| | | | | |
|---|---|---|---|---|
| **Diarrhea** | 98 (3.8%) | 83 (3.4%) | 88 (3.5%) | 79 (3.2%) |
| **Nausea** | 82 (3.2%) | 69 (2.8%) | 73 (2.9%) | 62 (2.5%) |
| **Vomiting** | 22 (0.8%) | 25 (1.0%) | | |

*Comparators include 151 subjects assigned to azithromycin regimens greater than 3 days.
** Incidence of treatment-related adverse events was <1% in both treatment groups.

Overall, similar proportions of subjects in the azithromycin 3-day and comparator groups experienced one or more treatment emergent adverse events. Gastrointestinal events and headache were the most common all causality adverse events in both treatment groups. In both groups, the majority (>85%) of gastrointestinal adverse events were treatment-related; the incidence of individual treatment-related gastrointestional adverse events was similar between groups, with the most frequent being abdominal pain, diarrhea, and nausea.

In both groups, the majority of gastrointestinal adverse events were of mild to moderate severity. Though the number of severe adverse events was small in either treatment group, among the more frequent treatment-related gastrointestinal events for which severe cases were reported, the proportion of severe events tended to be lower with azithromycin 3-day than with comparative agents, as shown in table below.

**Table 2: Summary of Severe Treatment-Related,Treatment-Emergent Gastrointestinal Adverse Events- Adult Subjects in Integrated Phase 2-4 Studies**

| | AZITHROMYCIN 3-DAY | | COMPARATORS* | |
|---|---|---|---|---|
| **ADVERSE EVENT** | **No. of Subjects with Adverse Event** | **No. of Severe Events (%)** | **No. of Subjects with Adverse Event** | **No. of Severe Events (%)** |
| **Diarrhea** | 88 | 5 (5.7%) | 79 | 6 (7.6%) |
| **Nausea** | 73 | 3 (4.1%) | 62 | 10 (16.1%) |
| **Abdominal pain** | 52 | 2 (3.8%) | 43 | 5 (11.6%) |
| **Vomiting** | 17 | 1 (5.9%) | 22 | 7 (31.8%) |
| **Dyspepsia** | 14 | 1 (7.1%) | 17 | 3 (17.6%) |
| **Flatulence** | 13 | 0 | 8 | 2 (25.0%) |
| **Dry Mouth** | 4 | 2 (50.0%) | 2 | 0 |
| **Glossitis** | 2 | 1 (50.0%) | 3 | 1 (33.3%) |
| **Anorexia** | 1 | 1 (100.0%) | 1 | 0 |
| **Constipation** | 1 | 0 | 4 | 2 (50.0%) |
| **GI disorder** | 1 | 0 | 5 | 1 (20.0%) |

*Comparators include 151 subjects assigned to azithromycin regimens greater than 3 days.

**Premature Discontinuation From the Study**

The following table summarizes the number of adult subjects discontinued from study in the integrated pool of Phase 2-4 studies.

**Table 3: Summary of All Subjects who Discontinued from Study in Integrated Phase 2-4 Studies**

| | ALL SUBJECTS | | US/Canada | | Non US/non Canada | |
|---|---|---|---|---|---|---|
| | AZ 3-day | Comparator | AZ 3-day | Comparator | AZ 3-day | Comparator |
| **Total Treated** | 2547 | 2466 | 92 | 99 | 2455 | 2367 |
| **Total Discontinued** | 204 (8.0%) | 227 (9.2%) | 11 (12.0%) | 13 (13.1%) | 193 (7.9%) | 214 (9.0%) |
| | | | | | | |
| **Related study drug** | 71 (2.8%) | 106 (4.3%) | 3 (3.3%) | 9 (9.1%) | 68 (2.8%) | 97 (4.1%) |
| **Adverse event** | 9 (0.4%) | 34 (1.4%) | 0 | 4 (4.0%) | 9 (0.4%) | 30 (1.3%) |
| **Lack of efficacy** | 62 (2.4%) | 72 (2.9%) | 3 (3.3%) | 5 (5.1%) | 59 (2.4%) | 67 (2.8%) |
| | | | | | | |
| **Unrelated study drug** | 133 (5.2%) | 121 (4.9%) | 8 (8.7%) | 4 (4.0%) | 125 (5.1%) | 117 (4.9%) |
| **Study default** | 72(2.8%) | 68 (2.8%) | 5 (5.4%) | 1 (1.0%) | 67 (2.7%) | 67 (2.8%) |
| **Adverse event** | 20 (0.8%) | 20 (0.8%) | 3 (3.3%) | 3 (3.0%) | 17 (0.7%) | 17 (0.7%) |
| **Death** | 4 (0.2%) | 7 (0.3%) | 0 | 0 | 4 (0.2%) | 7 (0.3%) |
| **Other** | 37 (1.5%) | 26 (1.1%) | 0 | 0 | 37 (1.5%) | 26 (1.1%) |

Note: Comparators include 151 subjects who received an assigned azithromycin regimen >3 days; Azithromycin subjects were from study A0661013.

Overall, comparable numbers of subjects receiving a 3-day regimen of azithromycin versus a comparative agent discontinued from the study.When one separates these data by the subgroups of U.S./Canada versus other sites, the pattern in rates of discontinuations in the nonU.S./nonCanadian subjects is similar to the group overall.The overall rates of discontinuation from study were similar between subjects receiving a 3-day regimen of azithromycin versus comparators. However, there was a trend toward a lower rate of discontinuation due to treatment-related adverse events in the azithromycin versus comparator groups (0.4% versus 1.4%, respectively).

**Adult Pivotal Studies - Study A0661013 and AZM-NY-93-007**

The following table by applicant presents the most commonly reported treatment- related adverse events in the two adult pivotal studies in this submission. Study A0661013 was a multicenter, global study conducted at sites in the U.S., Canada, Argentina, Brazil, Chile, Costa Rica, India and South Africa. Study AZM-NY- 93-007 was also a multicenter study conducted at sites in the U.K., Ireland, Belgium and Germany.

**Table 4: Summary of Most Commonly Reported Treatment- Related Adverse Events (≥1% in Either Treatment Group) by Body System- Adult subjects in Studies A0661013 and AZM-NY-93-007**

| | Azithromycin 3-day (N=299) | Clarithromycin* (N=302) |
|---|---|---|
| Subjects with at least one AE | 63 (21.1%) | 73 (24.2%) |
| Discontinued for AE | 0 | 7 (2.3%) |
| Body System/Adverse event | | |
| *Body as a Whole* | 21 (7.0%) | 26 (8.6%) |
| Abdominal pain | 11 (3.7%) | 13 (4.3%) |
| Asthenia | 0 | 3 (1.0%) |
| Back pain | 0 | 4 (1.3%) |
| Headache | 7 (2.3%) | 6 (2.0%) |
| *Digestive* | 37 (12.4%) | 39 (12.9%) |
| Diarrhea | 18 (6.0%) | 16 (5.3%) |
| Dyspepsia | 4 (1.3%) | 5 (1.7%) |
| Flatulence | 3 (1.0%) | 2 (0.7%) |
| Nausea | 14 (4.7%) | 13 (4.3%) |
| Vomiting | 3 (1.0%) | 3 (1.0%) |
| *Nervous* | 8 (2.7%) | 9 (3.0%) |
| Dizziness | 1 (0.3%) | 4 (1.3%) |
| Nervousness | 4 (1.3%) | 0 |
| *Skin and Appendages* | 3 (1.0%) | 4 (1.3%) |
| Pruritus | 3 (1.0%) | 2 (0.7%) |
| *Special Senses* | 6 (2.0%) | 16 (5.3%) |
| Taste perversion | 3 (1.0%) | 16 (5.3%) |
| *Urogenital* | 6 (2.0%) | 5 (1.7%) |
| Vaginitis | 5 (1.7%) | 3 (1.0%) |

*Clarithromycin was 500 mg twice daily x 10 days (study A0661013) or 250 mg twice daily (study AZM-NY-93-007). Note: The adult subjects exclude 2 azithromycin and 4 clarithromycin subjects <17 years old.

The pooled two pivotal studies showed a two-fold greater overall incidence of treatment-related, treatment emergent adverse events in both treatment groups than was seen in the integrated safety database. This difference is influenced by inclusion of U.S./Canada subjects from study A0661013, which tend to have a higher rate of adverse events than subjects from outside these countries in both the azithromycin 3-day and comparator group. The highest incidence of treatment related adverse events occurred in the gastrointestinal tract. Other than an increased incidence of taste perversion in the comparator group relative to the azithromycin 3-day group, which was largely due to subjects in the A0661013 study, the azithromcyin 3-day and

| BODY SYSTEM / Adverse Event | Azithromycin(n=200) | | Clarithromycin (n=204) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| METABOLIC AND NUTRITIONAL | 0 | | 1 | (0.5) |
| HYPERGLYCEMIA | 0 | | 1 | (0.5) |
| NERVOUS | 5 | (2.5) | 8 | (3.9) |
| ABNORMAL DREAMS | 0 | | 1 | (0.5) |
| AGITATION | 1 | (0.5) | 0 | |
| DIZZINESS | 0 | | 4 | (2.0) |
| HYPERTONIA | 0 | | 1 | (0.5) |
| INSOMNIA | 1 | (0.5) | 0 | |
| NERVOUSNESS | 1 | (1.5) | 0 | |
| PARESTHESIA | 0 | | 1 | (0.5) |
| SOMNOLENCE | 1 | (0.5) | 1 | (0.5) |
| TREMOR | 0 | | 1 | (0.5) |
| VERTIGO | 0 | | 1 | (0.5) |
| RESPIRATORY | 2 | (1.0) | 1 | (0.5) |
| DYSPNEA | 0 | | 1 | (0.5) |
| RESPIRATORY DISORDER | 1 | (0.5) | 0 | |
| RHINITIS | 1 | (0.5) | 0 | |
| SKIN AND APPENDAGES | 2 | (1.0) | 2 | (1.0) |
| PRURITUS | 2 | (1.0) | 1 | (0.5) |
| SWEATING | 0 | | 1 | (0.5) |
| SPECIAL SENSES | 6 | (3.0) | 15 | (7.4) |
| CONJUNCTIVITIS | 1 | (0.5) | 0 | |
| EAR PAIN | 1 | (0.5) | 0 | |
| TASTE PERVERSION | 3 | (1.5) | 15 | (7.4) |
| TINNITUS | 1 | (0.5) | 0 | |
| UROGENITAL | 3 | (1.5) | 3 | (1.5) |
| DYSURIA | 0 | | 1 | (0.5) |
| IMPOTENCE | 0 | | 1 | (0.5) |
| VAGINITIS | 1 | (2.8) | 1 | (0.5) |
| Total Preferred Term Events | 80 | | 104 | |

comparator groups were comparable. However, the comparator group had a higher rate of discontinuations for treatment-related adverse events. Overall, cases of severe treatment-related adverse events were less frequent in the azithromycin 3-day group (1 subject with a total of 1 severe event) than in the comparator group (8 subjects with a total of 14 severe events).

**Discontinuations from Studies A0661013 and AZM-NY-93-007**

In study A0661013, discontinuations from study for treatment-related adverse events were lower in the azithromycin 3-day group (0.0%) than in the clarithromycin group (2.5%). The related adverse events resulting in discontinuation in the clarithromycin group included abdominal pain, diarrhea, nausea, vomiting, flatulence, vertigo, dizziness, chest pain, headache, asthenia, glossitis, hypertonia, tremor, sweating and taste perversion. However, the incidence of study discontinuations for adverse events judged unrelated to study drug were somewhat greater in the azithromycin 3-day group than the clarithromycin group (3.0% vs. 1.5%, respectively). All of the six azithromycin subjects who were discontinued reported disorders that affected the respiratory system and these were attributed to the disease under study or a related illness of suspected allergic or infectious etiology. In addition, one of the six subjects complained of chills, which were considered to be related to the disease under study. In the clarithromycin group, three subjects discontinued due to adverse events unrelated to treatment which included disorders that affected the nervous and respiratory systems.

In study AZM-NY-93-007, no azithromycin 3-day and three clarithromycin (2.9%) subjects discontinued study drug due to adverse events. In two of the three clarithromycin subjects the adverse events were treatment-related and included asthenia, nausea, depression, taste perversion and rash. In the third subject pleural effusion unrelated to treatment was reported.

**Clinical Laboratory Test Abnormalities**

**Adult (Phase 2-4) Studies**

The following table by the applicant summarizes laboratory test abnormalities with clinical relevance and an incidence of >2% in either treatment group, excluding tests for which too few subjects were assessed to be clinically meaningful (i.e., ≤36). As noted previously, laboratory tests considered for analysis included those identified in the protocol or requested on the case report form. **Note: The table below has been modified by the reviewer as to its format.**

**Table 5: Incidence of Clinically Significant Laboratory Abnormalities in Adult Subjects treated in Phase 2-4 studies (Incidence >2%*) in Either Treatment Group**

| Laboratory Parameter | Azithromycin 3-day | | Comparators** | |
|---|---|---|---|---|
| | % | N | % | N |
| Overall | 16.1% | (183/1140) | 9.9% | (95/963) |
| Hematology | | | | |
| Increased Eosinophils | 2.9% | (18/628) | 2.7% | (12/439) |
| Increased Lymphocytes | 3.0% | (20/663) | 2.7% | (12/440) |
| Decreased Monocytes | 5.2% | (34/659) | 1.8% | (8/438) |
| Increased Monocytes | 3.3% | (22/659) | 1.4% | (6/438) |
| Liver Function | | | | |
| Decreased Albumin | 1.6% | (4/253) | 2.3% | (4/176) |
| Renal Function | | | | |
| Increased Creatinine | 5.1%*** | (27/531) | 1.2% *** | (4/324) |
| Urinalysis | | | | |
| Increased Urine Protein | 1.1% | (4/379) | 5.5% | (12/220) |

* Includes subjects without regard to whether baseline was abnormal or the baseline value was missing; ** Comparators include subjects assigned to azithromycin regimens greater than 3 days decreased. *** Incidence of increased creatinine without subjects from study AZM-NY-89-016B was 0.6% for azithromycin 3-day and 1.2% for comparators.

Overall, the incidence of laboratory test abnormalities identified as clinically significant by the applicant's algorithm was greater in the azithromycin 3-day group than in the comparator group. Specific tests assessed in a meaningful number of subjects contributing to this difference were increased creatinine and decreased monocytes. According to the applicant, these differences appear to be in part artifacts of the applicant's algorithm, which did not correct for an abnormal or missing baseline value. First, an analysis of the median change from baseline to last observation for these parameters showed no change from baseline in either the azithromycin 3-day group or the comparator group. Secondly, 22 of the 27 subjects in the azithromycin 3-day group and 2 of the 4 subjects in the comparator group with increased creatinine had an abnormal baseline value. All of the subjects with this abnormality in the azithromycin 3-day group were from two open-label, noncomparative studies (AZM-NY-88-002, AZM-NY-89-016B). It should be noted that in study AZM-NY-89-016B, conducted in South Africa, subjects were generally young black coal miners with elevated baseline values. When these data were regenerated without subjects from study AZM-NY-89-016B, creatinine levels were similar between the treatment groups (0.6% for azithromycin 3-day and 1.2 % for comparators). Similarly, 25 of the 34 azithromycin 3-day subjects with decreased monocytes had an abnormal baseline and in all these cases both the baseline and most abnormal values were identical. Again, the vast majority

of azithromycin 3-day subjects with decreased monocytes were from noncomparative study AZM-NY-88-002.

***MO COMMENT: Increased creatinine is being added to the current label of azithromycin.***

Six of the 12 comparator subjects and 2 of the 4 azithromycin 3-day subjects with urine protein had an abnormal baseline. All but one case of urine protein were from comparative study AZM-NY-92-009. Although some between group differences were also noted for random glucose and decreased potassium, the tests were obtained in too few subjects (≤36/group) to make meaningful comment.

Finally, a slightly higher incidence of SGPT elevation in the azithromycin 3-day group (1.2%, 10 of 831) versus the comparator group (0.3%, 2 of 613) was noted. However, an abnormal baseline was present for 5 of the 10 subjects with this abnormality in the azithromycin 3-day group versus no subjects in the comparator group and in 3 of these cases the values actually decreased from baseline.

***MO COMMENT: Azithromycin is already labeled as causing increased ALT. None of the patients in the clinical trials had clinical hepatitis.***

Pivotal AECB Study A0661013, which contributed all of the U.S./Canada subjects to the submission, did not routinely collect laboratory tests.

**Serious Adverse Events**

Overall, 3248 subjects received azithromycin as a 3-day regimen and 3188 subjects a comparative agent in the Pfizer sponsored Phase 2-4 studies supporting this application with routine safety data. An additional 24,070 subjects who received azithromycin, a comparative agent or placebo were enrolled in non-U.S. Phase 2-4 studies. Additionally, 185 subjects from Pfizer-sponsored studies (i.e., excludes Amsden study GA2000 and study CAM070191) received azithromycin. All 30,691 of these subjects were included in this serious adverse event analysis. It should be noted that in the serious adverse event analysis, the azithromycin group was not distinguished by regimen and that there was no attempt to exclude pediatric subjects who might have enrolled in these studies.

**Summary of Deaths**

The following table by applicant provides a summary of the deaths reported in Phase 1-4 trials as of October 25, 2000 is presented below:

**Table 6: Summary of Deaths Reported in Phase 1-4 Trials**

| | Azithromycin | Comparators |
|---|---|---|
| On Therapy or Within 35 days Post-therapy | 21* | 13 |
| ≥35 Days post-therapy | 5 | 7 |
| Missing or incomplete Dates of Death or Drug Stop | 1 | 1 |

* Death narratives for these patients are provided in Appendix V.

Neither the investigator nor the sponsor assessed any deaths in any treatment group as related to study drug. Note: The narratives for deaths and treatment-related serious adverse events are provided in the appendices.

***MO COMMENT: Review of the narratives and CRFs of the patient's deaths reported in the ISS did not appear related to the study drug but probably due to the patient's concurrent underlying diseases and other factors not specified in the report.***

**D. ISS 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. In both groups, the majority of treatment-emergent gastrointestinal adverse events were of mild to moderate severity. However, severe treatment-related gastrointestinal events tended to be lower with azithromycin 3-day than with comparative agents. Overall, the discontinuation rates for all causality adverse events were low and similar between the azithromycin 3-day (1.2%) and comparator (2.4%) groups. There were no consistent patterns to indicate clinically meaningful gender or age differences in the incidence of treatment-related, adverse events. In general, black subjects appeared to have more treatment-related adverse events than other subjects in each treatment group. There were too few Asian subjects to comment.

Overall, the incidence of laboratory test abnormalities identified as clinically significant by the applicant's algorithm generally appear to be similar between treatment groups (azithromycin 16.1%, comparator 9.9%). Within the azithromycin 3-day group in the non-U.S./non-Canada subjects, the incidence of increased creatinine was greater in males than females, and greater in blacks than other racial groups, likely due to the fact that most of the subjects came from a noncomparative study in black males and had elevated baseline values. Excluding this study, the rates of laboratory abnormalities were similar. There did not appear to be any consistent trends of age-related increased or decreased incidences of laboratory test abnormalities with age in either

treatment group. Overall, the azithromycin 3-day and the comparator groups were similar in the degree and direction of median changes in laboratory tests from baseline to last observation.

Neither the investigator nor the sponsor assessed any deaths in any treatment group as related to study drug. Serious adverse events were assessed as treatment related by the investigator for 9 subjects receiving azithromycin, and 3 subjects receiving a comparator.



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# APPENDICES

# APPENDIX 1

## Clinical Study Report - Study A0661013

**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY TRIAL COMPARING AZITHROMYCIN 500 MG DAILY FOR 3 DAYS WITH CLARITHROMYCIN 1 GRAM DAILY FOR 10 DAYS FOR THE TREATMENT OF ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS.**

**I. Study Dates:** 30 Nov 1999 – 16 Sep 2000

**II. Study Objectives:**

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

The secondary objective was to compare the safety and tolerance of the regimens.

**III. Study Design and Plan**

Male or female subjects between the ages of 35 and 75 years with ABECB entered this randomized, double-blind, comparative, multicenter study. They received either oral azithromycin 500 mg/day as a single daily dose for 3 days or oral clarithromycin 1000 mg/day divided as 500 mg morning and evening for 10 days. Subjects were followed for 21-24 days. There were no protocol amendments.

Within the 48 hours prior to baseline, as a screening procedure, all subjects had a physical examination and provided a medical history. Subjects were enrolled in the study after satisfying the inclusion/exclusion criteria, including provision of the appropriate informed consent. Chest X-rays were obtained to exclude the presence of pneumonia. Freshly expectorated sputum samples were examined macroscopically and microscopically to determine suitability for culture. Adequate specimens were submitted for culture with Gram stains to an approved local laboratory. The Gram stains and any culture isolates from the local laboratories were sent to the central laboratory to verify adequacy of the Gram stain and to confirm the identification of the bacteria. The central laboratory also conducted susceptibility testing on all respiratory pathogens using azithromycin and clarithromycin. Isolation of a baseline pathogen susceptible to azithromycin or clarithromycin was not

required to continue in the study. Subjects were assigned screening identification numbers sequentially at entry. Follow-up included visits to the site on day 10-12 (designated Visit 2, End of Therapy [EOT]) and day 21-24 (designated Visit 3, Test of Cure [TOC]). The clinical outcome at TOC, which was based on the investigator assessment, was the primary endpoint.

## IV. Study Population

### Inclusion Criteria

Subjects who met the following criteria were considered for enrollment into the study and could receive study drug, if eligible.

- Male or female outpatients between the ages of 35 and 75 years

- A medical history of chronic bronchitis, as defined by the presence of a persistent cough with sputum production on most days of the month during three consecutive months for > 2 successive years
- A clinical diagnosis of an acute bacterial exacerbation of chronic bronchitis. This diagnosis was based upon the presence of:

  a. Increased cough compared to pre-exacerbation status
  b. Increased sputum production compared to pre-exacerbation status
  c. Worsening dyspnea compared to pre-exacerbation status
  d. The presence of purulent sputum defined as >25 white blood cells (WBC) per field and <10 squamous epithelial cells at 100x magnification (low power, 10x objective) microscopic examination
  e. Sputum Gram stain indicative of a bacterial pathogen

- A chest x-ray within 48 hours prior to first visit that excluded the diagnosis of pneumonia

- Were suitable for outpatient therapy with an oral antibiotic

- Had provided written informed consent

### Exclusion Criteria

Subjects with any of the following conditions could not be enrolled in this study:

- Known or suspected hypersensitivity or intolerance to azithromycin, clarithromycin, erythromycin, or other macrolides

- Treatment with any systemic antibacterial within the previous 7 days

- Subjects who had any of the following conditions:
  a. Bronchiectasis or acute bronchitis
  b. Suspected pulmonary abscesses or empyema
  c. Known or suspected active tuberculosis
  d. Known HIV infection
  e. Neutropenia, defined as a total white blood cell count less than 2,500 leukocytes/mm or absolute neutrophil count less than 1,000/mm
  f. Immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including treatment with greater than or equal to 10 mg/day of systemic prednisone or equivalent)
  g. Cystic fibrosis
  h. Primary lung cancer or other malignancy metastatic to the lungs
  i. Significant psychiatric disorders (defined as any psychiatric disorder that impairs a subject's cognitive function or judgement to the extent that the subject would be unable to adhere to protocol specified procedures).
  j. A known FEV1 <35% of the predicted normal value prior to baseline during an exacerbation free period (within the last 3 months)

- Recent or current evidence of substance abuse or ethanol abuse

- A clinically significant hematological, renal, hepatic, gastrointestinal, cardiovascular, cerebrovascular, or other serious disease including non-cutaneous malignancies, or, clinically significant laboratory abnormalities which, in the judgment of the investigator, would interfere with the subject's participation in the study or evaluation of the subject's response to therapy (Subjects with cirrhosis or renal failure are, therefore, excluded.)

- Any condition which, in the opinion of the investigator, could affect subject safety, preclude evaluation of response, or make it unlikely that the contemplated course of therapy and follow-up can be completed

- Pregnant women, nursing mothers, or women of childbearing potential (including women who are not sterile by reason of surgery, chemotherapy, or radiation, or post-menopausal for less than two years) who were not practicing adequate contraceptive measures (e.g., oral contraceptives for at least two cycles, depot injection, implant, IUD or barrier method in conjunction with contraceptive foam or jelly), and/or subjects whose intent was to become pregnant during the study period or within 1 month after completion of the study. Urine pregnancy tests were required of all women of childbearing potential

- Known liver function test results > 2 X the upper limit of normal (ULN) for SGOT/AST or SGPT/ALT, > 1.5 X ULN for alkaline phosphatase or total bilirubin

- Another infection that required treatment with an antibacterial other than study drug
- Concomitant treatment with theophylline, digoxin, warfarin, ergotamine, triazolam, diazepam, phenytoin, carbamazepine, or benzodiazepines while receiving study drug
- Received treatment with terfenadine (Seldane®), loratadine (Claritin®), fexofenidene (Allegra®), fluoxetine (Prozac®), pimozide (Orap®), or cisapride (Propulsid®) within two weeks or astemizole (Hismanal®), within 30 days prior to the baseline visit. In addition, a subject enrolled in this study could not use any of these medications while receiving study drugs or within one month of completing therapy with the study drugs
- Received treatment with an investigational drug within 4 weeks prior to the baseline visit
- Prior enrollment in this trial. The inclusion of a subject more than once in this trial was not allowed.

*MO COMMENT:*

***The study submitted by the applicant is a single pivotal clinical trial in support of the claim for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB). This single study in conjunction with the biopharmaceutics data and some supportive evidence from the study support the claim for the treatment of ABECB. In addition, Zithromax is already approved for AECB using the 5-day regimen.***

***The study design is in accordance with FDA's Guidance document for Industry for the treatment of Acute Bacterial Exacerbation of Chronic Bronchitis. The study inclusion and exclusion criteria are acceptable. The study visits are consistent with FDA's Guidance document.***

***At the outset of the review, the MO performed a random sample analysis of CRFs from 80 subjects of the study in a blinded manner. Some subjects were noted with an assessment of "improvement" at the TOC visit who had an additional follow-up visit. The reviewer decided to review all the CRFs of the study with the exception of CRFs from the excluded sites. In addition to the primary clinical efficacy analysis, the medical reviewer and the biostatistics reviewers performed post-hoc analyses in the following conditions: 1) subjects in whom 3 signs and symptoms (cough, dyspnea and/or sputum production) at TOC 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 but present at TOC visit; and 3) subjects who had any additional signs and symptoms (i.e., rigors, chills, wheezing, rales and rhonchi) that were present at baseline and still present at TOC visit. The purposes of these***

***sensitivity analyses are to evaluate the clinical outcomes in correlation with the mentioned three clinical conditions.***

## V. Efficacy Assessments

### A. Clinical Assessment

- **Visit 1 (Baseline)**

The baseline visit (Visit 1) assessment included collection of demographic information, past medical history including smoking and allergy history, concurrent diseases, antibiotic therapy within the last 30 days, concomitant medications and supplemental oxygen use in addition to a physical examination. Pre-exacerbation information included cough frequency, sputum volume and sputum characteristics. If pulmonary function test (PFT) results or arterial blood gases had been acquired within the past 3 months, a copy of the most recent result was appended to the case report form. Chest x-rays were obtained to exclude the presence of pneumonia.

Assessment of current signs and symptoms of ABECB included documentation of increased sputum production, frequency of cough and increased dyspnea. These signs and symptoms were graded as 0 = absent, 1 = mild, 2 = moderate and 3 = severe. Qualitative and quantitative assessments of sputum were to be obtained in the study.

Spirometry was to be performed during the baseline visit using equipment provided by a centralized spirometry laboratory. Measurements were made according to applicable standards described in the American Thoracic Society, 1995 guidelines. A detailed manual describing testing procedures was issued to each site by the centralized spirometry laboratory. Testing was performed by a trained technician. To the extent possible, PFT was to be obtained at the same hour throughout the study by the same technician at each site. Information on healthcare resource utilization was also collected at baseline.

- **Visit 2 (End of Therapy Visit) and Visit 3 (Test of Cure Visit)**

Visit 2 (End of Therapy Visit, EOT) was designated to occur on study days 10-12. Visit 3 (Test of Cure Visit, TOC) was designated to occur on study days 21-24. Clinical assessment of efficacy was the same on both visits. The primary efficacy outcome time point for the study was TOC. All signs and symptoms identified at baseline (Visit 1) were assessed and numerically graded using the same criteria. Current qualitative and quantitative descriptions of sputum were obtained. Vital signs and concomitant medications were recorded. The investigator provided an evaluation of clinical response at both Visit 2 and Visit 3. Study medications were returned to the investigator and study drug accountability was performed at Visit 3. Spirometry was performed at Visits 2 and 3 using the same procedures as in Visit 1. A repeat chest x-ray was not obtained unless clinically indicated. If at Visit 3 it was unclear whether a subject met Cure or Failure

criteria, an additional follow-up visit was scheduled within 1-2 weeks. All clinical assessments were done as in Visits 2 and 3. The investigator then provided a final evaluation of clinical response as either Cure or Failure. Information on healthcare resource utilization was also collected at Visit 3.

**B. Bacteriologic assessment**

- **Visit 1 (Baseline)**

Freshly expectorated sputum samples were to be examined macroscopically for consistency and color and microscopically to determine suitability for culture. Specimens were considered to be suitable if > 25 WBC and < 10 squamous cells were present per low power (100x) field of Gram-stained specimen. Adequate specimens were to be submitted for culture with Gram stains to an approved local laboratory. The Gram stains and any culture isolates from the local laboratories were to be sent to the central laboratory to verify adequacy of Gram stain and to confirm the identification of the bacteria. The central laboratory also conducted susceptibility testing for azithromycin and clarithromycin on all respiratory pathogens.

- **Visit 2 (End of Therapy Visit) and Visit 3 (Test of Cure Visit)**

Sputum was to be obtained again on Visits 2 and 3 and was to be examined microscopically for adequacy as was done at Visit 1. The Gram-stained slides as well as culture isolates from the local laboratory were sent to the central laboratory for confirmation and susceptibility testing. The absence of an adequate sputum specimen and the reason were documented. If a follow-up visit was required after Visit 3, sputum was obtained and processed as in Visits 2 and 3. Serum was obtained at Visit 3 and stored at the central laboratory for possible serological testing for *Mycoplasma pneumoniae, Legionella spp.* and *Chlamydia pneumoniae.*

**VI. Efficacy Evaluation**

Analyses were as follows:

(1) Modified intent-to-treat (**MITT**) group which 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, and < 10 squamous cells were present per low power (100x) field.

(2) Per-protocol (**PP**) evaluable subgroup which included MITT subjects that had received 80-120% of protocol - specified doses of active therapy and had visits in the appropriate time windows.

Both the clinical MITT and clinical PP evaluable subgroups had bacteriological subsets that had positive baseline sputum cultures for *H. influenzae, H. parainfluenzae, S. pneumoniae* or *M. catarrhalis*. Groups were analyzed at both the end of therapy (EOT) and test of cure (TOC) time points. The primary endpoint was based on the investigator's assessment of clinical outcome (cure or failed) at the TOC visit.

**VII. Statistical Evaluation**

The percentages of subjects clinically cured versus failed at TOC and clinically cured, improved, and failed at EOT were to be determined. In addition, bacteriological success rates were to be calculated for EOT and TOC according to applicant. The 95% confidence intervals were computed for success rate differences between the two regimens using the normal approximation to the binomial distribution with a continuity correction. The percentage of subjects with specific signs/symptoms throughout the study was tabulated, including summary statistics on pulmonary function test results. **(Note: Please refer to the statistical review of Mushfiqur Rashid, Biostatistics reviewer, for details.)**



## APPENDIX II

## Principal Investigators

The following table lists the principal investigators in this study (*excluding* [redacted] with their respective countries (addresses)/study centers, total number of screened, randomized and evaluable subjects:

**Table 1: List of Principal Investigators**

| NAME OF PRINCIPAL INVESTIGATOR | ADDRESSES | CENTER NUMBER | TOTAL NUMBER OF SUBJECTS SCREENED | TOTAL NUMBER OF RANDOMIZED SUBJECTS | MITT-CLINICAL EVALUABLE | MITT - CLINICAL & MICRO EVALUABLE |
|---|---|---|---|---|---|---|
| Michael Brown, M.D. | Pensacola, FL | 5073 | 20 | 11 | 7 | 1 |
| Randy Dotson, M.D. | Mobile, AL | 5074 | 5 | 2 | - | 2 |
| Edward Kerwin, M.D. | Medford, OR | 5075 | 22 | 12 | 4 | 2 |
| Larry Gilderman, D.O. | Pembroke Pines, FL | 5076 | 5 | 2 | 2 | 0 |
| Robert Lapidus, M.D. | Wheat Ridge, CO | 5077 | 0 | 0 | 0 | 0 |
| Marcus Zervos, M.D. | Royal Oak, MI | 5078 | 137 | 6 | 5 | 1 |
| Geregory Fino, M.D. | Pittsburgh, PA | 5079 | 0 | 1 | 1 | - |
| James Patterson. M.D. | Portland, OR | 5084 | 3 | 1 | - | 1 |
| Curtis Mello, M.D. | Swansea, MA | 5085 | 0 | 0 | 0 | 0 |
| Glenn Giessel, M.D. | Richmond,VA | 5090 | 3 | 3 | - | 3 |
| Mauricio Reinoso, M.D. | Houston, TX | 5091 | 0 | 0 | 0 | 0 |
| Chandra Khurana, M.D. | Chicago,IL | 5093 | 6 | 3 | 3 | - |
| Guy Amsden, Pharm.D. | Cooperstown, NY | 5094 | 49 | 4 | 4 | - |
| Sanford Chodosh, M.D. | Boston, MA | 5097 | 0 | 4 | 1 | 3 |
| James Taylor, M.D. | Tacoma, Washington | 5098 | 12 | 6 | 2 | 1 |
| Joseph Follett, M.D. | Cheyenne, WY | 5099 | 0 | 0 | 0 | 0 |
| David Busch, M.D. | San Francisco, CA | 5103 | 0 | 0 | 0 | 0 |
| Steven Sahn, M.D. | Charleston, SC | 5104 | 4 | 2 | 1 | 1 |
| Donald England, M.D. | Eugene, OR | 5105 | 0 | 0 | 0 | 0 |
| Randall Smart, M.D. | Travis AFB, CA | 5106 | 2 | 2 | 0 | 0 |
| James Sullivan, M.D. | Birmingham, AL | 5107 | 0 | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Joseph Plouffe, Jr.,M.D. | Columbus, OH | 5110 | 0 | 0 | 0 | 0 |
| Lourdes Irizarry, M.D. | Albuquerque, NM | 5112 | 5 | 0 | 0 | 0 |
| Robert O'Connor, M.D. | Newark, DE | 5122 | 130 | 8 | 8 | 0 |
| Lawrence Repsher, M.D. | Wheat Ridge, CO | 5123 | 9 | 7 | 3 | 4 |
| Jeffry Jacqmein, M.D. | Jacksonville,FL | 5134 | 5 | 4 | 3 | 1 |
| John Wadleigh, D.O. | Tucson, AZ | 5147 | 0 | 0 | - | - |
| Rodney Wishnow, M.D. | Long Beach, CA | 5148 | 0 | 0 | - | - |
| James Kaplan, M.D. | Overland Park, KS | 5160 | 7 | 1 | 1 | 0 |
| Anthony Cammack, M.D. | Fort Walton Beach, FL | 5161 | 3 | 1 | 1 | 0 |
| Lawrence Earl, M.D. | Parsippany, NJ | 5170 | 0 | 0 | - | - |
| John Whitney, M.D. | Albany NY | 5176 | 0 | 0 | - | - |
| Charles Lieber, M.D. | Tamarac, FL | 5179 | 3 | 3 | - | - |
| William Smith, M.D. | New Orleans, LA | 5182 | 0 | 0 | - | - |
| John Milas, M.D. | Greer, SC | 5190 | 0 | 0 | - | - |
| Boyde Harrison, M.D. | Haleyville, AL | 5191 | 0 | 0 | - | - |
| Ian Baird, M.D. | Columbus, OH | 5192 | 31 | 6 | 5 | 1 |
| Robert Bettis, M.D. | Edmonds,WA | 5194 | 6 | 6 | 4 | 2 |
| Ernie Riffer, M.D. | Phoenix, AZ | 5195 | 0 | 1 | 1 | 0 |
| Mildred Farmer, M.D. | St. Petersburg,FL | 5198 | 0 | 0 | - | - |
| Timothy Bruya, M.D. | Spokane WA | 5200 | 8 | 6 | 6 | 0 |
| Daniel Shu, M.D. | Coquitlam, British Columbia CANADA | 5183 | 0 | 4 | 3 | 1 |
| Stephen Coyle, M.D. | Winnepeg, Manitoba CANADA | 5185 | 1 | 1 | 1 | 0 |
| Andrew Jacovides, M.D. | Midrand, SOUTH AFRICA | 4001 | 0 | 0 | - | - |
| Eric Bateman, M.D. | Cape Town, SOUTH AFRICA | 4002 | 0 | 0 | - | - |
| Pierre Jordaan, M.D. | Bloemfontein, Free State SOUTH AFRICA | 4003 | 14 | 4 | - | 4 |
| Ricardo Gene, M.D. | Beuenos Aires, ARGENTINA | 5082 | 13 | 10 | 3 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Eduardo Abbate, M.D. | Buenos Aires, ARGENTINA | 5083 | 20 | 17 | 10 | 8 |
| Maria Cristina De Salvo, M.D. | Buenos Aires, ARGENTINA | 5088 | 39 | 32 | 20 | 10 |
| Eduardo Schiavi, M.D. | Buenos Aires ARGENTINA | 5208 | 9 | 9 | 3 | 6 |
| Ricardo Lamberghini, M.D. | Cordoba ARGENTINA | 5209 | 3 | 2 | 2 | 0 |
| Juan Carlos Figueroa Casas | Santa Fe ARGENTINA | 5158 | 6 | 6 | 2 | 4 |
| Jose Roberto Jardim, M.D. | San Paulo, BRAZIL | 5124 | 28 | 18 | 14 | 4 |
| Jorge Hetzel, M.D. | Porto Alegre BRAZIL | 5125 | 0 | 0 | - | - |
| Jairo Sponholz Araujo | Curitiba BRAZIL | 5126 | 7 | 6 | 3 | 3 |
| Emilio Pizzichini, M.D. | Florianopolis, BRAZIL | 5127 | 0 | 0 | - | - |
| Elie Fiss, M.D. | Santo Andre BRAZIL | 5128 | 5 | 3 | - | - |
| Mara Rubia Andre-Alves, M.D. | Porto Alegre BRAZIL | 5129 | 38 | 21 | 7 | 14 |
| Alberto Lainez-Ventosilla, M.D. | San Jose COSTA RICA | 5168 | 105 | 35 | - | 28 |
| Tamara Soler, M.D. | Santiago CHILE | 5204 | 5 | 4 | - | - |
| Fabian Galleguillos, M.D. | Santiago CHILE | 5205 | 17 | 8 | 3 | 5 |
| Maria Teresa Parada, M.D. | Santiago CHILE | 5206 | 6 | 4 | 4 | 0 |
| Andrea Lagos, M.D. | Santiago CHILE | | 8 | 3 | 3 | 0 |
| Joy Philip, M.D. | Kerala INDIA | 5211 | 42 | 8 | 6 | 2 |
| Thekkinkattil Mohan-Kumar, M.D. | Tamil Nadu INDIA | 5212 | 11 | 10 | 10 | 0 |
| Ashok Anant Mahashur, M.D. | Mumbai, Maharashtra INDIA | 5215 | 3 | 2 | 2 | 2 |
| George Albert D'Souza, M.D. | Karnataka INDIA | 5216 | 11 | 5 | 2 | 3 |
| Shyambahari Agarwal, M.D. | Asarwa Ahmedabad INDIA | 5217 | 0 | 0 | - | - |
| Kamal Jayantilal Pathak, M.D. | Baroda INDIA | 5218 | 0 | 8 | 8 | 0 |

*MO COMMENT: The above list of investigators are acceptable and not among FDA's investigator's debardment list. The Principal Investigator at the Costa Rica site has the highest enrollment in the study.*





## APPENDIX III

## Narratives of Subjects who Discontinued Due to Adverse Events from the Pivotal study (Study A0661013)

***MO COMMENT: The following narratives have been excerpted from the applicant's final study report. In general, discontinuations due to AE in the azithromycin group were related to treatment failure, rather than adverse effects caused by the drug.***

### A. Azithromycin Treatment Group

**Subject ID # 1013-7**

This 62-year-old White male subject weighing 115.7 kg received a single 500 mg dose of azithromycin for 3 days for treatment of acute exacerbation of chronic obstructive bronchitis. He had a past history of seasonal allergy and a present history of chronic bronchitis since 1995, non-insulin dependent diabetes mellitus (NIDDM), hiatal hernia and gastroesophageal reflux disease (GERD), and hypertension. The subject was taking glipizide, cimetidine, and lisinopril for treatment of these conditions at study entry and continued to take them during the study. He experienced chest congestion and nasal inflammation of moderate severity from Study Days 3-16, leading to discontinuation from the study on Day 11 during the post-therapy follow-up period. The investigator considered the chest congestion related to disease under study and the nasal inflammation related to illness/seasonal allergy and not related to study drug. The investigator treated the adverse events and they resolved. In addition to those noted above, concomitant medications taken during the study were guaifenesin/phenylpropanolamine, sulfamethoxazole/trimethoprim, and furosemide. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject ID # 1013-8**

This 57-year-old White female subject weighing 77.1 kg received a single 500 mg dose of azithromycin for 3 days for treatment of acute exacerbation of chronic obstructive bronchitis. She had a past history of Wolfe-Parkinson-White syndrome and hysterectomy, and a present history of chronic bronchitis since 1995. The subject ended a course of amoxicillin treatment 19 days prior to study entry. She experienced chest congestion and chills of moderate severity from Study Days 17-21 (stop day for chest congestion was imputed from incomplete dates), leading to discontinuation from the study on Day 21 during the post-therapy follow-up period. The investigator considered these adverse events related to disease under study and unrelated to study drug. The investigator treated the adverse events and they resolved.
Concomitant medications taken during the study were levofloxacin and phenylpropanolamine/chlorpheniramine/aspirin/bicarbonate/citiric acid (Alka-Selzer® Plus

Cold). The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject ID# 1013-74**

This 67-year-old White female subject weighing 70.3 kg received azithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Azithromycin (500 mg daily) was administered orally from 03 February 2000 until 05 February 2000 (a total of 3 days). A Gram stain of a sputum sample obtained at baseline showed many white blood cells and moderate gram-positive cocci, but no pathogen was isolated from the culture. On 13 February 2000, the subject developed an ache on the right side of her chest. A chest x-ray performed on 15 February 2000 showed a right lower lobe infiltrate. A Gram stain of a sputum sample taken the same day showed gram-negative rods and many white blood cells. The culture grew *Pseudomonas aeruginosa.* The subject was hospitalized for pneumonia and treated with ceftazidime, tobramycin and levofloxacin. A chest x-ray performed on 24 February 2000 showed no infiltrate. The subject was discharged from the hospital on 27 February 2000. The subject completed treatment, but discontinued the study.

The subject had a past history of cataract surgery and hysterectomy, and a present history of chronic obstructive pulmonary disease, asthma, emphysema, congenital anomaly of the heart, right leg swelling, chronic sinusitis, sinus congestion, dyspepsia, headaches and difficulty sleeping. She was taking prednisolone acetate drops, prednisone, albuterol, triamcinolone, aspirin, multi-vitamins, temazepam, ipratropium and conjugated estrogens at the start of the study. Medications taken to treat the event are provided in the preceding paragraph.

In the opinion of the investigator, this event was due to other illness (suspected pseudomonal infection). Review by the applicant concluded the event was not related to azithromycin. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC.**

**Subject 1013-352**

This 63-year-old Hispanic male subject weighing 48.0 kg received a single 500 mg dose of azithromycin for 3 days for treatment of acute exacerbation of chronic obstructive bronchitis. He had a present history of chronic bronchitis since 1986, acute exacerbation of chronic bronchitis, vitiligo, osteoarthrosis of the left knee, hypertension, and varices. The subject was taking albuterol and enalapril at study entry and continued to take them during the study. He developed bronchopneumonia of mild severity from Study Days 13-20, leading to discontinuation from the study on Day 20 during the post-therapy follow-up period. The investigator considered this adverse event related to illness/infection and unrelated to study drug.

**B. Clarithromycin Treatment Group**

**Subject ID #1013-17**

This 64-year-old White female subject weighing 74.4 kg, was in the clarithromycin treatment group (500 mg twice daily), and received study drug for 2 days for the treatment of acute exacerbation of chronic bronchitis. Her medical history included adenoidectomy, breast lump removal, tubal ligation and tonsillectomy in the past, and allergic rhinitis, bronchitis, COPD, sinusitis, acne rosacea, chronic bronchitis, and hypertension present at study entry. The subject was taking albuterol, montelukast, brimonidine, metronidazole, benazepril/amlodipine, and fluticasone at study entry, and continued to take them during the study. She experienced severe vertigo from Day 3 to Day 6, and severe abdominal pain, moderate diarrhea, and moderate flatulence on Day 2 to Day 5, leading to discontinuation from treatment on Day 2 and discontinuation from the study on Day 6. No treatment other than discontinuation of study drug was noted for these adverse events, and all events resolved. All adverse events were considered treatment related by the investigator. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject ID #1013-22**

This 75-year-old White male subject weighing 102.1 kg, was in the clarithromycin treatment group (500 mg twice daily), and received study drug for 5 days for the treatment of acute exacerbation of chronic bronchitis. His medical history included aortic abdominal aneurysm, appendicitis, and cancer of the bladder, colon, lung, and prostate in the past, and gastroesophageal reflux disease, hypercholesterolemia and chronic bronchitis present at study entry. The subject was taking albuterol, salmeterol, ipratropium, triamcinolone, cervistatin, omeprazole, ascorbic acid, and alpha tocopherol at study entry, and continued to take them during the study. He experienced severe abdominal pain from Day 2 to Day 8 and severe dizziness from Day 2 to Day 17, leading to discontinuation from treatment on Day 5 and discontinuation from the study on Day 8. The investigator treated the events and they resolved. In addition to those noted above, a concomitant medication (meclizine) was added on Day 8. Both adverse events were considered to be treatment related by the investigator. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject ID #1013-56**

This 66-year-old White female subject weighing 61.2 kg, was in the clarithromycin treatment group (500 mg twice daily) and received study drug for 2 days for the treatment of acute exacerbation of chronic bronchitis. Her medical history included neck lymph node removal in the past, and spasmodic torticollis, menopause, and chronic bronchitis present at study entry. The

subject was taking trihexyphenidyl and cyclobenzaprine at study entry, and continued to take them during the study. She experienced mild hypertonia (increased neck spasms) from Day 2 to Day 3 and mild insomnia on Day 3, leading to discontinuation from treatment on Day 2 and discontinuation from study on Day 7. The investigator treated the events and they resolved. In addition to those noted above, a concomitant medication (clonazepam) was added on Day 3. Neither event was considered treatment related; the investigator attributed both to other illness (spasmodic torticollis). The subject was included in the MITT analysis of clinical response, with a final outcome of **improvement at end of treatment**.

**Subject ID #1013-82**

This 70-year-old White male subject weighing 84.1 kg received clarithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Clarithromycin was administered orally, bid, at a total daily dose of 1000 mg from 07 February 2000 until 17 February 2000, a total of 11 days. On 21 February 2000, during a follow-up examination, the subject was found to have severe dyspnea and was hospitalized for a left lower lobe infiltrate. On 02 March 2000, the subject was discharged to a rehabilitation unit and the event was considered resolved. The subject completed treatment, but discontinued the study.

The subject had a past history of coronary artery disease and a present history of chronic obstructive pulmonary disease [chronic bronchitis and chronic asthmatic bronchitis), hearing loss, allergies, insomnia, glaucoma, benign prostatic hypertrophy and depression. The subject was taking albuterol, aspirin, ipratropium, cetirizine, brimonidine, guaiphenesin, insulin, multivitamin/mineral mixture, fluticasone and theophylline at study entry and continued to take them during the study. Acetaminophen, tobramycin, cefotaxime, hydrocortisone, prednisone, vancomycin, piperacillin, mirtazapine and aminophylline were taken during the study.

In the opinion of the investigator, this event was due to (other) unknown cause, and not the study drug. Review by the applicant concluded the event was not related to clarithromycin. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject 1013-269**

This 33-year-old White female subject weighing 109.8 kg, was in the clarithromycin treatment group (500 mg twice daily) and received study drug for 9 days for the treatment of acute exacerbation of chronic bronchitis. Her medical history included cholecystectomy in the past, and intermittent sinus headaches and migraine headaches, irritable bowel syndrome, and intermittent and recurrent bronchitis present at study entry. The subject was taking celecoxib and psyllium at study entry, and continued to take them during the study. She experienced moderate diarrhea from Day 2 to Day 9, leading to discontinuation from treatment on Day 9. The subject continued in the study until Day 22. Discontinuation from the study on Day 22 was attributed to

The investigator treated the bronchopneumonia and it resolved. In addition to those noted above, concomitant medications taken during the study were ciprofloxacin, acetaminophen, diclofenac, hydrocortisone, and dextromethorphan. A chest x-ray was also obtained on Day 12. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject ID# 1013-636**

This 51-year-old White female subject weighing 55.0 kg received a single 500 mg dose of azithromycin for 3 days for treatment of acute exacerbation of chronic obstructive bronchitis. She had a past history of hysterectomy, and a present history of chronic bronchitis for >2 consecutive years. The subject was taking fenoterol and aspirin at study entry and stopped taking them on Study Day 1. Her acute illness worsened from Study Days 15-21 (start day was imputed from incomplete dates) and was considered severe by the investigator, leading to discontinuation from the study on Day 14 during the post-therapy follow-up period. The investigator considered this adverse event related to disease under study and unrelated to study drug. The investigator treated the worsening bronchitis exacerbation and it resolved. The subject also experienced treatment-related nausea during the study, but this did not contribute to discontinuation. In addition to those noted above, concomitant medications taken during the study were moxifloxacin and ranitidine. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject ID# 1013-714**

This 57-year-old Black female subject weighing 39.5 kg received a single 500 mg dose of azithromycin for 3 days for treatment of acute exacerbation of chronic obstructive bronchitis. She had a past history of esophageal stenosis, and a present history of chronic bronchitis for >5 years. The subject underwent spirometry testing the day before starting study treatment. She developed a worsening of her chronic bronchitis of moderate severity from Study Days 13-21, leading to discontinuation from the study on Day 13 during the post-therapy follow-up period. The investigator considered this adverse event related to disease under study and unrelated to study drug. The investigator treated the worsening bronchitis and it resolved. The only concomitant medication taken during the study was moxifloxacin. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

the same reason as discontinuation from treatment "adverse event (diarrhea)", although diarrhea was recorded as ending on Day 9. No treatment other than discontinuation of study drug was noted for the adverse event, and the event resolved. In addition to those noted above, concomitant medication added during the study were: albuterol (Days 1 to 6) and acetaminophen/codeine and diphenhydramine (Days 3 to 6). The adverse event resulting in discontinuation was considered to be treatment related by the investigator. The subject also experienced moderate halitosis and moderate taste perversion on Days 2 to 9, which the investigator considered related to study drug, but these events did not result in discontinuation. The subject was included in the MITT analysis of clinical response, with a final outcome of **cure at TOC.**

**Subject 1013-283**

This 41-year-old White female subject weighing 78 kg, was in the clarithromycin treatment group (500 mg twice daily), and received study drug for 2 days for the treatment of acute exacerbation of chronic bronchitis. Her medical history included hysterectomy and left and right hip surgeries in the past, and allergic rhinitis, asthma, anxiety, carpal tunnel syndrome, depression, hiatal hernia, fibrocystic breast, gestroesophageal reflux, lupus, muscular atrophy, costochondritis, spastic bladder, vocal cord polyps, chronic bronchitis, and gastritis present at study entry. The subject was taking salmeterol, diclofenac, hydroxychloroquine, prednisone, conjugated estrogens, fluticasone, amitryptyline, and theophylline at study entry, and continued to take them during the study. She experienced moderate chest pain from days 2 to 8, moderate headache from Days 2 to 3, moderate diarrhea, nausea, and dizziness from Days 2 to 7, and moderate vomiting on Day 2, leading to discontinuation from treatment on Day 2 and discontinuation from the study on Day 8. No treatment other than discontinuation of study drug was noted for these adverse events, and all events resolved. In addition to those noted above, concomitant medications used during the study were: albuterol, acetoaminophen/hydrocodone, ketorolac, ipratropium, aluminum salts/magnesium salts, and cascara (for Day 2 only), and cephalexin (Day 2, ongoing). All events were considered to be treatment related by the investigator. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

**Subject 1013-350**

This 44-year-old Hispanic female subject weighing 72 kg, was in the clarithromycin treatment group (500 mg twice daily) and received study drug for 2 days for the treatment of acute exacerbation of chronic bronchitis. Her medical history included hyper bronchial reactivity, insomnia, chronic bronchitis, and hypertension, all present at study entry. The subject was taking albuterol, enalapril, and amitryptyline at study entry, and continued to take them during the study. She experienced moderate asthenia, mild headache, moderate hypertonia (hands cramp), moderate tremor (hands tremor), and moderate sweating on Days 2 to 4, and mild

diarrhea, moderate glossitis, moderate taste perversion, and severe nausea on Days 2 to 7, leading to discontinuation from treatment on Day 2 and discontinuation from the study on Day 8. No treatment other than discontinuation of study drug was noted for these adverse events, and all events resolved. In addition to those noted above, concomitant medications (acetaminophen and diphenhydramine) were added on Day 1. All adverse events were considered to be treatment related by the investigator. The subject was included in the MITT analysis of clinical response, with a final outcome of **cure at TOC.**



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# APPENDIX IV

## Narratives of Subjects with Serious Adverse Events from the Pivotal study (Study A0660113)

***MO COMMENT: The following narratives, including the bolded comments have been excerpted from the applicant's final study report. There were no deaths in the azithromycin group in the pivotal trial. Serious AEs in the azithromycin-treated patients did not appear related to direct adverse effects of the drug.***

### A. Azithromycin Treatment Group

**Subject: 1013-328**

This 74-year-old White male subject weighing 61.0 kg received azithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Azithromycin (500 mg daily) was administered orally from 06 July 2000 until 08 July 2000, a total of 3 days. On 21 July 2000, the subject was diagnosed with congestive heart failure and was hospitalized. Severe mitral valve disease was diagnosed. The subject was treated with a nitroglycerin patch and furosemide. The mitral valve disease was not considered a serious adverse event since it was a pre-existing condition (previous undiagnosed bacterial endocarditis). On 11 August 2000, while hospitalized, an erosive gastroduodenal ulcer was detected by endoscopy, which explained the anemia present at baseline (7.4 g/dl hemoglobin and 23.6% hematocrit on 06 July 2000). The ulcer was treated with omeprazole. The subject was discharged from the hospital on 14 August 2000 and the event was considered resolved.

The subject had a past history of probable bacterial endocarditis with mitral valve involvement, gastric ulcer, myocardial infarction and community acquired pneumonia, and a present history of chronic anemia, arterial hypertension and chronic obstructive pulmonary disease. The subject was taking albuterol, enalapril, ipratropium, furosemide and ranitidine at study entry and continued to take them during the study. Additionally, lorazepam, nitroglycerin, omeprazole, digoxin, ceftriaxone, hydrocortisone methylprednisolone, iron, potassium chloride (1 day), heparin and hydrochlorthiazide were taken during the study. The subject also received a blood transfusion on Day 22.

**In the opinion of the investigator, this event was due to other illness (hypertension and anemia, previous gastric ulcer). Review by the applicant concluded the event was not related to azithromycin. The subject was included in the MITT analysis of clinical response, with a final outcome of failure at TOC.**