 9, 2002 and January 18, 2002 Electronic Submissions.

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1. Executive Summary

Introduction:

In this submission, the sponsor has sought the approval of 3-day regimen of azithromycin (500 mg/day) for the treatment AECB (Acute Exacerbation of Chronic Bronchitis) for adult patients. Note that Zithromax (azithromycin) was approved for the treatment of patients (500mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5) with mild to moderate acute bacterial exacerbation of chronic obstructive pulmonary disease, community acquired pneumonia of mild severity, pharyngitis /tonsillitis (as second therapy), and uncomplicated skin structure infections due to the indicated organisms

Overview of the Clinical Program and Study Reviewed (Study A0661013):

The efficacy claims for azithromycin in the treatment of AECB were supported by the results of the pivotal study, Study A0661013. This was a double-blind comparative study of 3-day regimen of azithromycin (500 mg/day) versus clarithromycin (1000mg daily as 500 mg bid for 10 days) in the treatment of AECB in adults. The primary efficacy results of the study are based on test of cure (TOC) follow up visit scheduled for days 21-24. The efficacy analyses included subjects who had the disease under study as defined by the study protocol, had a baseline purulent sputum, and received at least one dose of study drug. The secondary efficacy analyses were based on the bacteriologic culture data and clinical response at the end of therapy (EOT) scheduled for Days 10-12.

Principal Findings

Efficacy

The sponsor claimed that success rates for the two therapeutic regimens (azithromycin success rate 85%; clarithromycin success rate 82%) were equivalent for the clinical MITT subjects based on the 95% confidence intervals (-5%, 10%) for the difference between the azithromycin success rate minus the clarithromycin success rate using a delta (noninferiority margin) of 10%.

There were three problematic investigators [redacted] in the study. The conclusions of the study remained unchanged when these three problematic investigators were removed from the analysis. The 95% confidence interval for the difference between the azithromycin success rate minus the clarithromycin success rate was found to be (-6%, 12%). An additional analysis was conducted based on the medical officer's evaluability and outcome criteria. Two unevaluable subjects were dropped from

the MITT population as suggested by the medical reviewer. For this revised MITT patient population, the 95% confidence interval of the difference in success rates between azithromycin treated group and clarithromycin treated was (-6%, 12%). In addition, there were several sensitivity analyses conducted by this reviewer. These results demonstrated that the two treatments were equivalent based on a delta of 10%.

For the MITT bacteroliogical population, the study results showed that the two drugs were equivalent (95% CI: -7%, 15%) when the data of the problematic investigators were included based on a delta of 10%. The two drugs were also equivalent (95% CI : -10% , 21%) when the problematic investigators were removed from the study using a noninferiority margin (delta) of 10%.

Safety

For the safety evaluations, the total enrollment was 404 patients. Of these 200 were in the azithromycin treated group and 204 were in the clarithromycin treated group. No patients were excluded from the safety data base. This reviewer's assessment indicates that the incidence of treatment-related adverse events are comparable for both treatment regimens.

Conclusions and Recommendations

In summary, the treatment of acute bacterial exacerbation of chronic bronchitis with azithromycin 500 mg per day for three days is equivalent in efficacy to treatment with clarithromycin 500 mg twice a day for ten days with respect to the clinical outcome at TOC. The safety profile of the azithromycin treated group and the clarithromycin treatment group are comparable with respect to the severity of the adverse event.

2. Statistical Review and Evaluation of Evidence

2.1 Introduction and Background

Study Objectives:

The primary objective of this study was to test the hypothesis that azithromycin administered once daily as an oral dose 500 mg/day for 3 days had an efficacy equivalent to that of clarithromycin administered 500mg orally twice a day for 10 days for the treatment of acute bacterial exacerbation of chronic bronchitis in non-hospitalized adult subjects. A secondary objective was to compare the safety and tolerance of the two regimens.

Study Design:

Study A0661013 was a double blind multi-center parallel study comparing the efficacy and safety of azithromycin (500 mg qd for 3 days) and clarithromycin (1000 mg daily as 500 mg bid for 10 days) in subjects with AECB. An enrollment of 320 subjects was planned. Approximately 50 centers, none enrolling 10% of the total subjects, participated. This was the pivotal study for AECB. The primary measures of efficacy was based on investigator's assessment of the clinical outcome at the test of cure (TOC) visit. The bacteriological outcome was a secondary efficacy response variable. The objective was to show equivalence between the success rates of the two treatments.

Evaluation Groups:

Table 1 summarizes, by treatment group, the completion status of all patients randomized into the study.

Table 1 (Sponsor's): Patient Disposition

Population	azithromycin	clarithromycin
Randomized	201	206
Received Treatment	200	204
Received treatment excluding the problematic investigators	158	164
Evaluated at TOC for Efficacy (without problematic investigators)		
Clinical MITT	149	157
Bacteriological MITT	56	56
Clinical PP at TOC	140	145
Bacteriological PP at TOC	53	53
Assessed for safety (Adverse Events)	200	204

It can be seen that of the 407 patients randomized in the study, actually 404 received treatment drugs. These patients, who received the treatment drugs, comprised the ITT

population, as defined by the protocol. In this review, the efficacy analysis excluded data from the three sites: [redacted] due to data integrity problem per FDA's DSI recommendations. For the MITT analysis of clinical outcomes, subjects with missing observed values were excluded with the exception of cases where the sponsor assigned failure. As a result, the clinical MITT patients consisted of 149 in the azithromycin treated group and 157 in the clarithromycin treated group. Subjects with missing observed values were by definition also excluded from the per protocol population, again with the exception of sponsor assigned failures. However the safety analysis included all 404 patients.

Baseline Characterstics:

Table A.1 (in the Appendix) contains the demographic characterstics of the 200 subjects that received azithromycin and the 204 subjects that received clarithromycin.
Males accounted for 65% subjects receiving azithromycin and 61% of those receiving clarithromycin. In the age group < 65, azithromycin treatment group had less patients than the clarithromycin treated group (azithromycin 66% and clarithromycin. 77%). Study patients were predominantly white (azithromycin 63% and clarithromycin. 63%). Blacks accounted 17% of subjects assigned to azithromycin and 17% of subjects assigned to clarithromycin. The remaining subjects were either Asian or Other. The weight and the height were similar for the subjects assigned to the two treatment groups. The smoking history was also similar for both groups. The proportion of patients in the two treated groups by the geographical regions were comparable.

Diagnoses and Criteria for Inclusion of Subjects

Subjects of either gender between the ages of 35 and 75 years with a diagnosis of acute bacterial exacerbation of chronic bronchitis were eligible for entry into this study.

Efficacy Evaluation:

The modified intent to treat (MITT) group included subjects who had taken at least one dose of study medication, had a confirmed diagnosis of acute bacterial exacerbation of chronic bronchitis and had a baseline purulent sputum i.e., WBC>25. The clinical MITT subgroup had a bacteriological subset that had positive baseline sputum cultures for H. *infuenzae*, H. *paraninfluenzae,* S. *pneumoniae* or M. *catarrhalis*. The primary endpoint was based on the investigator's assessment of clinical outcome (cure or failed) at the TOC visit.

Drug Administration:

Dosage Form	Azithromycin 500 mg tablet, lot N9063-G1; Azithromycin Placebo, lot ED-O-074-297; Clarithromycin 500 mg tablet, Lot ED-O-372-899; Clarithromycin placebo, lot ED-O-376-899
Dosing	Azithromycin 500 mg per dayfor three days, or Clarithromycin 500 mg twice a day for 10 days
Duration	Blinded therapy for 10 days, follow-up until at least day 21-24

Efficacy Variables:

Primary Outcome (Clinical outcome)

The primary measure of efficacy was clinical outcome based on the investigator's assessment with sponsor exceptions described below.

At EOT the outcomes were cure, improvement and a failure. At TOC, the sponsor's clinical outcomes were usually cure and failure. However, if an investigator chose improvement at TOC, the subject was required to return for a follow-up visit within 1-2 weeks, and the investigator reclassified the subject as cure or failure.

The sponsor assigned the follow-up outcome to the TOC visit. If the subject had no follow-up, then sponsor assigned failure for the TOC visit. The sponsor assigned failure at TOC if the subject was a failure at EOT.

The sponsor assigned failure at a visit if the subject was given other antibiotics for failure prior to that visit. For the per protocol population analysis, if the antibiotic was given after the upper limit of the visit window, then failure was not assigned.

Secondary Outcome (Bacteriological Outcomes)

Bacteriological outcome was assessed on a by-subject basis as well as on a by-pathogen basis. Bacteriological outcome referred to the by-subject basis, and pathogen outcome referred to the by-pathogen basis.

The by-subject bacteriological outcomes were:

> *Eradication:* No trace of any respiratory pathogen in purulent sputum culture and sponsor clinical outcome was not failure (unless the sputum culture demonstrated

eradication on the same day as sponsor clinical outcome failure in which case it was classified as eradication)

Persistence: A baseline respiratory pathogen still present in sputum culture

Super infection: Baseline respiratory pathogens gone but another respiratory pathogen present in sputum culture

Presumed eradication: No sputum culture due to the subject not being able to expectorate or a nonpurlent sputum culture and the sponsor clinical outcome was cure or improvement

Presumed persistence: Sponsor clinical outcome was failure (unless a sputum culture demonstrated eradication on the same day as sponsor clinical outcome failure in which case it was classified as eradication)

Not available: No sputum culture (including "not doe" or missing for other reasons except for not being able to expectorate) and clinical outcome was failure

2.2 Statistical Evaluation on Efficacy (Sponsor's /Reviewer's)

Statistical Methodologies:

The percentages of subjects clinically cured versus failed at TOC and clinically cured, improved, and failed at EOT were determined. In addition, bacteriological success rates were calculated for EOT and TOC. The 95% confidence intervals were computed for success (i.e. cure) rate differences between the two regimens using the normal approximation to the binomial distribution with a continuity correction. Equivalence was assessed based on a two sided 95% confidence interval of the difference between the success (i.e. cure) rates using a noninferiority margin (delta) of 10%.

Sponsor's/Reviewer's Analyses

The efficacy analysis excluded data from the three sites: [redacted] due to data integrity problem per FDA's DSI recommendations. Therefore, the clinical MITT evaluable patients consisted of 149 in the azithromycin treated group and 157 in the clarithromycin treated group.

Primary Outcome:

The sponsor's summary of clinical outcome, clinical MITT subjects without investigators are reported in the following table:

Table 2 (Sponsor's): Clinical Response at the TOC for Clinical MITT Population (NDA -50-784 Submission N0. 005 Received From Ronald Trust of Pfizer Through CSO Mr. J. Clinton, Dated 11/13/01)

Population	azithromycin N (%)	clarithromycin N (%)	P-value	95% Confidence Limits
Subjects Evaluable at TOC	149 (100%)	157 (100%)		
Cure	127 (85%)	129 (82%)	0.537	(-6%, 12%)
Failure	22 (15%)	28 (18%)		

It is seen from the above table that the clinical cure rates in azithromycin and clarithromycin treated groups among the clinical MITT patient populations were 85% and 82% at the TOC visit. The 95% confidence intervals for the difference of clinical cure rates demonstrated that the azithromycin treated group was equivalent to clarithromycin treated group at the TOC visits based on a delta of 10%. The sponsor's efficacy analyses (Table 2) were validated by this reviewer and the results were consistent. Similar conclusions were valid at EOT.

The reviewer's summary of clinical outcome for the clinical per protocol population are reported in the following table:

Table 3 (Reviewer's): Clinical Response at the TOC for Clinical Per Protocol Population

Per Protocol Population	azithromycin N %	clarithromycin N %	95% Confidence Limits
Subject Evaluable at TOC	140	145	
Cure	118 (84%)	121 (83%)	(-8%, 10%)
Failure	22 (16%)	24 (17%)	

It is seen from the above table that the clinical cure rates in azithromycin and clarithromycin treated groups among the clinical per protocol population were 84% and

83%, respectively, at the TOC visit. The 95% confidence intervals for the difference of clinical cure rates demonstrated that the azithromycin treated group was equivalent to clarithromycin treated group at the TOC visit based on a delta of 10%.

Secondary Outcome (Bacteriological Outcome):

The following table gives bacteriological outcomes of bacteriological MITT subjects.

Table 4 (Sponsor's): Bacteriological Response at TOC for MITT Bacteriological Population (NDA -50-784 Submission N0. 005 Received From Ronald Trust of Pfizer Through CSO Mr. J. Clinton, Dated 11/13/01

Population	azithromycin	clarithromycin	P-value	95% confidence limits
Evaluable Subjects	56 (100%)	55 (100%)		
Success	48 (86%)	45 (80%)	0.62	(-10% , 21%)
Eradication	9 (16%)	5 (9%)		
Presumed	39 (70%)	40 (71%)		
Eradication				
Failure	8 (14%)	10 (20%)		
Persistence	4 (7%)	1 (5%)		
Presumed Persistence	4 (7%)	5 (9%)		
Superinfection	0	3 (5%)		

It is seen from the above table that among the evaluable subjects in MITT bacteriological population, there was numerically higher success (eradication + presumed eradication) rate (86% versus 80%) in the azithromycin treated group than that of the clarithromycin treated group at TOC. The 95% confidence interval for the difference in success rates demonstrated that the azithromycin treated group was equivalent to clarithromycin treated group at TOC based on a delta of 10%. The sponsor's analyses (Table 4) were validated by this reviewer, and in this reviewer's opinion the efficacy results were consistent. Similar conclusions were valid at EOT.

The following table gives bacteriological responses for bacteriological per protocol subjects.

Table 5 (Reviewer's): Bacteriological Response at TOC Per Protocol Bacteriological Population

Per Protocol Population	azithromycin N	%	clarithromycin N	%	95% Confidence Limits
Subject Evaluable at TOC	53		53		
Success (Eradiaction + Presumed Eradication)	45	(71%)	43	(81%)	(-13%, 20%)
Failure	8	(29%)	10	(19%)	

Bacteriological eradication (success) rates at TOC among per protocol bacteriological population differed from those of the bacteriological MITT population. Eradication (success) rates were 71% in azithromycin treated group and 81% in clarithromycin treated group. The 95% confidence interval for the difference in eradication (success) rates demonstrated that the azithromycin treated group was not equivalent to clarithromycin treated group at the TOC visit based on a delta of 10%. It is worth mentioning that the trial was not sized to show the equivalence in bacteriological eradication rates between the two the azithromycin treated group and the clarithromycin treated group.

2.3 FDA's Analysis (Reviewer's)

The following table summarizes the clinical outcomes for clinical MITT population when two unevaluable (determined by the medical reviewer) subjects were dropped from the clinical MITT population as examined by the medical reviewer.

Table 6 (Reviewer's): Clinical Response at TOC for Clinical MITT Population When the Two Unevaluable Subjects Were Dropped From the Azithromycin Treated Group

MITT Population	azithromycin N	%	clarithromycin N	%	95% Confidence Limits
Subject Evaluable at TOC	147		157		
Cure	125	(85%)	129	(82%)	(-6%, 12%)
Failure	22	(15%)	28	(18%)	

It is seen from the above table that the clinical cure rates in azithromycin and clarithromycin treated groups among the evaluable patient populations were 85% and 82%, respectively, at the TOC visit. The clinical outcome rates did not differ from the sponsor's analysis. The 95% confidence intervals for the difference in clinical cure rates demonstrated that the azithromycin treated group was equivalent to clarithromycin treated group at the TOC visit based on a delta of 10%.

The following table gives efficacy results for per protocol population when two unevaluable subjects are dropped from the MITT population examined by the medical reviewer.

Table 7 (Reviewer's): Clinical Response at TOC for Per Protocol Population When Two Unevaluable Subjects Were Excluded From the Azithromycin Treated Group

Per Protocol Population	azithromycin N	%	clarithromycin N	%	95% Confidence Limits
Subject Evaluable at TOC	138		145		
Cure	116	(84%)	121	(83%)	(-9%, 10%)
Failure	22	(16%)	24	(17%)	

It is seen from the above table that the clinical cure rates in azithromycin and clarithromycin treated groups among the evaluable patient populations were 84% and 83%, respectively, at the TOC visit. The 95% confidence intervals for the difference in clinical cure rates demonstrated that the azithromycin treated group was equivalent to clarithromycin treated group at TOC visit based on a delta of 10%.

2.4 Sensitivity Analysis (Reviewer's)

This reviewer conducted post-hoc analyses of FDA's clinical MITT population to evaluate the clinical outcomes at the TOC under three conditions:

1) subjects who had three signs and symptoms (cough, dyspnea and/or sputum production) at TOC but their signs and symptoms did not return to pre-excerbation level

2) subjects who had additional signs and symptoms (i.e., rigors, chills, wheezing, rales and rhonchi) that were absent at baseline but present at TOC

3) subjects who had additional signs and symptoms(i.e. rigors, chills, wheezing, rales and rounchi) that were present at baseline but still present at TOC.

The following tables (Table 8, Table 9 and Table 10) summarizes the signs and symptoms under three conditions stated above.

Table 8 (Reviewer's): Summary of Subjects with Cough, Dyspnea and/or Sputum Production at TOC Who Did Not Return to Pre-Exacerbation Level

Number of Subjects	azithromycin N= 147		clarithromycin N=157	
	n	%	n	%
Subjects with 0 sign and symptom	114	78	119	76
Subjects with 1 sign and symptom	20	14	20	13
Subjects with 2 signs and symptoms	12	8	10	6.
Subjects with 3 signs and symptoms	1	0.7	8	5

Table 9 (Reviewer's): Summary of Subjects Under Conditions 1 and 2

Number of Subjects	azithromycin N= 147		clarithromycin N=157	
	n	%	n	%
Subjects with 0 additional signs and symptom	135	92	143	91
Subjects with 1 additional sign and symptom	12	8	12	8
Subjects with 2 signs and symptoms	0	0	2	1

Table 10 (Reviewer's): Summary of Subjects Under Conditions 1, 2 and 3

Number of Subjects	azithromycin N= 147		clarithromycin N=157	
	n	%	n	%
Subjects with 0 Additional signs and symptom	109	74.	109	69
Subjects with 1 Additional sign and symptom	26	18	33	21
Subjects with 2 Additional signs and symptoms	11	8	14	9
Subjects with 3 Additional signs and symptoms	1	0	1	1

It is seen from the above three tables that the treatment groups were comparable with respect to clinical outcomes after adjusting for signs and symptoms.

The following table summarizes the clinical outcomes under condition 1.

Table 11 (Reviewer's): Clinical Outcome in Subjects Adjusted for Condition 1

Clinical Outcome	azithromycin N= 147		clarithromycin N=157		2-sided 95% CI
	n	%	n	%	
Cure	106	72	106	68	(-6%, 16%)
Failure	41	28	51	32	

It is seen from the above table that the clinical cure rates in the azithromycin treated group and the clarithromycin treated group dropped to 72% and 68%, respectively, under condition 1. The 95% confidence interval (-6%, 16%) showed that that the azithromycin treated group and the clarithromycin treated group were equivalent on the basis of delta =10%.

The following table summarizes the clinical outcomes under condition 1 and condition 2.

Table 12 (Reviewer's): Clinical Outcome in Subjects Adjusted for Condition 1 and Condition 2.

Clinical Outcome	azithromycin N= 147		clarithromycin N=157		2-sided 95% CI
	n	%	n	%	
Cure	99	67	99	63	(-7%, 16%)
Failure	48	33	58	37	

It is seen from the above table that the clinical cure rates in the azithromycin treated group and the clarithromycin treated group dropped to 67% and 63%, respectively, under condition 1 and condition 2. The 95% confidence interval (-7%, 16%) showed that that the azithromycin treated group and the clarithromycin treated group were equivalent on the basis of delta =10%.

The following table summarizes clinical outcomes under condition 1, condition 2 and condition 3.

Table 13 (Reviewer's): Clinical Outcome in Subjects with Additional Signs and Symptoms Absent at Baseline but Present at TOC

Clinical Outcome	azithromycin N = 147		clarithromycin N=157		2-sided 95% CI
	n	%	n	%	
Cure	73	50	71	45	(-7%, 16%)
Failure	74	50	86	55	

It is seen from the above table that the clinical cure rates in the azithromycin treated group and the clarithromycin treated group dropped to 67% and 63%, respectively, under condition 1, condition 2 and condition 3. The 95% confidence interval (-7%, 16%) showed that that the azithromycin treated group and the clarithromycin treated group were equivalent on the basis of delta =10%.

2.5 Findings in Special/Subgroup Populations

This reviewer conducted analyses of clinical outcomes at the TOC by gender, age, race, smoking history and geographic region (USA versus Outside USA) without the problematic investigators. These sub-group analyses showed mixed results.
Note that the trial was not sized for testing treatment differences in each subgroup separately and there is a problem of testing multiple hypotheses because of many subgroup analyses. These sub-group analyses are meaningless and difficult to interpret.

3. Statistical Evaluation on Safety (Sponsor's /Reviewer's)

It is mentioned earlier that a total of 404 subjects were randomized and treated in the study. Out of 404 subjects, 200 subjects were allocated to azithromycin treatment group and 204 subjects were allocated to clarithromycin treatment. The sponsor reported that all subjects who received at least one dose of study medication were included in the analysis of safety.

The following table summarizes the all causality and treatment-emergent adverse events.

Table 14 (Sponsor's): Summary of All Causality and Treatment-Emergent Adverse Events (Extracted from A00661013 Study Report, p. 43, July 27, 2001 Electronic Submission)

Number of subjects	azithromycin (N=200)	clarithromycin (N=204)
Number of Events	150	184
Subjects with Adverse Events (AE)	81 (41%)	93 (46%)
Subjects with Serous AE (SAE)	2 (1%)	5 (2.5%)
Subjects with Severe AE	6 (3%)	14 (7%)
Subjects discontinued due to AE	6 (3%)	6 (4%)
Subjects temporarily discontinued or dose reduced	0	1 (0.5%)

It is seen that from the above table that the percentages of adverse events in azithromycin treatment group were less than the clarithromycin treatment group.

The following table summarizes the incidence and severity of treatment-related and treatment-emergent adverse events.

Table 15 (Sponsor's): Summary of Incidence, Severity of Treatment-Related and Treatment-Emergent Adverse Events (Extracted from A00661013 Study Report, p. 44, July 27, 2001 Electronic Submission)

	azithromycin (N=200)	clarithromycin (N=204)
Total number of events	80	104
Number of Events (% of total events):		
Mild	58 (73%)	58 (56%)
Moderate	21 (26%)	36 (35%)
Severe	1 (1%)	10 (10%)

It is seen from the above table that azithromycin treatment group had lower percentage of adverse events (in the moderate and severe group) than the clarithromycin treatment group. However, the azithromycin treatment group had higher percentage of mild adverse events than the clarithromycin treatment group. Overall, the azithromycin treatment group had less events than the clarithromycin treatment group.

The following table summarizes the treatment-related, and treatment-emergent adverse events.

Table 16 (Sponsor's): Summary of Treatment -Related and Treatment-Emergent Adverse Events (Extracted From A00661013 Study Report, p. 43, July 27, 2001 Electronic Submission)

Number of subjects	azithromycin (N=200)	clarithromycin (N=204)
Number of Events	80	104
Subjects with Adverse Events (AE)	50 (25%)	60 (29.4%)
Subjects with Serious AE (SAE)	0 (0%)	0 (0%)
Subjects with Severe AE	1 (0.5%)	6 (2.9%)
Subjects discontinued due to AE	0 (3%)	5 (2.5%)
Subjects temporarily discontinued or dose reduced	0 (0%)	0 (0%)

It is seen that from the above table that the adverse events in azithromycin treatment group were comparable with clarithromycin treatment group.

4. Conclusions

4.1 Efficacy

Clinical Outcome

1. For the clinical MITT patient population, this reviewer's assessment indicates that the clinical outcomes are equivalent (two-sided 95% confidence interval: -6% to 12%) between the azithromycin treated group and the clarithromycin treated group using a noninferiority margin of 10%.

   This reviewer has conducted several sensitivity analyses and the results were consistent.

2. For the clinical per protocol patient population, this reviewer's assessment indicates that the clinical outcomes are equivalent (two-sided 95% confidence interval: -6% to 12%) between the azithromycin treated group and the clarithromycin treated group using a noninferiority margin of 10%.

Bacteriological Outcome

1. For the MITT bacteriological population, this reviewer's assessment indicates that the eradication and presumed eradication rates are equivalent (two-sided 95% confidence interval: -10% to 21%) between the treatment groups based on a noninferiority margin of 10%.

2. For the per protocol bacteriological population, the 95% confidence interval (-13%, 20%) for the difference in eradication rates demonstrated that the azithromycin treated group are not equivalent to clarithromycin treated group based on a noninferiority margin of 10%. However, the trial was not sized to show the equivalence in bacteriological eradication rates between the the azithromycin treated group and the clarithromycin treated group.

4.2 Safety

This reviewer's assessment indicates that the incidence of treatment-related adverse events are comparable for both treatment regimens.

4.3 Overall Conclusions

In summary, the treatment of acute bacterial exacerbation of chronic bronchitis with azithromycin 500 mg per day for three days is equivalent in efficacy to treatment with clarithromycin 500 mg twice a day for ten days with respect to the clinical outcome at TOC. The safety profile of the azithromycin treated group and the clarithromycin treatment group are comparable with respect to the severity of the adverse event.

/S/

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Mathematical Statistician

Concur: /S/

Dr. Daphne Lin

Appendix

Table A.1 (Reviewer's): Baseline Characterstics of the Randomized Patient Population

Characterstics	azithromycin (N=200)	clarithromycin (N=204)
Gender		
Male	129 (65%)	125 (61%)
Female	71 (35%)	79 (39%)
Age		
<65	133 (66%)	158 (77%)
>= 65	67 (34%)	46 (23%)
Race		
White	125 (63%)	128 (63%)
Black	35 (17%)	36 (17%)
Asian	18 (9%)	16 (8%)
Others	22 (11%)	24 (12%)
Weight (Kg)	72.0	74.16
Height (cm)	166.61 cm	167.61
Smoking Status		
Smoker	86 (43%)	98 (48%)
Ex-Smoker	82 (41%)	76 (37%)
Never Smoked	32 (16%)	30 (15%)
Country		
US/Canada	92 (46%)	99 (49%)
South America	89 (45%)	87 (42%)
India/South Africa	19 (9%)	18 (9%)

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