Corticosteroids	26 (13.0%)	28 (13.7%)
Drugs Used in Rheumatic Diseases	45 (22.5%)	43 (21.1%)
Respiratory Corticosteroids	36 (18.0%)	36 (17.6%)
Systemic Treatment of Symptoms of URI infections	24 (12.0%)	34 (16.7%)
Vitamins	15 (7.5%)	21 (10.3%)

MO COMMENT: Bronchodilators were commonly prescribed concomitant medications in both treatment groups. Corticosteroid use was comparable in both treatment groups. The reviewer performed a subset analysis of the subjects with concomitant use of corticosteroids in the study. (Please refer to the end of FDA's post-hoc analysis section on steroid-use subset analysis.)

Study Drug Discontinuations

Total number of discontinuations were very similar for both treatment groups, i.e., 15 subjects from the 158 assigned to receive azithromycin and 16 subjects from the 164 assigned to receive clarithromycin. However, while 10 subjects (6.1%) were discontinued from the clarithromycin treatment group for reasons considered to be related to study drug, only 4 subjects (2.5%) were discontinued for study drug related reasons in the azithromycin treatment group. No subjects were discontinued from the azithromycin treatment group for adverse events related to study drug while 5 (3.0%) of the subjects assigned to receive clarithromycin were discontinued for study drug related adverse events. The table below by the applicant summarizes the discontinuations from the study.

Table 9: Summary of Discontinuations from Study According to Applicant

REASONS	AZITHROMYCIN N= 158		CLARITHROMYCIN N= 164	
	n	%	n	%
Related to Study Drug	4	2.5	10	6.1
Adverse event	0		5	3.0
Lack of Efficacy	4	2.5	5	3.0
Not related to Study Drug	11	7.0	6	3.7
Adverse event	5	3.2	2	1.2
Other	2	1.3	2	1.2
Subject defaulted*	4	2.5	2	1.2

* Denotes subjects who were withdrawn from the study or lost to-follow-up.

MO COMMENT: The common reason for discontinuation from the study in the azithromycin treatment group was not related to the study drug. There was no discontinuation due to AE in the azithromycin treatment arm. The table above has been modified as to its format by the reviewer.

Protocol Deviations

The following table by the applicant lists the general category of protocol deviations in the study:

Table 10: List of General Category of Protocol Deviations and Numbers of Subjects

GENERAL CATEGORY OF PROTOCOL DEVIATIONS	AZITHROMYCIN	CLARITHROMYCIN
Subjects who were not between the ages of 35 and 75 years	14	4
Subjects without the presence of baseline purulent sputum	6	7
Subjects with no baseline sputum culture	2	3
Subjects without chest X-ray within 48 hours prior to first visit	3	3
Subjects without a history of chronic bronchitis	3	4
Subjects with anticipated need for or concomitant medications listed in study protocol (Section 6.2-Item 10)	9	11
Subjects who received treatment with medications listed in study protocol (Section 6.2-Item 11)	2	2
Subjects who received <80% or >120% of the study medication	8	3
Subjects with no sputum culture at End of Therapy	2	1
Subjects with no sputum culture at Test of Cure	3	1
Subjects who did not return for Visit 4 when TOC visit was neither a Cure or Failure	2	1
Subjects who were randomized out of sequence	2	1

MO COMMENT: The applicant granted waivers in subjects who did not meet a particular enrollment criterion which was to be specified in the CRFs. From the results of the above table, the general category of randomized and treated subjects <35 and >75 years old were higher with the azithromycin group than with the clarthromycin group. The number of subjects who use theophylline were comparable in both treatment groups.

A. Primary Outcome (Clinical Outcome)

Data Analyzed

The primary measure of efficacy was clinical outcome based on the investigator assessment. At EOT the outcomes were cure, improvement, and failure. At TOC the applicant clinical outcomes were cure and failure. If an investigator chose improvement at TOC, the subject was required to return for a follow-up visit within 1-2 weeks. The investigator assigned cure or failure at the later follow-up visit. The applicant assigned the follow-up outcome to the TOC visit. If the subject had no follow-up, then applicant assigned failure for the TOC visit. The applicant assigned failure at TOC if the subject was a failure at EOT. The applicant also assigned failure at a visit if the subject was given other antibiotics for failure prior to that visit. For the PP population analysis, if the antibiotic was given after the upper limit of the visit window, then failure was not assigned.

For the MITT analysis of clinical outcomes, subjects with missing observed values were excluded with the exception of cases where the sponsor assigned failure. Subjects with missing observed values were by definition excluded from the PP populations, again with the exception of applicant's assigned failures. The clinical outcome was summarized separately for each baseline respiratory pathogen and each geographical region by the applicant.

MO COMMENT:

Subjects with missing values included subjects who were withdrawn from the study or lost to follow-up. A total of twelve subjects had missing values in the study; six subjects (#00016; #00019; #00054; #00197; #00225; and #00323) in the azithromycin treatment group and six subjects (#00002;#00066; #00191;#00194; #000424; and #00680) in the clarithromycin treatment group.

CLINICAL EFFICACY RESULTS:

The following table summarizes the evaluation groups of clinical MITT subjects per applicant's analysis:

Table 11: Applicant's Analysis of Clinical MITT population

MITT	Azithromycin 3-days		Clarithromycin 10-days		2-sided 95% CI
	N	%	N	%	
Subjects Evaluable at EOT	149	(100%)	160	(100%)	
Success	138	(93%)	151	(94%)	(-8%,4.4%)
Cure	77		77		
Improvement	61		74		
Failure	11	(7%)	9	(6%)	
Subjects Evaluable at TOC	149	(100%)	157	(100%)	(-6%,12%)
Cure	127	(85%)	129	(82%)	
Failure	22	(15%)	28	(18%)	

MO Comment: The applicant's statistical analysis at EOT visit was based on categories of success (cure plus improvement) and failure. Cure assessment at TOC visit included subjects who were cured as well as subjects who were improved at TOC visit and cured at the follow-up visit (1-2 weeks later).

The next table summarizes the clinical MITT population results in the MO Analysis.

Table 12: MO's Analysis of Clinical MITT population at TOC visit

Clinical MITT	Azithromycin 3-days		Clarithromycin 10-days		2-sided 95% CI
	N	%	N	%	
Subjects Evaluable at TOC	147		157		
Cure	125	(85%)	129	(82%)	(-6%,12%)
Failure	22	(15%)	28	(18%)	

MO COMMENT: In the reviewer's MITT analysis, the clinical cure rates in both treatment groups are comparable. Azithromycin treatment group had a cure rate of 85%, while clarithromycin had a cure rate of 82% with the confidence limits of –6%, 12%, 2-sided 95% CI. The MO's analysis of clinical outcome at the TOC visit did not differ from the applicant's analysis.

Severity of Clinical Signs and Symptoms

The following table summarizes the mean signs and symptoms (cough, dyspnea and sputum production) by severity scores for the intervals of pre-exacerbation, baseline, end of therapy and test of cure for the MITT population according to applicant. The severity score was graded as follows: 0=Absent; 1=Mild; 2=Moderate; and 3=Severe.

Table 13: Summary of Mean Sign/Symptom severity scores for clinical MITT population

	Pre-Exacerbation			Baseline			End-of- therapy			Test of Cure		
	C	D	SP	C	D	SP	C	D	SP	C	D	SP
Azith	0.98	0.84	0.95	2.32	1.98	2.41	1.09	0.95	0.95	0.86	0.73	0.72
Clari	0.94	0.80	0.90	2.26	1.96	2.33	1.06	0.88	0.95	0.88	0.70	0.72

C=Cough; D=Dyspnea; SP=Sputum production

The mean assessments of severity for all clinical MITT subjects indicate that cough, dyspnea and sputum production were present in all time intervals studied. Mean scores for the baseline interval were very similar for both treatment groups. Overall, mean severity was mild at pre-exacerbation, increased to moderate to severe during baseline, and decreased throughout the remaining study period. Severity of all signs and symptoms were slightly lower at TOC relative to EOT. Severities at TOC were also slightly lower than the initial pre-exacerbation assessments. There were no apparent differences between the two treatment groups.

MO COMMENT: The mean scores are consistent with the expected course of illness for AECB. Signs and symptoms of cough, dyspnea and sputum production are worse at baseline than at pre-exacerbation.

B. Secondary Outcome (Bacteriological Outcome)

Bacteriological outcome was assessed on a by-subject basis as well as on a by-pathogen basis. For identification of the respiratory pathogens *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, and *M. catarrhalis*, both the central and local laboratory results were used. A manual review was to be done to confirm that all pathogens identified at either laboratory were appropriate. A purulent sputum culture was defined by having a Gram stain with >25 white blood cells (WBC) per field and <10 squamous epithelial cells at 100x magnification (low power, 10x objective) microscopic examination. A review of *in vitro* susceptibility testing methods is provided in the Microbiology review.

The bacteriological outcomes by subject were defined by the applicant as follows:

- 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

- Superinfection - 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 nonpurulent sputum culture and sponsor clinical outcome was cure or improvement

- Presumed Persistence - Sponsor's 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)

If a by-subject bacteriological outcome was both persistence and superinfection, the persistence outcome was used. The pathogen outcomes were the same as the by-subject with the exceptions: 1) Superinfection was not possible; 2) The sputum culture results in the above definitions applied only to the pathogen of interest. Pathogen outcome was summarized separately for each baseline respiratory pathogen. Urine samples were obtained for the Binax NOW® Streptococcus pneumoniae antigen test which was performed at the study site. Subjects were allowed to continue in the study if they did not have a pathogen isolated at baseline or if the pathogen was identified as resistant to any of the study medications. If the investigator felt that a subject needed to be discontinued because of failure to improve clinically, the subject was discontinued, evaluated as a treatment failure and appropriate therapy initiated. The appropriate therapy was noted in the case report form.

BACTERIOLOGICAL RESULTS:

The following tables (Tables 14 and 15) summarize the bacteriological assessments by-subject outcome and by baseline pathogen in the bacteriological MITT subjects according to applicant:

Table 14: Bacteriological Outcome by Subject Outcome - MITT population

BACTERIOLOGICAL OUTCOME	AZITHROMYCIN 3-days N= 56		CLARITHROMYCIN 10-days N=56	
	n	%	n	%
Success	48	85.7%	45	80.4%
Eradication	9	16.1%	5	8.9%
Presumed eradication	39	69.6%	40	71.4 %
Failure	8	14.3 %	11	19.6%
Persistence	4	7.1%	3	5.4%
Presumed Persistence	4	7.1%	5	8.9%
Superinfection	0	0	3	5.4%

The two-sided 95% CI for the difference between the two treatment groups is as follows: [-10.4%, 21.1%].

Table 15: Applicant's Clinical Cure Rates by Baseline Pathogen at TOC - MITT

PATHOGENS	AZITHROMYCIN 3-days		CLARITHROMYCIN 10-days	
	n/N	%	n/N	%
S. pneumoniae	29/32	91	21/27	78
H. influenzae	12/14	86	14/16	88
M. catarrhalis	11/12	92	12/15	80

MO COMMENT: The above clinical cure rates by baseline pathogens (MITT) are similar to the reviewer's analysis.

The next table by MO summarizes the clinical cure rates and eradication rates in the MITT population.

Table 16: MO's Clinical Cure Rates by Baseline Pathogen at TOC - MITT

PATHOGENS	AZITHROMYCIN 3-days		CLARITHROMYCIN 10-days	
	n/N	%	n/N	%
S. pneumoniae	29/32	91	21/27	78
H. influenzae	12/14	86	14/16	88
M. catarrhalis	11/12	92	12/15	80
H. parainfluenzae	2/4	50	1/2	50

MO COMMENT: The clinical cure rates for the three pathogens requested by the applicant are as follows: Azithromycin treatment group: S. pneumoniae, 29/32 (91%); H. influenzae, 12/14 (86%); and M. catarrhalis, 11/12 (92%)in the MITT analysis. Clarithromycin treatment group: S. pneumoniae, 21/27 (78%); H. influenzae , 14/16 (88%); and M. catarrhalis, 12/15 (80%)in the MITT analysis. H. parainfluenzae was not requested by the applicant. These

clinical outcomes by pathogen were reported in the CLINICAL STUDIES section of the azithomycin label.

FDA's Post-hoc Analysis

The medical and biostatistics reviewers performed post-hoc subset analyses of FDA's MITT population to evaluate the clinical outcomes in three conditions including: 1) subjects with cough, dyspnea and/or sputum production at Test of Cure (Visit 3) that did not return to pre-exacerbation level; 2) subjects who had any additional signs and symptoms (i.e., rigors, chills, wheezing, rales and rhonchi) that were absent at baseline (Visit 1) but present at TOC; and 3) Subjects with additional signs and symptoms (i.e., rigors, chills, wheezing, rales and rhonchi) present at baseline and still present at TOC. The total number of MITT population (304 subjects: 147 in the azithromycin treatment group and 157 in the clarithromycin treatment group) in this analysis reflect the number of evaluable MITT subjects per MO's analysis.

The following tables by MO identify patients who meet these conditions:

Table 1: Summary of Subjects with Cough, Dyspnea and/or Sputum production at TOC that did not return to pre-exacerbation level

Number of Subjects	Azithromycin (3-days) N= 147		Clarithromycin (10-days) N=157	
	n	%	n	%
Subjects with 0 sign and symptom	114	77.5	119	75.8
Subjects with 1 sign and symptom	20	13.6	20	12.7
Subjects with 2 signs and symptoms	12	8.1	10	6.3
Subjects with 3 signs and symptoms	1	0.68	8	5.1

Table 2: Summary of Subjects with Additional Signs and Symptoms absent

at Baseline but present at TOC

Number of Subjects	Azithromycin N= 147		Clarithromycin N=157	
	n	%	n	%
Subjects with 0 additional signs and symptom	135	91.8	143	91.0
Subjects with 1 additional sign and symptom	12	8.1	12	7.6
Subjects with 2 signs and symptoms	0	0	2	1.2

Table 3: Summary of Subjects with Additional Signs and Symptoms present at Baseline and still present at TOC

Number of Subjects	Azithromycin N= 147		Clarithromycin N=157	
	n	%	n	%
Subjects with 0 Additional signs and symptom	109	74.1	109	69.4
Subjects with 1 Additional sign and symptom	26	17.6	33	21.0
Subjects with 2 Additional signs and symptoms	11	7.4	14	8.9
Subjects with 3 Additional signs and symptoms	1	0.68	1	0.64

MO Comment: Overall, there are no significant differences in clinical outcomes observed between the two treatment groups after adjusting for signs and symptoms.

Based on the above sensitivity analyses, the clinical outcome rates adjusted according to the first and second conditions analyzed sequentially, the cure rates dropped to 67% in the azithromycin treatment group and 63% in the clarithromycin treatment group, 2-sided 95% CI [-6.4,15.0]. The

table below provides the adjusted clinical outcomes based on signs and symptoms specified in Tables 1 and 2:

Table 4: Clinical Outcomes in Subjects Adjusted for the First and Second Conditions

Clinical Outcome	Azithromycin N= 147		Clarithromycin N=157		2-sided 95% CI
	n	%	n	%	
Cure	99	67.3	99	63.0	-6.4%, 15.0%
Failure	48	32.6	58	36.9	

The table below provides the clinical outcomes of all three conditions.

Table 5: Clinical Outcome in Subjects Adjusted for First, Second, and Third Conditions

Clinical Outcome	Azithromycin N = 147		Clarithromycin N=157		2-sided, 95% CI
	n	%	n	%	
Cure	73	50.0	71	45.2	-6.8%, 15.7%
Failure	74	50.3	86	54.7	

MO COMMENT: The clinical outcomes adjusted according to the first, second, and third conditions analyzed sequentially, the cure rates dropped to 50 % in the azithromycin treatment group and 45% in the clarithromycin treatment group, 2-sided 95% CI [-6.8,15.7]. The total number of failures increased in both treatment groups. Overall, the clinical outcome rates are similar between the two treatment groups.

CONCOMITANT CORTICOSTEROID USE IN THE MITT POPULATION

A subset of subjects in the study were treated with corticosteroids either in the form of oral, systemic, inhalational (both oral and nasal), or topical administration. Subjects who received nasal inhalers or topical corticosteroids were excluded from this subset analysis. A total of 54 subjects (29 subjects in the azithromycin treatment group; and 25 subjects in the clarithromycin treatment group) received concomitant corticosteroids during the study excluding those subjects from the sites of [redacted]. There were 2 cures, 7 failures and one subject with no available response, due to being lost to follow-up, in the azithromycin group. In the clarithromycin group, there were 17 cures and 8 failures. The table below summarizes the clinical cure rates in the MITT subjects with and without corticosteroid use:

Table 1: Clinical Cure Rates in Subjects with and without Steroids – MITT

	AZITHROMYCIN n/N	%	CLARITHROMYCIN n/N	%	95% CI (2-sided)
CLINICAL CURE IN SUBJECTS WITH STEROIDS	21/28	75%	17/25	82%	
CLINICAL CURE IN SUBEJCTS WITHOUT STEROIDS	106/121	87.6%	112/132	84.8%	[-7, 12%]

MO COMMENT: When comparing the clinical cure rates in the total MITT subjects (85% in the azithromycin treatment group, 82% in the clarithromycin treatment group) with the clinical cure rates in the MITT subjects without use of cortiocosteroids, the cure rates are similar (87.6% in the azithromycin treatment group, 84.8% in the clarithromycin treatment group, with a two-sided 95% CI of [-7, 12%]).

The findings of DSI report revealed that in Study Center #5168, failed to report the use of concomitant corticosteroid therapy in Subjects # 184, #351 and # 355. In reanalysis of the data, excluding the subjects from this particular center, the results did not impact the overall outcome of the efficacy analysis.

D. Efficacy Conclusions

In the efficacy analysis of Study A066010113, submitted for the claim of acute bacterial exacerbation of chronic bronchitis (ABECB), the clinical success rates (85% in the azithromycin treatment group, 82% in the clarithromycin treatment group) for both treatment groups were equivalent at the TOC with a noninferiority margin of 10%, two-sided 95% CI [-6%,12%] in the MITT population. In the PP population, the clinical success rates between the azithromycin treatment group (84%) and the clarithromycin treatment group (83%) were also equivalent using a noninferiority margin of 10%, two-sided 95% CI [-8%,10%]. Signs and symptoms (cough, dyspnea and sputum production) improved throughout the course of the study for both treatment groups in the evaluable clinical cured subjects. The majority of the exacerbation signs and symptoms were categorized as mild to moderate in severity.

Comparison of success rates by major respiratory pathogens involved in ABECB, i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, also indicated that the two treatment groups were similar. The clinical outcome by the three pathogens requested by the applicant are as follows: Azithromycin treatment group: *S. pneumoniae*, 29/32 (91%); *H. influenzae*, 12/14 (86%); and *M. catarrhalis*,11/12 (92%) in the MITT analysis; Clarithromycin treatment group: *S. pneumoniae*, 21/27 (78%); *H. influenzae*, 4/16 (88%); and *M. catarrhalis*,12/15 (80%) in the MITT analysis.

Treatment of acute bacterial exacerbations of chronic bronchitis with azithromycin 500 mg per day administered orally for three days is equivalent in efficacy to treatment with clarithromycin 500 mg twice a day administered orally for ten days.

Safety Assessments

Adverse Events

All adverse events, either reported by the subject or observed by the investigator, were recorded on the adverse event (AE) page (s) of the case report form (CRF) at each visit or phone contact with information on their severity (mild, moderate, severe), date of onset, duration, treatment required, and the investigator's assessment of relationship to study drug. Adverse events included adverse drug reactions, illnesses with onset during the study, or exacerbation of pre-existing illnesses (including the disease under study). Insufficient benefit or lack of clinical response was not considered an adverse event. Thus the investigator had to distinguish between an exacerbation of pre-existing illness and lack of efficacy. Objective test findings (e.g., ECG changes, abnormal laboratory test results) specified in the protocol which resulted in a change in study drug dosage, treatment discontinuation, or intervention/diagnostic evaluation to assess risk were also recorded as adverse events, as were clinically significant changes in physical examination findings. Subjects were to be followed until adverse events (or their sequelae) resolved or stabilized.

Serious Adverse Events

The applicant defined a serious adverse event (SAE) as any adverse drug experience occurring at any dose that was life-threatening; resulted in death; resulted in inpatient hospitalization or prolongation of existing hospitalization; resulted in a persistent or significant disability/incapacity; or resulted in congenital anomaly/birth defect.

All serious adverse events regardless of treatment group or suspected relationship to the study drug were to be reported immediately by telephone to Pfizer. The investigator is obligated to pursue and provide information for all serious adverse events as requested by the applicant's clinical monitor or designated representative in addition to that on the CRF.

Clinical Laboratory Tests

The study protocol did not provide for routine assessment of laboratory values. Results of all laboratory tests required by the protocol were to be recorded in the subject's CRF. All clinically important laboratory test abnormalities occurring during the study were to be repeated at appropriate intervals until they returned either to baseline or to a level deemed acceptable by the investigator and the applicant's clinical monitor, or until a diagnosis that explained the abnormality was made. In cases of febrile subjects, the applicant allowed the investigator to obtain blood culture for use in the clinical management of the patient. In addition, any woman of childbearing potential had to provide a urine specimen for pregnancy testing.

MO Comment: The overall safety assessments performed by the applicant are acceptable. However, the clinical study protocol did not include the use of routine laboratory tests at posttherapy visits.

The safety analysis performed by the reviewer include all subjects randomized and all subjects who received at least one dose of study medication, including subjects from study sites of [redacted]. The Integrated Summary of Safety follows the Safety review of Study A0661013.

Safety Results

A total of 404 subjects were randomized and treated in the study (200 subjects received azithromycin and 204 subjects received clarithromycin). All subjects who received at least one dose of study medication were included in the safety analysis. The applicant included the adverse events of all causalities and treatment-related adverse events that occurred during therapy or up to 35 days after the last dose. The investigator noted severity of events as mild, moderate and severe. Adverse events both related and unrelated to treatment are summarized by body system and by severity.

The following table provides a summary of subjects evaluable for adverse events in the study:

Table 1: Summary of Subjects Evaluable for Adverse Events

	Azithromycin		Clarithromycin	
Number of Subjects	**200**		**204**	
	n	**(%)**	**n**	**(%)**
Number of adverse events	150		184	
Subjects with adverse events	81	(40.5)	93	(45.6)
Subjects with serious AE	2	(1.0)	5	(2.5)
Subjects with severe AE	6	(3.0)	14	(6.9)
Subjects discontinued due to AE	6	(3.0)	8	(3.9)
Subjects temporarily discontinued or dose reduced	0		1	(0.5)

Two subjects in the azithromycin treatment group experienced serious adverse events (SAEs). A total of five subjects assigned to the clarithromycin treatment group were noted to have serious adverse events including one death. None of these SAEs were considered to be related to study drug. Six subjects in the azithromycin group discontinued from the study due to AEs compared with eight subjects in the clarithromycin group. One subject in the clarithromycin group temporarily discontinued treatment during the study due to adverse events (abdominal pain, chest pain, flu syndrome, headache, diarrhea and nausea). These events were assessed by the investigator as mild in severity and resolved upon temporary discontinuation of the study drug.

Medical Officer's Comment: The safety analysis include all safety evaluable subjects according to the applicant's original analysis. The number of subjects with adverse events in the azithromycin group was 81 (40.5%) compared to 93 (45.6%) in the clarithromycin group. There were two subjects with serious AEs in the azithromycin treatment group and five subjects in the clarithromycin treatment group. None of the subjects in the azithromycin arm discontinued the study due to an adverse event. The table above was generated from the applicant's submission with slight modification in its format by the reviewer.

Table 2: Severity and Incidence of Treatment-Related Adverse Events

Treatment-Related AE	Azithromycin (N=200)	Clarithromycin (N=204)
Total # of Treatment-Related AE	80 (100 %)	104 (100 %)
Severity of Adverse Events		
Mild	58 (72.5)	58 (55.8)
Moderate	21 (26.3)	36 (34.6)
Severe	1 (1.3)	10 (9.6)

The majority of the treatment-related adverse events in the azithromycin (72.5%) treatment group and the comparator (55.8%) group were reported as mild in severity. One severe adverse event was reported in the azithromycin treatment group; ten events were reported in the clarithromycin treatment group.

Serious Adverse Events

Two subjects in the azithromycin treatment group had serious adverse events. Both patients required hospitalization. The first subject (#5088-328) suffered congestive heart failure and an erosive gastroduodenal ulcer. The second subject (#5100-74) was diagnosed with suspected pseudomonal pneumonia. Both serious events occurred after active treatment period was completed. Both events resolved at posttherapy.

Five subjects in the clarithromycin treatment group had serious adverse events. One subject (#1013-245) expired and is discussed below in the death narrative. Of the remaining four subjects, one subject (#1013-635) had bronchospasm which resolved without hospitalization. Subject 1013-640 was diagnosed with bronchial pneumonia and heart failure which required hospitalization. At the EOT visit on day 12, subject #1013-640 had a clinical outcome of improved and a bacteriological outcome of eradicated. However, at the TOC visit on day 26, which was the onset day for the SAE, the subject's response was categorized clinically as failed and bacteriologically as superinfection. Subject # 1013-82 was diagnosed with a left lower lobe infiltrate that required hospitalization with an onset of day 15. Subject # 1013-424 had *H.*

influenzae pneumonia that resulted in hospitalization with an event onset of day 4. Neither of these subjects had an EOT or TOC visit. All four of these adverse events eventually resolved and all were classified as post-therapy events.

Note: The narratives of subjects with Serious Adverse Events are provided in APPENDIX IV.

Death in the Study: There were no deaths in the azithromycin group. The narrative of a single death in the clarithromycin group is as follows:

Subject Number: 1013-245

This 73-year old, white female patient in the U.S. was randomized on 31 March 00 to clarithromycin for the treatment of acute exacerbation of chronic bronchitis. Study drug was administered from 31 March 00 until 05 April 00. On 04 April 00, the subject was admitted to the hospital for exacerbation of chronic obstructive pulmonary disease (COPD) and pneumonia. On 05 April 00 the subject was discontinued from the study due to exacerbation of COPD. The pneumonia resolved on 11 April 00. The subject expired on 07 May 00 due to respiratory failure, COPD and aspergillosis.The investigator attributed the respiratory failure, COPD and pneumonia to the aspergillosis. The aspergillosis was attributed to steroid use and was unrelated to study drug. The subject had a history of chronic obstructive pulmonary disease, atrial fibrillation, irritable bowel syndrome, cancer of the lungs, mild neuropathy, and cataract removal. In the opinion of the investigator, the subject's death was due to respiratory failure, COPD and aspergillosis that were not related to study drug.

Discontinuations due to Adverse Events

All of the six subjects assigned to the azithromycin treatment group that were discontinued due to adverse events reported disorders that affected the respiratory system and were attributed to the disease under study or a related illness of suspected allergic or infectious etiology. In addition, one of the six subjects (#1013-8) complained of chills that were considered to be related to the disease under study. With the exception of one subject (#1013-7) with chest congestion and nasal inflammation that began on day 3, all other adverse events resulting in discontinuation from the azithromycin treatment group began on days 13-17 which was long after the three day duration of active drug administration. There were no subjects from the azithromycin treatment group that were discontinued from the study for reasons related to study drug.

Eight subjects from the clarithromycin treatment group were discontinued from study due to adverse events. However, five of these discontinuations were felt to be due to reasons that were related to the study drug. The study drug-related adverse events that resulted in these five subjects included abdominal pain, diarrhea, nausea, vomiting, flatulence, vertigo, dizziness, chest

pain, headache, asthenia, glossitis, hypertonia, tremor, sweating and taste perversion. Adverse events that were not related to study drug that resulted in the three additional discontinuations from the clarithromycin treatment group included disorders that affected the nervous and respiratory systems.

Note: The narratives of subjects who discontinued from the study due to adverse events are provided in APPENDIX III.

Clinical Laboratory Test Results

The study protocol did not include scheduled clinical laboratory tests. One subject (1013-150) was noted to have SGOT (aspartate aminotransferase) and SGPT (alanine aminotransferase) values considered to be clinically significant, i.e., greater than three times the upper limit of normal. The normal range for both tests was 10-45 U/l. The subject was randomized to the clarithromycin treatment group and received active therapy on days 1-10. The evening dose of clarithromycin 500 mg was missed on both day 5 and day 6 . The laboratory values (SGOT and SGPT) are summarized in the table below:

Table 3: SGOT and SGPT values for Subject 1013-150

	Day 1	Day 14	Day 25	Day 25	Day 57	Day 102
SGOT (U/l)	N.D.	189	126	236	83	76
SGPT (U/l)	N.D.	349	220	440	120	112

N.D. = not done

There were no other clinically significant laboratory abnormalities noted in the study. Since there were no protocol specified laboratory tests, the applicant did not perform a formal assessment of clinical laboratory test abnormalities. The investigators were allowed by the applicant to perform laboratory tests at their discretion.

Incidence of Adverse Events

All Causality Adverse Events

The next table summarizes all causalities treatment-emergent adverse events by body system.

Table 4: Treatment-Emergent AEs by Body System (All Causalities)

Number of Subjects with Adverse events by Body System:	Azithromycin = 200		Clarithromycin =204	
	n	(%)	n	(%)
Body as a Whole	31	(15.5%)	46	(22.5%)
Cardiovascular	4	(2.0%)	4	(2.0%)
Digestive	39	(19.5%)	35	(17.2%)
Metabolic and Nutritional	1	(0.5%)	1	(0.5%)
Nervous	8	(4.0%)	14	(6.9%)
Respiratory	27	(13.5%)	22	(10.8%)
Skin and Appendages	3	(1.5%)	2	(1.5%)
Special Senses	8	(4.0%)	17	(8.3%)
Urogenital	3	(1.5%)	5	(2.5%)

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Table 5 : Incidence and Severity of Treatment-Emergent Adverse Events (All Causalities)

BODY SYSTEM/ Adverse Events	Azithromycin (n= 200)	Clarithromycin (n=204)

		Severity				Severity		
	n (%)	Mild	Moderate	Severe	n (%)	Mild	Moderate	Severe
BODY AS A WHOLE	31 (15.5)	21	8	2	46 (22.5)	26	14	6
Abdomen enlarged	1 (0.5)	1	0	0	0	0	0	0
Abdominal pain	11 (5.5)	7	4	0	12 (5.9)	9	0	3
Accidental injury	0	0	0	0	3 (1.5)	1	2	0
Allergic reaction	0	0	0	0	2 (1.0)	0	2	0
Asthenia	5 (2.5)	2	3	0	5 (2.5)	2	2	1
Back pain	0	0	0	0	6 (2.9)	2	3	1
Chest pain	1 (0.5)	1	0	0	2 (1.0)	1	1	0
Chills	1	0	1	0	1 (0.5)	1	0	0
Drug level increased	1 (0.5)	1	0	0	0	0	0	0
Flu syndrome	0	0	0	0	4 (2.0)	4	0	0
Halitosis	0	0	0	0	1 (0.5)	0	1	0
Headache	12 (6.0)	9	2	1	17 (8.3)	13	4	0
Infection	0	0	0	0	2 (1.0)	1	1	0
Infection fungal	0	0	0	0	1 (0.5)	1	0	0
Malaise	0	0	0	0	1 (0.5)	1	0	0
Pain	3 (1.5)	2	0	1	1 (0.5)	1	0	0
CARDIOVASCULAR	4 (2.0)	1	2	1	4 (2.0)	3	0	1
Bradycardia	1 (0.5)	0	1	0	0	0	0	0
Congestive Heart Failure	1 (0.5)	0	0	1	1 (0.5)	0	0	1
Hypertension	2 (1.0)	1	1	0	1 (0.5)	1	0	0
Palpitation	0	0	0	0	2 (1.0)	2	0	0
Vasodilation	0	0	0	0	1 (0.5)	1	0	0

Table 5 (cont'd)

BODY SYSTEM/ Adverse Events	Azithromycin (n= 200)				Clarithromycin (n=204)			
	n (%)	Severity Mild	Moderate	Severe	n (%)	Severity Mild	Moderate	Severe
DIGESTIVE	39 (19.5)	31	7	1	35 (17.2)	20	11	4
Abnormal stools	0	0	0	0	1 (0.5)	0	1	0
Constipation	2 (1.0)	2	0	0	0	0	0	0
Diarrhea	21 (10.5)	16	5	0	16 (7.8)	11	4	1
Dry mouth	3 (1.5)	2	0	1	2 (1.0)	2	0	0
Dyspepsia	4 (2.0)	4	0	0	5 (2.5)	3	2	0
Dysphagia	0	0	0	0	1 (0.5)	0	0	0
Enterocolitis	1 (0.5)	1	0	0	0	0	0	0
Flatulence	3 (1.5)	2	1	0	2 (1.0)	0	1	1
Gastritis	0	0	0	0	1 (0.5)	1	0	0
Glossitis	0	0	0	0	2 (1.0)	0	2	0
Increased appetite	0	0	0	0	1 (0.5)	1	0	0
Liver function tests abnormal	0	0	0	0	1 (0.5)	0	1	0
Nausea	13 (6.5)	9	4	0	13 (6.4)	7	4	2
Oral moniliasis	1 (0.5)	1	0	0	0	0	0	0
Peptic ulcer	1 (0.5)	1	0	0	2 (1.0)	2	0	0
Rectal disorder	1 (0.5)	1	0	0	0	0	0	0
Rectal hemorrhage	1 (0.5)	1	0	0	0	0	0	0
Vomiting	3 (1.5)	1	2	0	3 (1.5)	1	2	0
METABOLIC AND NUTRITIONAL	1 (0.5)	1	0	0	1 (0.5)	1	0	0
Hyperglycemia	0	0	0	0	1 (0.5)	1	0	0
Thirst	1 (0.5)	1	0	0	0	0	0	0

Table 5 (cont'd)

BODY SYSTEM/ Adverse Events	Azithromycin (n= 200)				Clarithromycin (n=204)			
	n (%)	Severity Mild	Moderate	Severe	n (%)	Severity Mild	Moderate	Severe
NERVOUS	8 (4.0)	4	4	0	14 (6.9)	7	4	3
Abnormal dreams	0	0	0	0	1 (0.5)	0	0	1
Agitation	1 (0.5)	0	1	0	0	0	0	0
Anxiety	1 (0.5)	0	1	0	0	0	0	0
Depression	0	0	0	1	1 (0.5)	0	1	0
Dizziness	0	0	0	0	6 (2.9)	3	2	1
Hypertonia	1 (0.5)	0	1	0	2 (1.0)	1	1	0
Insomnia	3 (1.5)	3	1	0	2 (1.0)	2	0	0
Nervousness	3 (1.5)	2	1	0	0	0	0	0
Paresthesia	0	0	0	0	1 (0.5)	1	0	0
Somnolence	1 (0.5)	0	1	0	2 (1.0)	2	0	0
Tremor	0	0	0	0	1 (0.5)	0	1	0
Vertigo	0	0	0	0	1 (0.5)	0	0	1
RESPIRATORY	27 (13.5)	13	12	2	22 (10.8)	3	13	6
Asthma	1 (0.5)	0	1	0	5 (2.5)	1	2	2
Bronchitis	7 (3.5)	2	4	1	6 (2.9)	1	5	0
Cough increased	1 (0.5)	0	1	0	0	0	0	0
Dyspnea	2 (1.0)	2	0	0	2 (1.0)	1	1	1
Epistaxis	1 (0.5)	0	1	0	1 (0.5)	0	1	0
Hemoptysis	1 (0.5)	1	0	0	0	0	0	0
Hyperventilation	0	0	0	0	1 (0.5)	1	0	0
Pharyngitis	1 (0.5)	1	0	0	3 (1.5)	1	2	0
Pneumonia	2 (1.0)	1	0	1	3 (1.5)	0	1	2
Pulmonary infiltrate	0	0	0	0	1 (0.5)	0	0	1
Respiratory disorder	8 (4.0)	4	4	0	3 (1.5)	0	1	2
Respiratory tract infection	4 (2.0)	1	3	0	2 (1.0)	1	1	0
Rhinitis	3 (1.5)	2	1	0	2 (1.0)	1	1	0
Sinusitis	1 (0.5)	1	0	0	0	0	0	0

Table 5 (cont'd)

BODY SYSTEM/ Adverse Events	Azithromycin (n= 200)				Clarithromycin (n=204)			
	n (%)	Severity Mild	Moderate	Severe	n (%)	Severity Mild	Moderate	Severe
SKIN AND APPENDAGES	3 (1.5)	3	0	0	3 (1.5)	1	2	0
Dry skin	1 (0.5)	1	0	0	0	0	0	0
Herpes simplex	0	0	0	0	1 (0.5)	0	1	0
Pruritus	2 (1.0)	2	0	0	1 (0.5)	1	0	0
Sweating	0	0	0	0	1 (0.5)	0	1	0
SPECIAL SENSES	8 (4.0)	6	2	0	17 (8.3)	9	8	0
Abnormal vision	1 (0.5)	1	0	0	0	0	0	0
Conjunctivitis	1 (0.5)	0	1	0	1 (0.5)	0	1	0
Deafness	0	0	0	0	1 (0.5)	0	1	0
Ear disorder	1 (0.5)	1	0	0	0	0	0	0
Ear pain	1 (0.5)	1	0	0	1 (0.5)	1	0	0
Taste perversion	3 (1.5)	2	1	0	15 (7.4)	9	6	0
Tinnitus	1 (0.5)	1	0	0	0	0	0	0
UROGENITAL	3 (1.5)	1	1	1	5 (2.5)	4	1	0
Breast pain	1 (0.5)	0	0	1	0	0	0	0
Cystitis	0	0	0	0	1 (0.5)	1	0	0
Dysuria	0	0	0	0	2 (1.0)	2	0	0
Impotence	0	0	0	0	1 (0.5)	0	1	0
Vaginitis	2 (2.8)	1	1	0	1 (0.5)	1	0	0
Total Preferred Term Events	150	96	47	7	184	98	65	21

MO Comment: The incidence of treatment-emergent adverse events in all patients treated was 20.9% with azithromycin and 26.8% with clarithromycin. The most common adverse events mainly gastrointestinal were abdominal pain, diarrhea and nausea in the azithromycin treatment group. Abdominal pain was reported with an incidence rate of 6.3% in azithromycin treated patients with a comparable rate of 6.1% in the clarithromycin group. Taste perversion was reported more frequently (7.9%) in the clarithromycin treatment group compared with 0.6% in the azithromycin treatment group. The three most common adverse events were reported predominantly as mild in severity.

The following table summarizes the treatment-emergent adverse events (treatment-related) by Body system:

Table 6: Treatment-Emergent AEs by Body System (Treatment-Related)

	Azithromycin		Clarithromycin	
Number of Subjects with Adverse events by Body System:	**n**	**(%)**	**n**	**(%)**
Evaluable for adverse events	**200**		**204**	
With adverse events	**50**	**(25.0)**	**60**	**(29.4)**
Discontinues due to adverse events	**0**		**5**	**(2.5)**
Body as a Whole	19	(9.5)	23	(11.3)
Cardiovascular	1	(0.5)	1	(0.5)
Digestive	32	(16.0)	33	(16.2)
Metabolic and Nutritional	0		1	(0.5)
Nervous	5	(2.5)	8	(3.9)
Respiratory	2	(1.0)	1	(0.5)
Skin and Appendages	2	(1.0)	2	(1.0)
Special Senses	6	(3.0)	1.5	(7.4)
Urogenital	2	(1.0)	3	(1.5)

Table 7: Incidence of Treatment-Emergent AEs (Treatment-related) in Both Treatment Groups

BODY SYSTEM/Adverse Event	Azithromycin(n=200)		Clarithromycin (n=204)	
	n	(%)	n	(%)
BODY AS A WHOLE	19	(9.5)	24	(11.3)
ABDOMEN ENLARGED	1	(0.5)	0	
ABDOMINAL PAIN	10	(5.0)	11	(5.4)
ASTHENIA	0		2	(1.0)
BACK PAIN	0		4	(2.0)
CHEST PAIN	0		1	(0.5)
DRUG LEVEL INCREASED	1	(0.5)	0	
HALITOSIS	0		1	(0.5)
HEADACHE	6	(3.0)	6	(2.9)
MALAISE	0		1	(0.5)
PAIN	1	(0.5)	0	
CARDIOVASCULAR	1	(0.5)	1	(0.5)
HYPERTENSION	1	(0.5)	0	
VASODILATATION	0		1	(0.5)
DIGESTIVE	32	(16.0)	33	(16.2)
ABNORMAL STOOLS	0		1	(0.5)
CONSTIPATION	1	(0.5)	0	
DIARRHEA	17	(8.5)	15	(7.4)
DRY MOUTH	2	(1.0)	2	(1.0)
DYSPEPSIA	3	(1.5)	5	(2.5)
DYSPHAGIA	0		1	(0.5)
FLATULENCE	3	(1.5)	2	(1.0)
GASTRISTIS	0		1	(0.5)
GLOSSITIS	0		2	(1.0)
INCREASED APPETITE	0		1	(0.5)
LIVER FUNCTION TESTS ABNORMAL	0		1	(0.5)
NAUSEA	12	(6.0)	11	(5.4)
RECTAL DISORDER	1	(0.5)	0	
RECTAL HEMORRHAGE	1	(0.5)	0	
VOMITING	2	(1.0)	3	(1.5)

Table 7 (cont'd)

A. Brief Statement of Conclusions

Overall, similar proportions of subjects in the azithromycin 3-day and comparator groups experienced one or more treatment emergent all causality adverse events, with gastrointestinal events and headache most common in both treatment groups. The incidence of individual treatment-related gastrointestinal adverse events was similar between groups, with the most frequent being abdominal pain, diarrhea, and nausea.

B. Description of Patient Exposure

The overall summary of safety submitted by the applicant includes safety data for 2547 adult subjects (≥17 years old) receiving azithromycin as 500 mg/day for three days and 2466 subjects receiving a comparative agent. Comparators include 151 subjects who received azithromycin by protocol-specified regimens of >3 days . It should be noted that some of these studies allowed for a wide age range of subjects, enrolling 170 subjects <17 years old for whom safety data are available in the individual study reports . In addition, 624 azithromycin 3-day subjects and 629 comparator subjects provide routine safety data from four studies not integrated with other Phase 2-4 studies (066-326, AZM-F-93-001, AZM-F-94-002, and AZM-NY-90-003-Swiss). Similarly, safety data are presented for 197 azithromycin-treated adult subjects from Phase 1 studies. All subjects, regardless of age, enrolled in Phase 1-4 adult studies in this submission were included in the pooled serious adverse event analysis.

All Phase 2-4 studies in adults employed a protocol defined regimen of azithromycin 500 mg/day for 3 days for treatment of adult subjects with [redacted] AECB, [redacted] [redacted] The safety data cutoff date was October 25, 2000.

For "completed" Phase 2-4 studies, this section provides both routine safety data (i.e., adverse events, discontinuations, laboratory test abnormalities) and serious adverse events. For the purposes of this submission, a "completed" Phase 2-4 study included those Phase 4 studies sponsored by the U.S. Division of the Pfizer Pharmaceutical Group, headquartered in New York, for which the project database was officially released by October 25, 2000, or country-sponsored studies (except for Japan) which were filed for country regulatory approval for a labeling change between January 1, 1998 and October 25, 2000. Routine safety and serious adverse event data are also summarized by-study for the adult Phase 1 studies.

Other studies are also included for which serious adverse events data only are provided. These studies did not meet the above criteria for routine safety data submission as they were still enrolling subjects on October 25, 2000, had completed enrollment but were still awaiting database release or data entry as of October 25, 2000, and for country-sponsored studies, were not filed for a country regulatory labeling change between January 1, 1998 and October 25, 2000.

All treated subjects were included in the analysis of safety. Routine safety analyses included summaries of the incidence and severity of adverse events, the proportions of subjects who prematurely discontinued the study, and the incidence of clinically significant laboratory test abnormalities. Serious adverse events, including deaths, were summarized separately. Safety data (adverse events and laboratory test abnormalities) were also analyzed by region (U.S./Canada and Non-U.S./Canada) by the applicant.

Phase 1 Studies: Safety data from 197 of 205 azithromycin-treated adult subjects enrolled in ten Phase 1 studies are provided on a study-by-study basis and are not included in any pooled safety analyses except for serious adverse events. Pharmacokinetic data from three additional Phase 1 studies (066-095, 066-683 and 066-220) support this adult application.

Phase 2-4 Studies: As of the October 25, 2000 (cutoff date), 2547 adult subjects received azithromycin as 500 mg/day for 3 days and 2466 received comparative agents in the Phase 2-4 integrated studies. The great majority of study subjects in the integrated database were from countries outside of the U.S./Canada. According to the applicant, this is expected as most of the studies contributing to the integrated database were post-marketing studies or country-sponsored studies conducted by Pfizer's Pharmaceutical Group. All of the U.S. and Canadian subjects (191 total) came from study A0661013, the pivotal study for AECB.

The following table by applicant lists the number of subject's treated in the US or Canada versus those that were not:

Table 1: Number of Adult Subjects Treated by Study Drug- Integrated Phase 2-4 Studies

Treatment	US/Canada	Non-US/Non-Canada	Total
Azithromycin 3-day	92	2455	2547
Azithromycin 3-5 day*	0	50	50
Azithomycin 5-day**		101	101
Amoxicillin	0	243	243
Augmentin	0	376	376
Penicillin	0	239	239
Roxithromycin	0	322	322
Cefaclor	0	242	242
Clarithromycin	99	794	893
TOTAL	191	4822	5013

*Study AZM-NY-89-017: OPEN-LABEL, COMPARATIVE, RANDOMIZED PILOT STUDY TO DETERMINE THE EFFICACY AND SAFETY OF A 3-5 DAY AZITHROMYCIN REGIMEN VERSUS A 7- 10 DAY AMOXICILLIN REGIMEN IN THE TREATMENT OF ADULT SUBJECTS WITH AECB. LENGTH OF STUDY TREATMENT DEPENDED ON SEVERITY OF INFECTION. AZITHROMYCIN: 500 MG ONCE DAILY FOR 3- 5 DAYS (ORAL) AMOXICILLIN: 500 MG THREE TIMES DAILY FOR 7- 10 DAYS (ORAL). Study Date: January 29,199, conducted in Argentina

** Study AZM-F-92-004: A DOUBLE-DUMMY, RANDOMIZED, MULTICENTER STUDY COMPARING THE EFFICACY AND TOLERATION OF A SHORT (3-DAY) COURSE OF AZITHROMYCIN AND A 10-DAY COURSE OF AUGMENTIN® IN THE TREATMENT OF ADULT PATIENTS WITH ACUTE LOWER RESPIRATORY TRACT INFECTIONS. Study Dates: Oct. 28, 1992-April 15, 1994, conducted in Belgium.

According to the applicant, in the four non-integrated Phase 2-4 studies, an additional 624 azithromycin 3-day, 398 amoxicillin, 95 amoxicillin-clavulanic acid, and 136 roxithromycin subjects were treated in sites outside the U.S./Canada. According to the applicant, the safety studies were included in the studies submitted for the original NDA in 1990. All the serious adverse events were included in the safety reporting. Additionally, 108 of 205 treated subjects from adult Phase 1 studies were from the U.S. and provided routine safety data. All of these studies enrolled adult subjects except for one pediatric subject (16 years old) receiving amoxicillin in study 066-326.

C. Specific Findings of Safety Review

Adverse Events

All Adult Studies (Phase 2-4 Studies)

The following table summarizes the most common adverse events (≥1%) for subjects in the integrated pool of Phase 2-4 studies.

Table 2: Summary of the Most Commonly reported Treatment Emergent Adverse Events (≥1%) for Subjects in either Treatment group by Body System – Adult Subjects in Integrated Phase 2-4 Studies

	All Causality		Treatment-Related	
	Azithromycin 3-day	Comparators*	Azithromycin 3-day	Comparator*
Number of Subjects	2547	2466	2547	2466
Subjects with at least one Adverse event	426 (16.7%)	470 (19.1%)	281 (11.0%)	307 (12.4%)
Body System/ Adverse Event				
Body as a Whole	124 (4.9%)	147 (6.0%)	77 (3.0%)	77 (3.1%)
Abdominal pain	60 (2.4%)	48 (1.9%)	52 (2.0%)	43 (1.7%)
Headcahe	26 (1.0%)	28 (1.1%)	-**	-**
Digestive	227 (8.9%)	217 (8.8%)	196 (7.7%)	194 (7.9%)