# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-144**

# STATISTICAL REVIEW(S)

# Statistical Review and Evaluation

## A Large Phase III Clinical Safety Study of Telithromycin Compared to Amoxicillin-clavulanic acid in a Usual Care Setting

| | |
|---|---|
| **NDA number:** | 21-144 |
| **Indications:** | (1) Community-acquired pneumonia |
| | (2) Acute exacerbation of chronic bronchitis |
| | (3) acute bacterial sinusitis |
| **Generic name:** | telithromycin |
| **Route of administration:** | Oral |
| **Formulation:** | 400 mg tablet |
| **Trade name:** | KETEK |
| **Submission date:** | July 24, 2002 |
| **Date review completed:** | January 24, 2003 |
| **Submission date:** | July 24, 2002 |
| **PDUFA date:** | January 24, 2003 |
| **Statistical Reviewer:** | George Rochester, Ph.D., HFD-725 |
| **Division of Biometrics III, Director:** | Mohammed Huque, Ph.D., HFD-725 |
| **Medical Team Leader:** | David Ross, M.D., Ph.D., HFD-520 |
| **Clinical Reviewers:** | Tom Smith, M.D., HFD-520 |
| | Janice Pohlman, M.D., HFD-520 |
| | Charles Cooper, M.D., HFD-520 |
| **Documents reviewed:** | Electronic data sets for Study 3014 |
| | Case report forms |
| | Clinical study reports |
| **Distribution list:** | Chuck Anello, Sc.D., HFD-700 |
| | Janice Soreth, M.D., HFD-520 |
| | Judit Milstein, B.S., HFD-520 |

**Statistical key words**: Statistical review, safety review, hepatic effects, visual effects

# Contents

# List of Tables

# List of Figures

# 1 Executive summary

## 1.1 Conclusions

This was a large simple safety study conducted to further characterize the safety of telithromycin in the treatment of subjects with respiratory tract infections. This study was requested by the agency in an approvable letter at the end of the first review cycle. The study consisted of approximately 12,000 subjects per treatment arm (telithromycin [TEL] versus amoxicillin-clavulanic acid [AMC]). There were 4 primary safety endpoints: visual, hepatic, cardiac, or vasculitic events, otherwise referred to as adverse events of special interest (AESIs). A separate clinical expert committee (CEC) was established for each endpoint was establishe to make final adjudication on each primary endpoint. Adjudication was to be carried out blinded to treatment assignment. Adjudication was scheduled at regular periods but were largely done at the end of the trial.

Positively adjudicated visual adverse events (AEs) occurred in 0.61% of telithromycin-treated subjects and 0.04% of AMC-treated subjects. Telithromycin-treated subjects had 14.5 times the risk of a visual AE (95% confidence interval [C.I.] of [6.2, 41.0] ) compared to AMC-treated subjects. Visual AEs were reported most commonly as "blurred vision." Eighty-two (82%) percent of telithromycin-treated subjects with visual AEs were women. Among telithromycin-treated subjects the incidence of visual AEs was similar between AECB subjects treated for $\leq$7 days and those treated for >7 days.

There was insufficient data to describe the time of onset or time to resolution due to missing case information. The onset of visual disturbances were reported to occur from a few hours to days from start of therapy. Temporal patterns of occurrence were unpredictable. Subjects experienced blurred vision after a single dose, multiple doses, or any time during or after completion of treatment. The median time to resolution was approximately 3 days, with a range of 1 to 18 days. Telithromycin-treated subjects with visual AEs reported being unable to drive, unable to perform usual work activities, and experienced difficulty reading. Approximately one third of the subjects with a visual AE in telithromycin-treated subjects discontinued treatment due to this event. All subjects appeared to resolve after the cessation of treatment. No long-term follow up data are available.

The incidence of CEC confirmed hepatic endpoint was low and similar between treatment groups (TEL: 3; AMC: 2). The relative risk of significant hepatic injury in telithromycin-treated subjects was 1.47 times (95% C.I. [0.24, 14.5]) that of AMC-treated subjects. Telithromycin-treated subjects had a slightly higher frequency of elevations in hepatic analytes, particularly alanine aminotransferase (ALT) > 8 x ULN (upper limit of normal range) compared to AMC-treated subjects. Elevations in ALT > 8 x ULN tended to persist through the late-posttherapy period (day 30 - 35). There were no reports of liver failure or death of a hepatic etiology.

The frequency and profile of treatment emergent adverse events (TEAEs) was similar between telithromycin (23.1%) and AMC (22.9%). The majority of all TEAEs were mild to moderate and discontinuation of study medication due to a TEAE was uncommon for both treatment groups. TEAEs of the gastrointestinal disorders system organ class were the most common events reported in both treatment groups. The frequency of serious TEAEs was similar between treatment groups.

There were no subjects positively adjudicated with vasculitic or cardiac endpoints.

## 1.2 Recommendations

**Visual effects**: Patients and prescribers should be warned prominently, in labeling (preferably in the section: "*WARNINGS*" ), of the potential visual effects of telithromycin. This drug is intended for use in the ambulatory care setting. The time of onset is unpredictable and the pathophysiology associated with visual disturbances is not known at this time. Visual disturbances impair one's ability to perform activities of daily living. They impair one's ability to drive, or operate other heavy machinery which could lead to injury or incapacity. Visual adverse events occurred most frequently in subjects treated for the less serious indications, primarily acute bacterial sinusitis. Although this event occurs in $\leq$1% of subjects in this study, anti-infectives for respiratory tract infections are prescribed widely, therefore, it is strongly recommended that this adverse event be described fully in labeling.

**Hepatic effects**: The effects on the liver should be described in labeling. Subjects who experience clinically overt signs of hepatic injury may require close follow-up. Although there were no cases of liver failure or death of a liver related etiology, telithromycin demonstrates an effect on the liver which lasts at least through 30 days from start of treatment.

## 1.3 Overview of clinical study

After the first review cycle the agency issued an approvable letter which requested the applicant to provide additional safety data to further characterize the safety profile of telithromycin in patients with respiratory tract infections. Study 3014, was a randomized, open-label, comparative, multi-center, clinical safety trial conducted in the United States, in a usual care setting. In previous studies, telithromycin-treated subjects treated for CAP appeared to exhibit increased risk of AEs. To investigate whether duration of treatment could account for the increased frequency of AEs among subjects treated for CAP, at least 40% of subjects with an indication of CAP or AECB was a target of the study.

## 1.4 Statistical issues and findings

In previous phase III studies of 3,265 telithromycin-treated subjects a signal of potential clinically significant hepatic injury emerged. Study was sized to detect AEs with an incidence of $\geq$1/4,000. This study was not sized to detect all four AESIs because to do so could prohibitively increase the size of the study. The agency agreed that 12,000 subjects per treatment group was a reasonable effort to provide additional pre-marketing safety data. To improve the chance of detecting potential safety signals the study enrolled subjects with co-morbid conditions, such as, hepatic impairment, renal impairment, cardiac disorders, subjects with concomitant drug use. Subjects identified as having a potential AE or a serious AE were to be followed through resolution of the event. Additional documentation via a questionnaire which elicited history and physical examination findings was to be provided for all subjects with a potential AESI.

During study design the agency recommended that the applicant develop management algorithms for each AESI. These algorithms could provide consistency in documentation and minimize the potential for missing critical information necessary for case ascertainment. The applicant agreed to submit these algorithms for agency review. These algorithms which were not submitted to the agency or utilized during the study. Review of source data showed wide variability in follow-up. The CECs carried out most of the adjudications at the end of the study. This did not offer opportunity to request time sensitive information which could have decreased the chance of missing critical information.

The safety-evaluable population was defined as all subjects who took study medication and had investigator contact at any time after start of study medication. The analysis of the incidence rates for each

of the clinical safety endpoints involved using the number of safety-evaluable subjects with known AE status on Day 28 or later as the denominator. Positively adjudicated visual endpoints occurred in 0.61% of telithromycin-treated subjects and 0.04% AMC-treated subjects. The relative risk (RR) was 14.5 ( 95% C.I. [6.2, 41.0] ). The incidence of positively adjudicated significant hepatic injury occurred in of telithromycin-treated subjects was 0.025% and 0.017% in AMC-treated subjects. The RR was 1.47 (95% C.I.. [0.24, 14.85] ). There were no subjects with cardiac, or vasculitic endpoints.

The incidence of CEC confirmed hepatic safety endpoints was low and similar between treatment groups (telithromycin 3 subjects: AMC 2 subjects). The relative risk of significant hepatic injury among telithromycin-treated subjects was 1.47 times that of AMC-treated subjects (95% C.I. [0.24, 14.5]). Telithromycin-treated subjects had a slightly higher likelihood of experiencing elevations in hepatic analytes, particularly ALT > 8 x ULN compared to AMC. These levels of elevations persisted through the late-posttherapy period, day 30 to day 35. There were no liver failures or deaths of a hepatic etiology.

# 2 Introduction

## 2.1 Indications

The applicant requested claims for the use of telithromycin for the treatment of infections in the specific conditions listed below for patients 18 years old and above:

1. *Community-acquired pneumonia*
2. *Acute bacterial exacerbation of chronic bronchitis*
3. *Acute bacterial sinusitis*

## 2.2 Background

The objective of this study was to characterize the safety and effectiveness of telithromycin when used for the treatment of respiratory tract infection for 5 to 10 days. During a previous review cycle it was observed that telithromycin-treated subjects treated for CAP appeared to exhibit increased risk of AEs. To further understand whether longer duration of treatment, 7-10 days versus 5 days, might account for increased frequency of AEs group, at least 40% of enrollment in this study was targeted at subjects treated for CAP or AECB. Subjects with CAP comprised 10% of the study population and 30% of the subjects had a diagnosis of AECB.

# 3 Statistical evaluation

## 3.1 Study design

Visits took place on Day 1 at the start of treatment (Visit 1, pretherapy/entry), between Days 17and 22 (Visit 2, post-therapy), and between Days 30 and 35 (Visit 3, late post-therapy), as shown in Figure 1. Safety was assessed at Visits 2 and 3. Visit 3 could be a telephone or clinic visit. Subjects who experienced a potential AESI were for adjudication. All subjects who met a pre-specified laboratory threshold of changes in hepatic analytes from baseline were categorized as subjects with potential hepatic AESI and were to be followed to resolution or return to baseline status. The subset of patients with hepatic related AESIs were followed for up to 6 months.

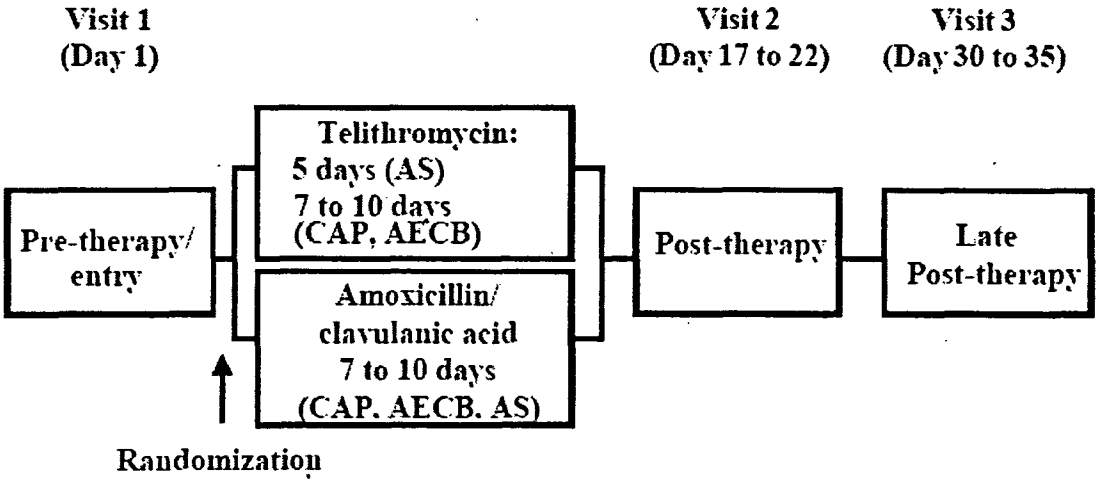


Figure 1: Study design (Source: Clinical Suty Report, p. 77)

## 3.2 Subject disposition

The data reviewed for this report consisted of data tables in the electronic archive, case report forms, and clinical study reports. All tables in this report were independently verified and sources are indicated where applicable. A total of 24,140 subjects were randomized and treated in Study 3014 as shown in Table 1. Three subjects (TEL: 2; amoxicillin-clavulanic acid: 1) had no post-baseline assessments and were not safety-evaluable. Therefore, 24,137 subjects (TEL: 99.2%; AMC: 99.5%) constitute the safety-evaluable population. Nearly all safety-evaluable subjects (TEL: 99.5%; AMC: 99.7%) had available adverse event information at least at the 28 day follow-up time point. At least partial follow-up information was available for > 99% of the safety-evaluable population. The population with available adverse event information at day 28 or later is used for computing incidence rates.

Table 1: Subject accounting

| | Number of subjects (%) | | |
|---|---|---|---|
| **Population** | **TEL** | **AMC** | **Total** |
| Total number of subjects treated | 12,161 (100.0) | 11,979 (100.0) | 24,140 (100.0) |
| Total safety-evaluable subjects | 12,159 (> 99.9) | 11,978 (> 99.9) | 24,137 (> 99.9) |
| Total with follow-up of > 28 days | | | |
| Vital status (dead or alive) | 12,138 (99.8) | 11,941 (99.7) | 24,079 (99.7) |
| Adverse event information > 28 days | 12,096 (99.5) | 11,883 (99.1) | 23,979 (99.3) |

TEL=telithromycin, AMC=amoxicillin-clavulanic acid

Exposure by indication and treatment duration is shown in Table 2.

## 3.3 Demographic and baseline characteristics

Age, race, and sex characteristics of the study population are shown in Table 3. Nearly half of all subjects were ≥ 50 years of age (TEL: 46.6%; AMC: 46.2%). Almost 20% of the population (TEL: 18.7%; AMC: 18.4%) were ≥ 65 years of age. Over 7% of study subjects (TEL: 7.3%; AMC: 7.3%) were over 75 years. Thirteen subjects (TEL: 7; AMC: 6) did not have their ages recorded. Approximately 60% of the study

Table 2: Subject exposure

| | Telithromycin | | | Amoxicillin-clavulanic acid | | |
|---|---|---|---|---|---|---|
| Indication | Treatment Regimen (days) | Number of Subjects (%) | Duration ± SD (days) | Treatment Regimen (days) | Number of Subjects (%) | Duration ± SD (days) |
| Total evaluable subjects | | $N = 12159$ | | | $N = 11978$ | |
| CAP | 7 to 10 | 1092 (9) | 10 ± 2 | 7 to 10 | 1053 (9) | 10 ± 2 |
| AECB | 7 to 10 | 3786 (31) | 10 ± 2 | 7 to 10 | 3668 (31) | 10 ± 2 |
| ABS | 5 | 7281 (60) | 6 ± 2 | 7 to 10 | 7257 (60) | 10 ± 2 |

CAP = Community-acquired pneumonia, ABS = Acute bacterial sinusitis
AECB = Acute exacerbation of chronic bronchitis

population were females. The sex ratio was consistent between treatment groups and within indications. Neither body weight nor vital signs information were collected. The treatment groups were balanced with respect to age, race, and sex.

Table 3: Demographic characteristics

| | Number of subjects (%) | | | |
|---|---|---|---|---|
| Demographic characteristics | TEL | | AMC | |
| Total safety-evaluable population | $N = 12159$ | | $N = 11978$ | |
| Age (years) | | | | |
| Subjects 16-50 | 6481 | (53.3) | 6436 | (53.7) |
| Subjects ≥ 50 | 5671 | (46.6) | 5536 | (46.2) |
| Subjects 50-64 | 3398 | (27.9) | 3333 | (27.8) |
| Subjects 65-74 | 1381 | (11.4) | 1330 | (11.1) |
| Subjects 75-84 | 766 | (6.3) | 747 | (6.2) |
| Subjects ≥ 85 | 126 | (1.0) | 126 | (1.1) |
| No. of subjects with information | 12152 | | 11972 | |
| Mean ± SD | 49.3 ± (15.7) | | 49.1 ± (15.9) | |
| Median (Range) | 48.0 (18 – 99) | | 48.0 (16 – 100) | |
| Sex | | | | |
| Male | 4755 | (39.1) | 4786 | (40.0) |
| Female | 7404 | (60.9) | 7192 | (60.0) |
| Race | | | | |
| Caucasian | 10443 | (88.9) | 10270 | (85.7) |
| Black | 1028 | (8.5) | 970 | (8.1) |
| Asian/Oriental | 245 | (2.0) | 248 | (2.1) |
| Other | 441 | (3.6) | 489 | (4.1) |

TEL=telithromycin, AMC=amoxicillin-clavulanic acid

## 3.4 Concomitant illnesses and concomitant drug use

Conducting a large safety trial, in a usual care setting, with few restrictions on inclusion/exclusion criteria should enhance enrollment of subjects with a variety of co-morbid illnesses and concomitant drug use. The frequency of concomitant illnesses are shown in Table 4. Approximately one third of study subjects (TEL: 32.8%; AMC: 32.9%) had an underlying cardiovascular disease(e.g., coronary artery disease, angina/myocardial infarction, or congestive heart failure). About 25% of the population had a history of

chronic obstructive pulmonary disease or asthma. Less than 1% of subjects had a history of hepatic impairment (TEL: 0.8%; AMC: 1.0%). Subjects with hepatic compromise included subjects with known liver cirrhosis, and hepatitis B or hepatitis C infections. The AMC group included slightly more subjects with hepatitis C infection (TEL: 38; AMC: 56). A total of 40 subjects (median age 74 years) had a known history of severe renal impairment, i.e., for whom creatine clearance of <30 mL/min was recorded (TEL: 23; AMC: 17), men out numbered women (57.5% to 42.5%). The distribution of concomitant illnesses was similar between treatment arms.

Table 4: Concomitant illnesses

| | Number of subjects (%) | | | |
|---|---|---|---|---|
| **Concomitant illness** | **TEL** | | **AMC** | |
| Total safety evaluable subjects | 12159 | | 11978 | |
| Cardiovascular disease | | | | |
| Coronary artery disease | 837 | (6.9) | 872 | (7.3) |
| Angina/myocardial infarction | 305 | (2.5) | 315 | (2.6) |
| Other cardiovascular diseases | 2211 | (18.2) | 2168 | (18.1) |
| Arrhythmias | 305 | (2.5) | 274 | (2.3) |
| Ventricular arrhythmia | 41 | (0.3) | 38 | (0.3) |
| Congestive heart failure | 277 | (2.3) | 270 | (2.3) |
| Symptoms present with minimal effort/rest | 7 | (0.1) | 5 | (0.0) |
| Chronic obstructive pulmonary disease | 1658 | (13.6) | 1582 | (13.2) |
| Asthma | 1393 | (11.5) | 1340 | (11.2) |
| Hepatic impairment | 97 | (0.8) | 119 | (1.0) |
| Renal impairment | 78 | (0.6) | 76 | (0.6) |
| Known creatinine clearance < 30 mL/min | 23 | (0.2) | 17 | (0.1) |
| Diabetes mellitus | 1126 | (9.3) | 1075 | (9.0) |
| Collagen vascular disease | 54 | (0.4) | 61 | (0.5) |
| Human immunodeficiency virus | 27 | (0.2) | 30 | (0.3) |

Source: CSR No. B2002CLN0064, p. 112

Concomitant non-antimicrobial drug use is summarized in Table 5. Nearly 20% of subjects enrolled were taking CYP3A4 inhibitors, and nearly half were taking drugs metabolized by CYP3A4 enzymes. About 4% of subjects were taking drugs metabolized by the CYP2D6 enzymes. Just over 11% of subjects were taking HMG-CoA reductase inhibitors. Concomitant drug use was similar between treatment groups.

# 4 Adverse events of special interest

## 4.1 Safety results

Frequency of subjects who were positively adjudicated for an AESI is shown in Table 6. Telithromycin-treated subjects were approximately 15 times as likely to experience a visual AE compared to AMC-treated subjects.

## 4.2 Visual adverse events

Positively adjudicated visual endpoints occurred in 0.61% of telithromycin-treated subjects and 0.04% AMC-treated subjects. The relative risk (RR) of 14.5 with 95% exact C.I. of (6.2, 41.0). Telithromycin is associated with a statistically significantly higher incidence of visual events compared to AMC. Adjudicated visual events

Table 5: Concomitant non-antimicrobial drug use

| Concomitant non-antimicrobial drug use | Number of subjects (%) TEL | | AMC | |
|---|---|---|---|---|
| Total safety evaluable subjects | 12159 | | 11978 | |
| Theophyline | 213 | (1.8) | 178 | (1.5) |
| Anticoagulants | 411 | (3.4) | 396 | (3.3) |
| Warfarin | 27 | (0.2) | 37 | (0.3) |
| Antiarrhythmic drugs | 32 | (0.3) | 59 | (0.5) |
| Class Ia | 4 | (0.0) | 11 | (0.1) |
| Class III | 28 | (0.2) | 48 | (0.4) |
| Taking CYP3A4 inhibitors[a] | 2309 | (19.0) | 2201 | (18.4) |
| Mild | 1027 | (8.4) | 945 | (7.9) |
| Moderate | 1341 | (11.0) | 1264 | (10.6) |
| Strong | 142 | (1.2) | 181 | (1.5) |
| Taking drugs metabolized by CYP3A4 | 5834 | (48.0) | 5795 | (48.4) |
| Taking drugs metabolized by CYP2D6 | 514 | (4.2) | 531 | (4.4) |
| Diuretics | 1776 | (14.6) | 1710 | (14.3) |
| Cardiac glycosides | 220 | (1.8) | 230 | (1.9) |
| Drugs with potential to prolong QT interval | 1965 | (16.2) | 1899 | (15.9) |
| Corticosteroids | 823 | (6.6) | 797 | (6.7) |
| Central nervous system drugs | 3649 | (30.0) | 3474 | (29.0) |
| Acetaminophen | 1337 | (11.0) | 1295 | (10.8) |
| Simvastatin/Atorvastatin/Lovastatin | 1420 | (11.7) | 1341 | (11.2) |

[a]CYP3A4 inhibitor classification proposed in this study are those of the sponsor and should not be taken to represent regulatory classification or definition

Source: CSR No. B2002CLN0064, p. 113

are summarized in Table 7. The median age of those with a visual AESI was 48.5 years (TEL: 48 years; AMC: 56 years).

The incidence of visual AESIs in telithromycin-treated subjects was more common in women. In the AMC group, all seven visual AESIs were reported in women (2 AMC subjects had a history of visual problems prior to entering the study). A single telithromycin-treated subject taking a strong CYP3A4 inhibitor, a single telithromycin-treated subject taking mild, and none taking moderate CYP3A4 inhibitors reported blurred vision. Among telithromycin-treated subjects the incidence of visual AESIs was similar between AECB subjects treated for $\leq$7 days and those treated for >7 days. Visual events in 3 telithromycin-treated subjects were considered serious.

The vast majority of subjects complained of blurred vision associated with distant, and/or distant and

Table 6: Frequency of positively adjudicated endpoints

| Endpoint | Subjects positively adjudicated | | Relative Risk (RR) | Exact 95% confidence interval[a] |
|---|---|---|---|---|
| | Treatment | | | |
| | TEL | AMC | | |
| Visual | 74/12096 | 5/11883 | 14.5 | (6.2, 41.0) |
| Hepatic | 3/12096 | 2/11883 | 1.47 | (0.24, 14.85) |
| Cardiac | 0/12096 | 1/11883 | 0 | – |
| Vasculitic | 0/12096 | 0/11883 | 0 | – |

[a]Exact C.I. were obtained using the StatXact 5 software (2002)

Table 7: Subjects with positively adjudicated visual adverse events

| | Number of subjects | |
|---|---|---|
| | TEL | AMC |
| Total with visual endpoints | 74 | 5 |
| Vision blurred | 64 | 4 |
| Diplopia | 4 | 1 |
| Vision abnormal NOS | 4 | 0 |
| Visual disturbance NOS | 3 | 0 |
| Visual hallucination | 1 | 0 |

TEL=telithromycin, AMC=amoxicillin-clavulanic acid

near vision disturbances. Approximately half the subjects who reported visual difficulties in the telithromycin group (33/74, 44.6%) reported that this event significantly impacted their activities of daily living. Among subjects for whom the type of activity affected was reported: 5 subjects were unable to carry on usual work activities, 7 had difficulty reading, and 5 were unable to drive. Most subjects required no change in their study medication, although 25/74 telithromycin-treated subjects and 1/5 AMC-treated subjects discontinued treatment due to the event. Visual AEs were more common in females, and among subjects treated for acute bacterial sinusitis (46/74, 62.2%).

Table 8 shows characteristics of the subjects who experienced a visually related adverse event. In the telithromycin group, the majority of subjects had confirmed visual safety endpoints were of mild to moderate intensity. All (5/5) cases of severe, possibly drug-related blurred vision occurred among telithromycin-treated subjects. Only two telithromycin-treated subjects were evaluated by an opthalmologist during the study. To characterize the visual events it would have been helpful to have in place a management algorithm which guides specific ophthalmological follow-up of these subjects during and after these events. This could have improved the characterization of the visual adverse events. No known sequelae have been reported among subjects who experienced a visual AE.

The time course of visual events was difficult to assess because the majority of cases did not have information on the time of onset or time of resolution of a visual AE. The median time from first dose of study medication to visual event onset for telithromycin-treated subjects was generally 2 days with a range of 1 to 18 days. The median duration was about 3 days (range: 1 - 12 days) among positively adjudicated cases.

## 4.3 Hepatic adverse events

A hepatic adverse event of special interest was defined as a potentially drug related hepatic injury with clinically overt, symptomatic liver damage (with manifestations including nausea/vomiting, right upper quadrant abdominal pain, rash/pruritus, significant or unusual fatigue which impacts daily activities, fever, dark urine, and jaundice), with associated alanine aminotransferase (ALT) values of at least 3 x ULN (upper limit of normal/reference range) occurring during the period of observation in the absence of other causes, such as viral hepatitis, excessive alcohol or acetaminophen ingestion, acute cholelithiasis, decompensated heart failure, malignant neoplasm, or other well-defined pathological processes. New onset of symptoms or later than Day 5 of therapy were used to ensure possible temporal relationship to study drug and help to differentiate potential drug-induced liver injury from symptoms of the underlying disease processes.

Table 8: Characteristics of subjects with visual adverse events

| | Number of subjects | |
|---|---|---|
| | **TEL** | **AMC** |
| Total subjects with *confirmed* visual endpoints | 74 | 5 |
| Occurred during the on-therapy period | 74 | 4 |
| History of visual abnormalities | 16 | 2 |
| Symptoms associated with event | | |
| Blurred vision | 69 | 5 |
| Near vision only | 13 | 5 |
| Distant vision only | 10 | 0 |
| Distant and near vision | 46 | 4 |
| Abnormalities of color vision | 2 | 0 |
| Abnormalities of light perception | 6 | 0 |
| Significantly impacted subjects' activities | 33 | 2 |
| Discontinued study drug due to AE | 25 | 1 |
| Females/Males | 63/11 | 5/0 |
| Intensity of event | | |
| Mild | 51 | 4 |
| Moderate | 17 | 1 |
| Severe | 5 | 0 |
| Recovered without "known" sequelae | 74 | 5 |

[a]Excludes one telithromycin subject who reported blurred vision in the left eye for 106 days
TEL=telithromycin, AMC=amoxicillin-clavulanic acid

Three telithromycin-treated subjects and 2 AMC-treated subjects were positively adjudicated for a significant, clinically overt hepatic AE. Case summaries for all positively adjudicated subjects with a hepatic AE are described in Appendix A.0.1. Hepatic AEs included all reports of hepatitis, jaundice, or any worsening of a preexisting hepatic impairment and all ALT elevation of $\geq 3$ x ULN. The frequency of hepatic AEs was similar between telithromycin and comparator (TEL: 0.9%; AMC: 0.8%). These 209 subjects (TEL: 111; AMC: 98) were followed until resolution or return to baseline values with follow-up obtained on 93.8% of subjects which for approximately 6 months.

Characteristics of subjects with symptoms of hepatic AE are shown in Table 9. Fewer than a quarter of the subjects with hepatic AESIs presented with clinically overt symptoms of possible hepatic injury (TEL: 18.9%; AMC: 23.5%). The most common symptoms were fatigue and nausea. Three subjects presented with jaundice (TEL: 2; AMC: 1). All three had elevated bilirubin levels confirmed by laboratory assays.

Table 9: Characteristics of subjects with hepatic adverse events

| | Number of subjects | |
|---|---|---|
| **Characteristics of subjects with hepatic AEs** | **TEL(%)[a]** | **AMC(%)** |
| Number of subjects with hepatic AESI | 111 (100) | 98 (100) |
| Number of subjects with symptoms | 21 (18.9) | 23 (23.4) |
| Fatigue | 14 (12.6) | 11 (11.2) |
| Nausea | 6 | 9 |
| Fever | 6 | 2 |
| Jaundice | 2 | 1 |
| Rash or pruritus | 0 | 3 |
| Right upper quadrant abdominal pain | 3 | 3 |
| Dark urine | 1 | 4 |

[a]A single subject could have exhibited more than one characteristics listed above.

Number of subjects with hepatic AEs are shown in Table 10. The most common hepatic AE seen was liver function test abnormal NOS (not otherwise specified) and ALT increased. The distributions of these AEs were similar between treatment groups.

Table 10: Number of subjects with hepatic adverse events

| | Number of subjects | |
|---|---|---|
| **Event code** | **TEL[a]** | **AMC** |
| Number of subjects with hepatic AESI | 111 | 98 |
| Liver function tests abnormal NOS | 54 | 46 |
| Alanine aminotransferase increased | 40 | 42 |
| Hepatitis C | 5 | 2 |
| Hepatitis B | 2 | 0 |
| Aspartate aminotransferase increased | 1 | 0 |
| Autoimmune hepatitis | 1 | 0 |
| Bile duct stone | 1 | 0 |
| Blood bilirubin increased | 2 | 1 |
| Hepatitis A | 1 | 0 |
| Hepatitis C antibody positive | 1 | 1 |
| Hepatitis NOS | 1 | 1 |
| Hepatitis C virus | 0 | 1 |
| Hepatitis viral NOS | 1 | 0 |
| Hepatorenal failure | 1 | 0 |
| Choledocolithiasis | 1 | 0 |
| Hepatic function abnormal NOS | 0 | 1 |
| Jaundice | 2 | 1 |
| Liver fatty | 0 | 1 |
| Pancreatitis acute | 0 | 1 |

[a]Subjects may experience more than one adverse event

### 4.3.1 Elevations in hepatic analytes

Table 11 displays the frequency of subjects with a clinically relevant elevation in hepatic related analyte values at post-therapy and late post-therapy irrespective of baseline values. At Visit 2, both treatment arms showed low overall frequency and similar distributions of clinically relevant changes in hepatic analytes. Almost twice as many telithromycin-treated subjects persisted with elevations in both ALT and AST compared to AMC-treated subjects.

Table 12 displays frequencies of subjects with a clinically relevant elevation in hepatic related analyte values during the post-treatment period among subjects with normal baseline values. Two subjects in each treatment group had bilirubin increases of > 3 x ULN. Three subjects in both treatment groups had ALT > 3 x ULN with concurrent increase in total bilirubin of at least 1.5 x ULN.

Table 13 displays the frequencies of subjects with a clinically relevant elevation in hepatic related analyte values at post-therapy for subjects with abnormal values at baseline.

### 4.3.2 Changes in ALT among subjects with normal baseline values

Changes in ALT among subjects with normal values at study entry are shown in Table 14. At post-therapy telithromycin-treated subjects had a slightly higher proportion of subjects with increases in ALT compared to AMC-treated subjects. Subjects with > 8 x ULN were more likely to receive telithromycin.

Table 11: Frequency of elevations in hepatic analytes at post-therapy and late post-therapy irrespective of hepatic analyte values at study entry

| | n/N (%) Subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Post-therapy | | | | Late follow-up | | | |
| **Analyte status** | **TEL** | | **AMC** | | **TEL** | | **AMC** | |
| ALT > 3 x ULN | 94/10661 | (0.9) | 81/10359 | (0.8) | 47/1087 | (4.3) | 28/1122 | (2.5) |
| AST > 3 x ULN | 48/10450 | (0.5) | 45/10159 | (0.4) | 30/1070 | (2.8) | 17/1097 | (1.5) |
| Total bilirubin > 3 x ULN | 2/10039 | | 2/9784 | | 1/1027 | (0.1) | 0/1033 | |
| ALT $\geq$ 3 x ULN and total bilirubin $\geq$ 1.5 x ULN | 3/9991 | | 5/9723 | | 0/1026 | (0.0) | 2/1027 | |
| Alk. phos. $\geq$ 3 x ULN | 4/10809 | | 1/10535 | | 0/1094 | (0.0) | 1/1126 | |

Table 12: Frequency of elevations in hepatic analytes at post-therapy among subjects with normal baseline values

| | n/N (%) Subjects | | | |
|---|---|---|---|---|
| **Analyte status** | **TEL** | | **AMC** | |
| ALT > 3 x ULN | 27/7708 | (0.4) | 17/7515 | (0.2) |
| AST > 3 x ULN | 20/570 | (0.3) | 14/7389 | (0.2) |
| Total bilirubin > 3 x ULN | 2/7339 | | 2/7199 | |
| ALT $\geq$ 3 x ULN and Total bilirubin $\geq$ 1.5 x ULN | 3/7314 | | 3/7163 | |
| Alk. phos. $\geq$ 3 x ULN | 2/7796 | | 0/7626 | |

TEL = telithromycin, AMC = amoxicillin-clavulanic acid

Note: Denominator based on number of subjects with a valid assay

Table 13: Frequency of elevations in hepatic analytes at post-therapy in subjects with abnormal values at pretherapy/entry

| | n/N (%) Subjects | | | |
|---|---|---|---|---|
| **Analyte status** | **TEL** | | **AMC** | |
| ALT > 3 x ULN | 63/1646 | (3.8) | 59/1624 | (3.6) |
| AST > 3 x ULN | 26/1613 | (1.6) | 30/1579 | (1.9) |
| Total bilirubin > 3 x ULN | 0/1598 | | 0/1577 | |
| ALT $\geq$ 3 x ULN and Total bilirubin $\geq$ 1.5 x ULN | 0/1590 | | 2/1562 | |
| Alkaline phosphatase $\geq$ 3 x ULN | 2/1673 | | 1/1655 | |

TEL = telithromycin, AMC = amoxicillin-clavulanic acid

Denominator based on number of subjects with a valid assay

Table 14: Frequency of elevations in ALT levels at post-therapy in subjects with normal baseline values

| | n/N (%) Subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Post-therapy | | | | Late post-therapy | | | |
| **Changes in ALT** | **TEL** ($N = 7708$) | | **AMC** ($N = 7516$) | | **TEL** ($N = 664$) | | **AMC** ($N = 659$) | |
| $\leq$ 1 x ULN | 7158 | (92.9) | 7044 | (93.8) | 585 | (87.5) | 659 | (92.3) |
| >1 to $\leq$ 2 x ULN | 488 | (6.3) | 433 | (5.8) | 57 | (8.9) | 42 | (6.2) |
| >2 to $\leq$ 3 x ULN | 35 | (0.5) | 22 | (0.3) | 6 | (1.0) | 4 | (0.6) |
| >3 to $\leq$ 5 x ULN | 12 | (0.2) | 8 | (0.1) | 4 | (0.7) | 3 | (0.3) |
| >5 to $\leq$ 8 x ULN | 8 | (0.1) | 7 | (0.1) | 4 | (0.7) | 0 | (0.0) |
| > 8 x ULN | 7 | (0.1) | 2 | (0.0) | 8 | (1.4) | 3 | (0.5) |

TEL = telithromycin, AMC = amoxicillin-clavulanic acid, ULN= upper limit of normal

Note: Denominator based on number of subjects with a valid assay

Table 15 shows the frequency of elevation in ALT post-treatment in telithromycin-treated subjects with normal ALT at baseline among those treated with telithromycin for 7 to 10 days (CAP or AECB) versus those treated with telithromycin for 5 days (AS). Subjects treated for < 7 days versus > 7 days were similar with respect to ALT increases.

Table 15: Frequency of elevations in ALT at post-therapy in telithromycin-treated subjects by treatment duration

| | n/N (%) Subjects Telithromycin | | | |
|---|---|---|---|---|
| **Changes in ALT** (normal baseline) | **7 to 10-days** ($N = 3020$) | | **5-days** ($N = 4680$) | |
| $\leq$ 1 x ULN | 2779 | (91.9) | 4379 | (93.5) |
| >1 to $\leq$ 2 x ULN | 210 | (6.9) | 278 | (5.9) |
| >2 to $\leq$ 3 x ULN | 19 | (0.6) | 16 | (0.3) |
| >3 to $\leq$ 5 x ULN | 7 | (0.2) | 5 | (0.1) |
| >5 to $\leq$ 8 x ULN | 4 | (0.1) | 4 | (0.1) |
| > 8 x ULN | 5 | (0.2) | 2 | (0.0) |

ULN= upper limit of normal

Denominator based on number of subjects with a valid assay

Table 16 shows the frequency of elevations in ALT at post-therapy by subgroup. The frequency of hepatic AESI among subjects taking drug metabolized by CYP3A4 enzyme or taking concomitant CYP3A4 inhibitors, HMG-COA reductase inhibitors of interest were similar between the two treatment groups. There were no subjects with hepatic AEs among subjects with severe renal impairment.

Most subjects classified as hepatic AESI were asymptomatic (TEL: 81% [90/111]; AMC: 77% [75/98]). Fatigue was the most common symptom observed. Jaundice was not commonly observed (TEL: 2; AMC: 1). The subject (subject 156/009) who presented with dark urine in the telithromycin group had 4.6 x ULN total bilirubin level. The four subjects in the AMC group had total bilirubin levels ranging from normal up to 5.1 x ULN. History of use of substances which may be associated with transaminase increase or hepatic injury was similar between both treatment groups.

In summary, the characteristics of subjects with hepatic AEs were comparable between telithromycin and AMC-treated subjects. The majority of the subjects with hepatic AEs were asymptomatic. Most cases were identified by elevations in transaminases. Three subjects in the telithromycin group, and none in the AMC group, discontinued therapy due to a hepatic AE. Gender, age, duration of therapy ( < 7 days or > 7 days) did not appear to increase the risk of experiencing an hepatic AESI.

### 4.3.3 Changes in ALT among subjects with abnormal values at baseline

Table 17 shows the frequency of changes in ALT among subjects with abnormal ALT, AST or total bilirubin values at study entry. The vast majority of treated subjects remained at or below their baseline values. The majority of subjects remained at or below their baseline values at post-therapy (TEL: 66.4%; AMC: 71.2%). The increases in ALT were similar for treatment groups.

Table 16: Frequency of elevations in hepatic analytes at post-therapy in pre-specified subgroups of interest

| | Number of subjects (%) | | | | | |
|---|---|---|---|---|---|---|
| | TEL | | | AMC | | |
| Subgroups | Changes in ALT values | | | | | |
| | N | >3xULN | >5xULN | N | >3xULN | >5xULN |
| Males | 4191 | 41 (1.0) | 7 (0.1) | 4134 | 45 (1.1) | 9 (0.2) |
| Females | 6470 | 50 (0.8) | 22 (0.3) | 6225 | 36 (0.6) | 13 (0.2) |
| $\geq$ 50 years | 5530 | 72 (1.3) | 19 (0.3) | 5397 | 51 (0.9) | 11 (0.2) |
| < 50 years | 5125 | 22 (0.4) | 10 (0.2) | 4959 | 30 (0.6) | 11 (0.2) |
| Hepatic impairment | 86 | 11 (12.8) | 3 (3.5) | 104 | 14 (13.5) | 3 (2.9) |
| Abnormal baseline– (ALT or AST or T. Bili) | 1646 | 63 (3.8) | 14 (0.8) | 1621 | 59 (3.6) | 13 (0.8) |
| Severe renal impairment | 22 | 0 (0.0) | 0 (0.0) | 15 | 0 (0.0) | 0 (0.0) |
| Reduce dose of study medication | 169 | 0 (0.0) | 0 (0.0) | 138 | 1 (0.7) | 1 (0.7) |
| Cardiovascular disorders | 2673 | 17 (0.6) | 6 (0.2) | 2619 | 17 (0.6) | 5 (0.2) |
| Moderate or strong - CYP3A4 inhibitors | 197 | 2 (1.0) | 0 (0.0) | 235 | 1 (0.4) | 0 (0.0) |
| 7 to 10 days on study drug | 4230 | 41 (1.0) | 14 (0.3) | 4050 | 33 (0.8) | 8 (0.2) |
| HMG-CoA reductase inhibitors of interest[a] | 1307 | 8 (0.6) | 1 (0.1) | 1220 | 8 (0.7) | 5 (0.3) |

[a]Simvastatin, atorvastatin, lovastatin

Table 17: Frequency of elevations in ALT values at post-therapy in subjects with abnormal baseline values

| | n/N (%) Subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Post-therapy | | | | Late post-therapy | | | |
| Changes in ALT | TEL | | AMC | | TEL | | AMC | |
| | ($N$ = 1645) | | ($N$ = 1623) | | ($N$ = 216) | | ($N$ = 215) | |
| $\leq$ baseline | 1093 | (66.4) | 1155 | (71.2) | 139 | (64.4) | 153 | (71.2) |
| >baseline and $\leq$ baseline+$\Delta$ | 501 | (30.5) | 415 | (25.6) | 60 | (27.8) | 53 | (24.7) |
| >baseline+ $\Delta$ and $\leq$baseline+2$\Delta$ | 33 | (2.0) | 37 | (2.3) | 8 | (3.7) | 3 | (1.4) |
| >baseline+2$\Delta$ and $\leq$baseline+4$\Delta$ | 15 | (0.9) | 12 | (0.7) | 5 | (2.3) | 5 | (2.3) |
| >baseline+4$\Delta$ and $\leq$baseline+7$\Delta$ | 2 | (0.1) | 2 | (0.1) | 3 | (1.4) | 1 | (0.5) |
| >baseline+7$\Delta$ | 1 | (0.1) | 2 | (0.1) | 1 | (0.5) | 0 | (0.0) |

$\Delta$=numerical values of 1xULN, ULN= upper limit of normal

Note: Denominator based on number of subjects with a valid assay

Table 18: Frequency of elevations in AST values at post-therapy in subjects with normal baseline values

| Changes in AST | n/N (%) Subjects TEL ($N = 7570$) | | AMC ($N = 7381$) | |
|---|---|---|---|---|
| $\leq$ 1 x ULN | 7264 | (96.0) | 7129 | (96.5) |
| >1 to $\leq$ 2 x ULN | 267 | (3.5) | 227 | (3.1) |
| >2 to $\leq$ 3 x ULN | 19 | (0.2) | 20 | (0.3) |
| >3 to $\leq$ 5 x ULN | 10 | (0.1) | 12 | (0.1) |
| >5 to $\leq$ 8 x ULN | 5 | (0.1) | 1 | (0.0) |
| > 8 x ULN | 5 | (0.1) | 1 | (0.0) |

ULN= upper limit of normal

Note: Denominator based on number of subjects with a valid assay

Table 19: Frequency of elevations in AST values at post-therapy in subjects with abnormal baseline values

| Changes in AST | n/N (%) Subjects Post-therapy TEL ($N = 1577$) | | AMC ($N = 1533$) | |
|---|---|---|---|---|
| $\leq$ baseline | 1099 | (69.7) | 1102 | (71.9) |
| >baseline and $\leq$ baseline+$\Delta$ | 450 | (28.5) | 395 | (25.8) |
| >baseline+ $\Delta$ and $\leq$baseline+2$\Delta$ | 17 | (1.1) | 23 | (1.5) |
| >baseline+2$\Delta$ and $\leq$baseline+4$\Delta$ | 8 | (0.5) | 8 | (0.5) |
| >baseline+4$\Delta$ and $\leq$baseline+7$\Delta$ | 2 | (0.1) | 4 | (0.3) |
| >baseline+7$\Delta$ | 1 | (0.1) | 2 | (0.1) |

$\Delta$=numerical values of 1xULN, ULN= upper limit of normal

Note: Denominator based on number of subjects with a valid assay

### 4.3.4 Changes in AST among subjects with normal baseline values

Table 18 presents frequency of AST elevations among subjects with normal baseline AST, ALT and total bilirubin values. Elevations of $\leq$ 5 x ULN in AST were similar for both treatment arms. However, at the higher elevations of AST (> 5 x ULN or >8 x ULN) telithromycin-treated subjects more frequently experienced this magnitude of change in AST compared to the AMC-treated subjects.

### 4.3.5 Changes in AST among subjects with abnormal baseline values

Most subjects in both treatment groups had values at or below pretherapy/entry at the post-therapy visit as shown in Table 19. There were slightly more subjects with increases of up to an additional 1 x ULN increase above baseline among the telithromycin-treated subjects. Overall, the frequency of subjects with elevated AST values at post-therapy was similar between treatment groups.

### 4.3.6 Summary of laboratory findings

Assessment of clinically overt significant liver injury was one of the key analyses for this trial. Laboratory data were collected to ensure complete case ascertainment and case recovery. Since laboratory findings may be of some interest in the assessment of drug-related liver effects, an analysis of all laboratory values for post-therapy values and changes from pretherapy/entry was performed. Results showed slightly more frequent occurrence of increases in hepatic analytes among telithromycin-treated subjects.

In subjects with normal ALT values at pretherapy/entry, increases in ALT tended to be more frequent

at post-therapy for the telithromycin group as compared to AMC, but primarily at the lower levels (<3 x ULN). While there tended to be more of the higher elevations of ALT observed in the telithromycin group as compared to AMC, the number of hepatic endpoint cases were balanced between treatments. Subjects with > 8 x ULN were more likely to have been treated with telithromycin. Telithromycin showed more frequent ALT (> 5 x ULN) elevations the late-post therapy follow up period. In subgroup analyses that included age, gender, pretherapy/entry hepatic laboratory abnormality, CYP3A4 inhibitors and HMG-CoA reductase inhibitors, the risk of ALT elevation was no different between treatment groups. No increased risk was seen by duration of telithromycin treatment.

### 4.4 Cardiac adverse events

Cardiac events of special interest was defined as a combined endpoint consisting of all cases of torsades de pointes, sustained ventricular tachycardia, syncope, cardiac arrest, and unwitnessed or unexplained death which occurred after first ingestion of study drug through 48 hours after study drug intake. Definitions of these component terms were as follows:

- Torsades de pointes: pause-dependant characteristic polymorphic ventricular tachycardia associated with QT interval prolongation. All three components were required on the expert adjudicated ECGs to qualify as torsades de pointes.
- Sustained ventricular tachycardia: documented ventricular tachycardia (monomorphic or polymorphic) which persisted for more than 30 seconds or required termination because of hemodynamic compromise and/or symptoms of impaired perfusion.
- Syncope: total loss of consciousness.
- Cardiac arrest: loss of consciousness associated with resuscitation where a lethal cardiac arrhythmia had been implicated.
- Unwitnessed or unexplained death: any outpatient death which had not been observed and/or where no proximal cause was obvious to the investigator on follow-up. This would not include terminally ill patients or patients with imminently lethal diagnoses.
- All reported arrhythmias were to be documented by ECG rhythm strips or 12-lead ECGs. In order to meet the endpoint definition, other likely causes for the event should have been excluded. These other causes include evidence of acute myocardial infarction within 7 days prior to the event, and significant uncorrected hypokalemia (potassium <2.5 mEq/L) and/or hypomagnesemia (magnesium <1.5 g/dL).

Characteristics of subjects with cardiac AEs are shown in Table 20. There were three ventricular arrhythmias among telithromycin treated subjects and none in the AMC group. There were no subjects with positively adjudicated cardiac endpoint in the telithromycin group.

## 5 Summary

Positively adjudicated visual adverse events (AEs) occurred in 0.61% of telithromycin-treated subjects and 0.04% of AMC-treated subjects. The relative risk (RR) of the occurrence of visual events for telithromycin compared to AMC was 14.5 ( 95% C.I. [6.2, 41.0] ). Telithromycin-treated subjects had a statistically, significantly higher incidence of visual events compared to AMC-treated subjects. Visual AEs were reported

Table 20: Characteristics of subjects with cardiac adverse events

| | Number of subjects | |
|---|---|---|
| | TEL | AMC |
| Subjects with cardiac AEs | 39 | 34 |
| Symptoms | 31 | 26 |
| Shortness of breath | 18 | 15 |
| Chest pain | 15 | 9 |
| Light headedness | 12 | 5 |
| Palpitations | 9 | 8 |
| Nausea | 1 | 3 |
| Ventricular arrhythmia | 3 | 0 |
| Hospitalized for this AE | 19 | 20 |

Source: Clinical Study Report, p. 136.

most commonly as blurred vision. Eighty-two (82%) percent of telithromycin-treated subjects with visual AEs were women. The median age of those with a visual AEs was 48.5 years. Among telithromycin-treated subjects the incidence of visual AEs was similar between AECB subjects treated for $\leq$7 days and those treated for >7 days.

There were insufficient data to describe the time of onset and time to resolution because the majority of subjects did not have complete documentation. Based on the partial data available visual events were reported from a few hours to days after the first dose of therapy. The median time to resolution was approximately 3 days (range 1 - 18 days). The majority of case reports did not describe the effects of a visual AE and activities of daily living (ADLs). Among telithromycin-treated subjects for whom effect on ADLs was documented subjects reported they were unable to drive, unable to carry on usual work activities, or had difficulty reading. Approximately a third of the subjects with a visual AE in telithromycin-treated subjects discontinued treatment due to the event. All subjects appeared to resolve after the cessation of treatment and no known sequelae have been described.

The incidence of CEC confirmed hepatic safety endpoints was low and similar between treatment groups. The relative risk of significant hepatic injury among telithromycin-treated subjects was 1.47 times that of AMC-treated subjects (95% C.I. [0.24, 14.5]). This is not statistically significant but one should bear in mind that this study was now powered to exclude liver effects which occur less frequently than 1/4000. Telithromycin-treated subjects had a slightly higher frequency of experiencing elevations in hepatic analytes, particularly ALT > 8 x ULN compared to AMC which persisted through the late-posttherapy period. There were no liver failures or deaths of a hepatic cause observed during the study. In subgroup analyses that included age, gender, pretherapy/entry hepatic laboratory abnormality, CYP3A4 inhibitors and HMG-CoA reductase inhibitors, the risk of ALT elevation was no different between treatment groups. No increased risk was seen by duration of telithromycin treatment.

The frequency and profile of TEAEs was similar between telithromycin ( 23.1%) and AMC ( 22.9%). The majority of all TEAEs were mild to moderate and discontinuation of study medication due to a TEAE was uncommon for both treatment groups (TEL: 3.8%; AMC: 4.7%). TEAEs of the gastrointestinal disorders system organ class were the most common events reported in both treatment groups (TEL: 1292/12159, 10.6%; AMC: 1417/11978, 11.8%). The frequency of serious TEAEs was similar between treatment groups (TEL: 1.3%; AMC: 1.1%). The safety profile of subgroups: older subjects, subjects with diabetes, and hepatic impairment was similar between treatment groups was similar for both treatment groups. There were no cases of positively adjudicated cardiac or vasculitic events in telithromycin-treated subjects.

# A Appendix 1

## A.1 Adjudicated cases of hepatic AESIs

### A.1.1 Subject 3440/001 (telithromycin)

A 75-year-old white female, commenced telithromycin treatment on 21 January 2002 and ended on 25 January 2002 (completed 5-day treatment course) for acute sinusitis. Past medical history of coronary artery disease, angina/myocardial infarction, hypertension, cholecystectomy, gastroesophageal reflux disorder, degenerative joint disease, hyperlipidemia and hypothyroidism. Subject reported no known drug or food allergies. She had no history of liver disease or alcohol intake and baseline liver function panel was normal. The subject reported a history of use of the following: acetaminophen (2-3 per day) since [redacted] for joint pain. On [redacted] days from the start of treatment), the subject experienced severe epigastric and abdominal pain. When she arrived at the emergency room her vital signs were: temperature: 101°F, pulse 88 bpm, respirations 20/min, and blood pressure 166/80. Associated symptoms included fatigue, nausea, fever, right upper quadrant tenderness and jaundice. Her liver function tests were abnormal (T.Bili 1.8 mg/dL, AST 782, ALT 531, Alk Phos 260). All coagulation parameters were negative and eosinophils were 0.5%.

The subject was hospitalized on [redacted] She was kept on nothing by mouth and given intravenous fluids. Her pravastatin was withheld. Hepatitis A, B and C antibodies, ANA, anti-smooth muscle, anti-double stranded DNA, and anti-mitochondrial antibodies were all negative. Acetaminophen level was 2 mg/L within 4 hours after last dose (toxic range >150 mg/L). An abdominal CT scan was notable for signs of previous cholecystectomy. There was no stone in the gall bladder or duct dilation (per investigator, report not available). By day 4 of hospitalization her liver function tests were (T.Bili 0.7 mg/dL [max 1.8, i.e., 31 $\mu$mol/L], AST 108 [max 1357], ALT 396 [max 969], Alk Phos 243 [max 285]). She continued to improve, felt better and was discharged home on [redacted] The treating physician summarized her presentation as "Hepatitis, probably drug related versus possible stone passage. The drug could be Ketec." Last communication with treating physician was on [redacted] who stated that while the patient's abdominal pain has resolved she still experienced tenderness with deep palpation on exam. Further follow-up with a gastroenterologist presented no further competing etiology for the hepatitis episode. Laboratory values for liver-related tests are shown in the Table 21.

*CEC Adjudication Summary: This case represented a clinically overt significant hepatic injury with compatible temporal relationship. This case is felt to be a clinically serious problem. This patient had increases in ALT to 969, AST to 1357 and bilirubin to 1.8 mg/dL associated with fatigue, nausea, jaundice and severe epigastric pain. A relation to drug use is possible or probable, but passage of a stone cannot be excluded.*

### A.1.2 Subject 1567/009 (telithromycin)

A 58-year-old black female was enrolled in the study on 05 December 2001, with acute exacerbation of chronic bronchitis. The last dose of study medication was taken on 14 December 2001 (i.e., completed 10 days of study drug). On [redacted] 2001, the subject experienced abdominal pain , flatulence, dry mouth and headache. Study medication was not changed. The investigator assessed the events as nonserious, of mild intensity, and possibly related to study medication. The events resolved without sequelae on 09 December 2001. On 25 December 2001, the subject experienced pyelonephritis. Urinalysis showed 2+ bilirubin, occasional RBCs, 10-20 WHC/hpf, and many bacteria. The investigator assessed the event as nonserious, of moderate intensity,

Table 21: Laborarory data for telithromycin- treated subject 3440/001

| Analyte (Units) | Normal Range | Baseline | Date | Date | Date | Date | Date |
|---|---|---|---|---|---|---|---|
| | | Day 1 x ULN | Day 119 x ULN | Day 19 x ULN | Day 21 x ULN | Day 22 x ULN | Day 29 x ULN |
| ALT (L-U) | 6 - 32 | 0.3 | | | | | 1.03 |
| ALT (L-U)[a] | 25 - 65 | | **14.9** | **8.2** | **8.1** | | |
| AST (L-U) | 9 - 34 | 0.5 | | | | | |
| AST (L-U)[a] | 15 - 37 | | **36.7** | **21.1** | **9.0** | **2.9** | |
| Alk. Phos (L-U) | 35 - 164 | 0.5 | | | | | 0.6 |
| Alk. Phos (L-U)[a] | 50 -136 | | **2.1** | **1.9** | **1.9** | **1.7** | |
| Total bilirubin ($\mu$mol/L) | 3 - 21 | 0.3 | | | | | 0.2 |
| Total bilirubin ($\mu$mol/L)[b] | 0 - 17 | | **1.8** | 0.9 | 1.1 | 0.7 | |

H = high (above the upper limit of normal range, L= low (below the lower limit of normal range
[a]Local laboratory measurement
[b]Local laboratory measuremen converted from mg/dL using conversion factor of 1 mg/dL = 17 $\mu$mol/L.

and possibly related to study medication. The subject developed gross hematuria and was seen in emergency on [redacted], pyelonephritis was diagnosed and the subject was prescribed ciprofloxacin 500 mg BID for 10 days, although urine culture subsequently showed <100,000 colony count. On [redacted], the subject experienced blood bilirubin increased. Associated symptoms included fatigue, fever, abdominal pain and dark urine. Laboratory values for liver-related tests are shown in the table below. Alkaline phosphatase, total bilirubin, ALT and AST were within the normal range at pretherapy/entry and on [redacted] (Visit 2). No diagnosis was established for the elevated bilirubin. Follow up labs for bilirubin done on [redacted] were normal. The investigator assessed the event to be nonserious, of mild intensity, and possibly related to study medication. Increased bilirubin and pyelonephritis resolved without sequelae on [redacted] This event was an AESI and was adjudicated as a confirmed safety endpoint by the CEC. Laboratory values for this subject are shown in Table 22.

*CEC Adjudication Summary: This is a medically complicated case. This patient had a symptomatic illness with high bilirubin, but little elevation of transaminase. This occurred in the setting of a febrile illness, apparently a urinary tract infection. The illness, whatever its cause, resolved. There is a compatible temporal relationship to study drug. We believe this illness is possibly related to study drug, although renal infection cannot be ruled out.*

### A.1.3 Subject 2004/002 (telithromycin)

A 72-year-old Hispanic male, enrolled in the study on 19 December 2001 and treated with 10 days of telithromycin for community-acquired pneumonia (completed treatment on 28 December 2001). Past medical history of diabetes mellitus type II, prostate cancer (without known metastases), chronic lower left extremity lymphedema, hypertension, congestive heart failure (systolic and diastolic dysfunction), coronary artery disease, chronic pleural effusion, and chronic anticoagulation for questionable clot in the heart. No history of risk factors for liver disease or hepatitis or previous hepatic dysfunction. Baseline liver function panel was normal. On [redacted] (13 days after completing study drug, at visit 2), the subject experienced abnormal liver function tests abnormal. He otherwise felt well, but was noted on examination to have

Table 22: Laborarory data for telithromycin-treated subject 1567/009

| Analyte (Units) | Normal Range | Baseline | Date | Date | Date |
|---|---|---|---|---|---|
| | | Day 1 x ULN | Day 17 x ULN | Day 26 x ULN | Day 27 x ULN |
| ALT (L-U) | 6 - 34 | 0.4 | 0.5 | | 22 |
| ALT (L-U)[a] | 8 - 35 | | | **1.9** | |
| AST (L-U) | 9 - 34 | 0.5 | 0.6 | | 0.5 |
| AST (L-U)[a] | 8 - 37 | | | **1.8** | |
| Alkaline Phos (L-U) | 35 -123 | 0.7 | 0.7 | | 0.7 |
| Alkaline Phos (L-U)[a] | 30-120 | | | **1.6** | |
| Total bilirubin ($\mu$mol/L) | 3 - 21 | 0.1 | 0.4 | | 0.4 |
| Total bilirubin ($\mu$mol/L)[a] | 1.7 - 17 | | | **4.6** | |

ULN = upper limit of normal range, L= lower limit of normal range
[a]Local laboratory measurement [b]Local laboratory measurement,converted from mg/dL using conversion factor of 1 mg/dL =17 $\mu$mol/L.

jaundice (jaundice was not reported as a symptom on the AESI form).

The following procedures/laboratory evaluations were performed: transaminases, alkaline phosphatase and bilirubin. These laboratory tests were repeated on [redacted] along with bilirubin (total and fractional), Epstein Barr Virus titers, ANA, anti-dsDNA, hepatitis A, B, and C titers, white blood cell count with differential, prothrombin time and ultrasound and high resolution CT scan of the abdomen with and without contrast. The CT scan revealed bilateral pleural effusion and segmental atelectasis at the right lung base anterior segment, mild eventration of the right dome of the diaphragm and what appeared as a small defect in the diaphragm (Morgagni hernia) with some colonic loops of bowel protruding anteriorly near the right cardiophrenic angle, and the gallbladder with increased wall thickness and increased density suggestive of gallbladder filled with stones and/or a significant amount of sludge. A sonogram of the gallbladder performed on [redacted] revealed increased gallbladder wall thickness of up to 0.9 cm. There was also some sludge and very small low density calculi varying between 1.0 to 2.0 mm with the largest one of higher density of about 5.0 mm. The sonogram confirmed a significant degree of cholelithiasis and increased gallbladder wall thickness. It was considered that the increased wall thickness was probably secondary to chronic cholecystitis.

The subject was admitted on [redacted] with the diagnosis of jaundice. His hospital work up included a cardiology consultation for medical clearance and this showed cardiac S1 and S2 to be regular with no murmur. A 2-D echocardiogram showed left ventricular dilation with moderate systolic dysfunction and possible diastolic dysfunction with an ejection fraction estimated at 35%-45%, mild mitral and tricuspid regurgitation, a small ASD, and borderline pulmonary hypertension.

The subject started Levaquin on the same day [redacted] for a complication of the primary infection. On [redacted] the subject underwent a laparoscopic cholecystectomy, and the pathological report was consistent with cholelithiasis and cholecystitis. A post-procedure, intraoperative cholangiogram revealed no common bile duct stones, and this was confirmed on endoscopic retrograde cholangiopancreatography. A biopsy of the liver was performed at the same time and this showed cholestasis with normally-maintained parenchyma, and no significant portal inflammatory changes or lobular inflammation. The investigator considered this event to be serious, of mild intensity and not related to study medication. The event resolved without sequelae on [redacted]. His final diagnosis was choledocholithiasis. This event was an AESI and was adjudicated as a confirmed safety endpoint by the CEC.

Concomitant medications were Aceon, Coumadin, Glyburide, Lasix, Promethazine/codeine, Spironazide, Levaquin, Robitussin A-C, Vitamin K, Ambien, Milk of Magnesia, Unasyn, Aldactone. Laboratory values for liver-related tests are shown in Table 23. Hepatitis and autoimmune titers were negative.

*CEC Adjudication Summary: This was a very difficult case to interpret because of the gallbladder disease and was extensively discussed by the group. It was clearly a serious clinical event. Laboratory values were normal at baseline. There was a subsequent increase in ALT to 158, with drop to 50. Bilirubin rose to 104. Uncontrolled heart failure was also reported. This subject had an intercurrent laporascopic cholecystectomy. Liver biopsy showed cholestasis. An effect of drug cannot be discounted (possibly related to study drug), but may also be related to the concurrent gallbladder disease, as the possibility of passage of small calculi cannot be excluded.*

Table 23: Laborarory data for telithromycin-treated subject 2004/002

| Analyte (Units) | Normal Range | Baseline | Date | Date | Date | Date |
|---|---|---|---|---|---|---|
| | | Day 1 x ULN | Day 23 x ULN | Day 29 x ULN | Day 45 x ULN | Day 58 x ULN |
| ALT (L-U) | 6 - 35 | 0.5 | **7.7** | **4.5** | **1.4** | 0.7 |
| ALT (L-U)[a] | 11 - 36 | 0.5 | **4.5** | **2.8** | **1.0** | 0.7 |
| Alkaline Phosphatase (L-U) | 35 -156 | 1.0 | **3.0** | **4.0** | **1.3** | 0.8 |
| Total bilirubin ($\mu$mol/L) | 3 -21 | .8 | **4.9** | **3.8** | | 0.4 |
| Absolute eosinophil cells (cells/MCL) | 50 - 550 | | | | **1.2** | |
| Eosinophils (%) | 0 - 6.8 | | | 1.0 | | |

ULN =upper limit of normal range, L= lower limit of normal range

[a]Local laboratory measurement

[b]Local laboratory values converted from mg/dL using conversion factor of 1 mg/dL = 17 $\mu$mol/L.

### A.1.4 Subject 0604/004 (AMC)

A 43-year-old white male, was enrolled in the study on 15 January 2002, with AS. The subject completed treatment on 25 January 2002. On [redacted] the subject experienced diarrhea NOS (verbatim term: diarrhea). Study medication was not changed. The investigator assessed the event as nonserious, of mild intensity, and possibly related to study medication. The event resolved without sequelae on [redacted]. On [redacted], the subject experienced alanine aminotransferase increased (verbatim term: elevated ALT). Associated symptoms included rash and pruritus. The following procedures/laboratory evaluations were performed: transaminases, alkaline phosphatase and total bilirubi as shown in Table 24. ALT was increased above the ULN at pretherapy/entry and ALT and AST were increased above the normal range on [redacted].

The investigator assessed the event to be nonserious, of mild intensity, and not related to study medication. The event was ongoing at the time of the report. The subject withdrew from the study on 11 February 2002, because he did not wish to continue. He refused to return for followup lab work due to his work schedule. This event was an AESI and was adjudicated as a confirmed safety endpoint by the CEC. Concomitant medication was Zovirax. CEC Adjudication Summary: This case represents clinically overt symptomatic hepatic injury with compatible temporal relationship to study drug. Baseline ALT was elevated at 50. ALT increased to 154 with normal bilirubin. The subject developed diarrhea, rash and pruritus, but refused any

Table 24: Laborarory data for amoxicillin-clavulanic acid-treated subject 0604/004

| Analyte (Units) | Normal Range | Baseline | Date |
|---|---|---|---|
| | | Day 1 x ULN | Day 23 x ULN |
| ALT (L-U) | 6 - 43 | 1.2 | **3.6** |
| ALT (L-U)[a] | 11 - 36 | 1.0 | **1.9** |
| Alkaline Phosphatase (L-U) | 35 -129 | 0.5 | 0.5 |
| Total bilirubin ($\mu$mol/L) | 3-21 | 0.3 | 0.4 |

ULN =upper limit of normal range, L= lower limit of normal range
[a]Local laboratory measurement

follow-up. The increase in transaminases was felt to be possibly related to study drug, but abnormal baseline and scant follow-up limit assessment.

*CEC Adjudication Summary: This case represents clinically overt symptomatic hepatic injury with compatible temporal relationship to study drug. Baseline ALT was elevated at 50. ALT increased to 154 with normal bilirubin. The subject developed diarrhea, rash and pruritus, but refused any follow-up. The increase in transaminases was felt to be possibly related to study drug, but abnormal baseline and scant follow-up limit assessment.*

### A.1.5 Subject 2326/004 (AMC )

A 64-year-old white female was enrolled in the study on 09 Januar 2002 with AECB. The subject completed study treatment on 19 January 2002, but Augmentin was continued from 20 January 2002 for treatment of the primary infection. On — the subject experienced cholestasis (verbatim term: cholestasis/ hypersensitivity RX). Associated symptoms included nausea, pruritus, dark urine and jaundice. Laboratory values for liver-related tests are shown in the table below. Liver-related tests were within the normal range on — pretherapy/entry) and — Visit 2). The subject had been doing well but returned for follow-up on — complaining of dark urine and itching; laboratory results at that time demonstrated elevated transaminases associated with an elevated total bilirubin, alkaline phosphatase, and 6.4% eosinophils. On — laboratory evaluation was again repeated. Transaminases, alkaline phosphatase and total bilirubin had decreased but remained abnormal. Direct bilirubin was also found to be abnormal at this time (1.2 mg/dL (normal range: $0-0.4$ mg/dL). Eosinophils were now normal at 3.0%. Hepatitis A, B and C serology were negative. All results returned to normal by —

The investigator treated the subject with tapering doses of prednisone over 16 days starting at 40 mg daily. The investigator assessed the event to be nonserious, of mild intensity, and possibly related to study medication. He also commented that the event may also have been caused by the subject's longstanding treatment with Zocor. The event resolved without sequelae on — This event was an AESI and was adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Zocor, Miacalcin, Prilosec, Serevent, Flovent, Calcium with vitamin D, Prednisone.

*CEC Adjudication Summary: This was a case of great interest. The subject was symptomatic. Baseline ALT, AST and bilirubin were normal. There was a rise in ALT to 571 and bilirubin to 5.1 mg/dL, with subsequent fall to normal for both. The subject was treated with prednisone. Eosinophils were as high as 6.4%. This event has a probable association to study drug.*

Table 25: Laborarory data for amoxicillin-clavulanic acid-treated subject 2326/004

| Analyte (Units) | Normal Range | Baseline Day 1 x ULN | Date Day 18 x ULN | Date Day 29 x ULN | Date Day 34 x ULN | Date Day 65 x ULN |
|---|---|---|---|---|---|---|
| ALT (L-U) | 6 - 34 | 0.6 | 0.6 | | **11.3** | 1.0 |
| ALT (L-U)[a] | 10 - 60 | | | **9.5** | | |
| ALT (L-U) | 9 - 34 | 0.5 | 0.6 | | **4.8** | 1.1 |
| ALT (L-U)[a] | 10 - 42 | | | **8.3** | | |
| Alkaline Phosphatase (L-U) | 35 -123 | 0.3 | 0.3 | | 1.2 | 0.4 |
| Alkaline Phosphatase (L-U)[a] | 42-121 | | | **1.5** | | |
| Total bilirubin ($\mu$mol/L) | 3 -21 | 0.5 | 0.5 | | **2.1** | 0.4 |
| Total bilirubin ($\mu$mol/L)[a] | 3.4-17 | | | **5.1** | | |
| Eosinophils (%) | 0 - 6.8 | | | 0.9 | 0.4 | 0.6 |
| Absolute eosinophils (GG/L) | 0 - 0.57 | | | | 0.5 | 0.6 |

ULN =upper limit of normal range, L=lower limit of normal range

[a]Local laboratory measurement

[b]Local laboratory values converted from mg/dL using conversion factor of 1 mg/dL = 17 $\mu$mol/L.

---

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

---

/s/
---
George Rochester
3/22/04 10:11:39 AM
BIOMETRICS

David Ross
3/24/04 10:53:55 PM
MEDICAL OFFICER

Mohammad Huque
3/31/04 11:44:03 AM
BIOMETRICS

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

| | |
|---|---|
| **NEW DRUG APPLICATION (NDA):** | NDA 21-144 Amendment |
| **NAME OF DRUG:** | Telithromycin |
| **INDICATION(S):** | CAP, AECB, ABS |
| **APPLICANT:** | Aventis Pharmaceuticals, Inc. |
| **SUBMISSION DATE:** | July 24, 2002 |
| **PRESCRIPTION DRUG USER FEE ACT (PDUFA) DATE:** | January 24, 2003 |
| **DOCUMENTS REVIEWED:** | \\CDSESUB1\N21144\N_000\ (electronic data) |
| **STATISTICAL REVIEWER:** | Thamban Valappil, Ph.D. (HFD-725) |
| **STATISTICAL TEAM LEADER:** | Daphne Lin, Ph.D. (HFD-725) |
| **CLINICAL REVIEWERS:** | John Alexander, M.D. (HFD-520)<br>Alma Davidson, M.D. (HFD-520) |
| **PROJECT MANAGER:** | Judit Milstein (HFD-520) |

# TABLE OF CONTENTS

Page

# LIST OF TABLES

**Page**

# 1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

## 1.1 Conclusions and Recommendations

This review document was focused on the efficacy of KETEK™ (telithromycin) for the indications of Community Acquired Pneumonia (CAP) and Acute Exacerbation of Chronic Bronchitis (AECB) based on the new studies submitted on July 24, 2002. In addition, the efficacy of Telithromycin against infections due to drug-resistant *Streptococcus pneumoniae* isolates (resistant to penicillin G and/or erythromycin A-macrolides) for the treatment of CAP and Acute Bacterial Sinusitis (ABS) were also (based on all the new and old trials submitted) reviewed.

Community Acquired Pneumonia: In study 4003, Telithromycin and Clarithromycin demonstrated equivalence with respect to clinical cure rates in the treatment for CAP. However, the observed cure rates in the MITT population for telithromycin (5-days and 7-days) was low compared to the PP population. The number of subjects in the microbiological population was small to draw any statistically meaningful conclusion. The microbiological cure rates were also not consistent in the bacteriological PP and MITT populations. In the open label study 3012, although the clinical and bacteriological cure rates were similar as those in study 4003, a 6.5% drop in clinical cure rates were observed in the MITT compared to PP population.

Drug-Resistant *Streptococcus pneumoniae*: The efficacy of the treatment for infections due to drug-resistant *Streptococcus pneumonia* was reviewed for the indications of CAP and ABS. There were 7 western trials (3000, 3001, 3006, 3009OL, 3010, 3012 and 4003) and two Japanese trials (3107 and 2105). Overall, there is no substantial evidence available in support of the efficacy of this drug in the treatment of CAP or ABS due to PRSP or ERSP isolates. There were limited numbers of bacteremic patients with relatively low success rates. The collective evidence is substantially low to draw any statistically meaningful conclusion.

Acute Exacerbation of Chronic Bronchitis: There were three studies (3003, 3007 and 3013) submitted in the treatment of patients with acute bacterial exacerbation of chronic bronchitis (AECB) and this review was focused on study of 3013. Results from the other studies were also provided for collective evidence. Based on the data provided, the clinical efficacy of Telithromycin was at least as good as the comparators in patients with mild to moderate AECB infections although the true placebo effect for this drug is unknown.

For the major respiratory pathogens leading to AECB including *S. Pneumoniae*, *H. Influenzae* and *M. Catarrhalis*, the evidence was not substantial to draw any statistically meaningful conclusion.

Overall, the approval of this drug for all the above indications should be based on the collective and corroborative evidence provided on safety and efficacy.

## 1.2 Overview of Clinical Program and Studies Reviewed

The applicant, Aventis Pharmaceuticals Inc. initially submitted NDA 21-144 to the Division on 28 February 2000 for telithromycin drug substance formulated as tablets for the indications Community Acquired Pneumonia(CAP), Acute Exacerbation of Chronic Bronchitis (AECB),

Acute Bacterial Sinusitis (ABS), and tonsillitis/pharyngitis. Additional studies have been submitted for the indications of CAP, AECB in response to the points raised in the FDA Approvable Letter. A Not Approvable Letter was sent on 1 June 2001 for the indication tonsillitis/pharyngitis and

This review is mainly focused on the efficacy of Telithromycin (TEL) for the indications of CAP and AECB based on the submission of July 24, 2002. In addition, the efficacy of Telithromycin against infections due to drug-resistant *Streptococcus pneumoniae* isolates (resistant to penicillin G and/or erythromycin A-macrolides) for the treatment of CAP (based on all the trials submitted) and ABS (based on all the trials submitted) were also reviewed. For the safety, refer to Dr. George Rochester and medical officer's reviews.

## I. Community Acquired Pneumonia (CAP)

The applicant submitted 2 new additional studies 4003 and 3012 in subjects with CAP to provide more efficacy data and the trial designs were as follows:

- Study 4003: Double-blind active-controlled study of the efficacy and safety of oral HMR3647 (800 mg once daily) 5 days versus 7 days versus 10 days of oral clarithromycin (500 mg twice daily) in the treatment of community-acquired pneumonia.
- Study 3012: Open label, multicenter, multinational, uncontrolled, noncomparative study of the efficacy and safety of 7 days of oral telithromycin (HMR3647 800 mg once daily) in the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae* in adolescents and adults.

## II. Infections due to Drug-Resistant *Streptococcus pneumoniae*

### a. Community Acquired Pneumonia (CAP)

The review of the efficacy due to drug resistant *S. pneumoniae* isolates in CAP was performed based on Western and Japanese Trials. The Western trials included all the studies 3000, 3001, 3006, 3009OL, 3010, 3012(new) and 4003(new). The two Japanese studies, 3107 (new) and 2105 were evaluated separately from the Western trials due to various issues as discussed in the corresponding section of the review.

### b. Acute Bacterial Sinusitis (ABS)

In this review of efficacy, *Streptococcus pneumoniae* isolates resistant to penicillin G and/or erythromycin A (macrolides) were analyzed based on the previously submitted studies (studies 3002, 3005 and 3011).

The decision to approve a PRSP or ERSP claim for ABS, would depend upon establishing the clinical efficacy of telithromycin against PRSP and ERSP in a more serious indication (e.g., CAP).

III. Acute Exacerbation of Chronic Bronchitis (AECB)

The applicant submitted a total of three randomized, double-blind, controlled studies (Study 3003, Study 3007, and the new Study 3013) of telithromycin in the treatment of patients with acute bacterial exacerbation of chronic bronchitis (AECB). Studies 3003 and 3007 were submitted during the original submission. The previous submission for *H. influenzae* and *M. catarrhalis* was insufficient due to low numbers of isolates. Study 3013, in subjects with AECB was submitted to provide further efficacy data for *H. influenzae* and *M. catarrhalis* (irrespective of ß–lactamase production by either organism). This review was focused on the recently submitted study 3013 although the results from the other two trials would be provided for corroborative evidence.

Study 3013: This was a comparative study of telithromycin 800 mg once daily for 5 days versus clarithromycin (CLA) 500 mg bid for 10 days in subjects with AECB. This study was conducted to support the overall efficacy of telithromycin for the AECB indication and the clinical activity of telithromycin against *H. influenzae* and *M. catarrhalis* (including ß–lactamse producing strains of both species).

## 1.3 Principal Findings

I. Community Acquired Pneumonia (CAP)

This review was only focused on 2 new additional studies (4003 and 3012) in subjects with CAP to provide additional efficacy data. However, the overall efficacy and safety results based on all CAP trials (including the previous trials) should be evaluated to make the decision of approval of this indication.

Study 4003

Among the Clinical Per Protocol (PPc) patients, the clinical cure rates at the Follow-Up Visit were; Telithromycin 5-day: 89.3% (142/159 subjects); Telithromycin 7-day: 88.8% (143/161 subjects); and Clarithromycin 10-day: 91.8% (134/146 subjects). The 97.5% CI (-10.0, 5.0) for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days) and Telithromycin 800 mg once daily (for 7 days) was marginally equivalent (97.5% CI: -10.5, 4.6) to Clarithromycin 500 mg, using a non-inferiority margin of 10%.

Among the MITT patients, the clinical cure rates at the Follow-Up Visit were; Telithromycin 5-day: 82.4% (154/187 subjects); Telithromycin 7-day: 82.2% (157/191 subjects); and Clarithromycin 10-day: 81.2% (147/181 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was equivalent (97.5% CI for 5-days: -7.9, 10.2; 7-days: -8.5, 10.5) to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.

Bacteriological cure rates at the Follow-Up Visit among evaluable patients (PPb) were; telithromycin 5-day: 87.7% (57/65 subjects); telithromycin 7-day: 80.0% (52/65 subjects); and clarithromycin 10-day: 83.3% (45/54 subjects). The 97.5% CI for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was not equivalent (97.5% CI for 5 days: -11.9, 20.6; 7-days: -20.9, 14.3) to Clarithromycin

500 mg (twice daily for 10 days), using a non-inferiority margin of 10%. Note that the number of subjects were small in each treatment group.

Bacteriological cure rates at the Follow-Up Visit among bacteriological mITT patients were; telithromycin 5-day: 80.2% (89/111 subjects); telithromycin 7-day: 76.4% (94/123 subjects); clarithromycin 10-day: 73.5% (75/102 subjects). The 97.5% CI (-7.2, 20.5) for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent and Telithromycin 800 mg once daily (for 7 days) was not equivalent (97.5% CI: -11.0, 16.8) to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.

Study 3012

In this open label trial, at posttherapy/TOC in the FPc population, the clinical cure rate was 424/473(89.6%, 95%CI: 86.8, 92.4). In the mITT population, the clinical cure rate was 447/538(83.1%, 95%CI: 79.9, 86.3). The clinical cure rate was dropped by 6.5% even though there were 65 more subjects in the mITT population.

The microbiologic cure (eradication) rate at the posttherapy/TOC Visit among the PPb patients was 161/179(89.9%, 95%CI: 85.5, 94.3) and in the bmITT population, microbiological eradication rate was 229/265(86.4%, 95%CI: 82.2, 90.5).

For Streptococcus pneumoniae, the eradication rate at the posttherapy/TOC visit in the PPb population was 96.7% and the eradication rate for Haemophilus influenzae was 90.5%. Similar rates were reported in the MITT population.

II. Infections due to Drug-Resistant *Streptococcus pneumoniae*

The efficacy of the treatment for infections due to drug-resistant *streptococus pneumonia* was reviewed for the indications of CAP and ABS.

a. Community Acquired Pneumoniae

In this review of the efficacy of Infections due to drug-resistant *S. pneumoniae* isolates in CAP was performed based on studies 3000, 3001, 3006, 3009OL, 3010, 3012 and 4003. The two Japanese studies, 3107 (new) and 2105 were evaluated separately for additional evidence.

In the PP population, there were 19 isolates with Penicillin G-resistant S. pneumoniae, of which 16/19 (84.2%, 95% CI: 60.4, 96.6) were clinical cures and in the MITT population, there were 28 isolates with Penicillin G-resistant S. pneumoniae, of which 19/28 (67.9%, 95% CI: 47.6, 84.1) were clinical cures. Similar bacteriological cure rates were observed. The cure rates in the MITT population was considerably low compared to PP population. Based on the sponsor's results, of the nine additional patients in the MITT, 4 of them had a fine score of 3 or greater. The numbers of isolates were too small to draw any statistically meaningful conclusion.

In the PP population, among the 29 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, of which 25/29 (86.2%, 95% CI: 68.3, 96.1) were clinical cures and in the MITT population, of the 37 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, 29/37 (78.4%, 95% CI:61.8, 90.2) were clinical cures.

The cure rates among the subjects with both PRSP and ERSP isolates were; 8/11 (73%) in the PP and 10/16 (62.5%) in the MITT populations.

Among the bacteremic patients due to PRSP, the clinical cure rate was 5/7(71.4%) in the PP population and 5/10 (50%) in the MITT population. For bacteremia due to ERSP, the clinical cure rate was 8/10 in the PP and 8/11 in the MITT populations.

Based on the Japanese studies, subjects with S. pneumoniae isolates resistant to penicillin G and/or erythromycin A, in the PP population among those with PRSP and ERSP, there were 8/8 clinical and bacteriological cures. Among the 21 macrolide- (erythromycin A-) resistant S. pneumoniae, 19/21(90.5%, CI: 69.6, 98.8) were clinical and bacteriological cures. There were no bacteremic patients in this group.

Overall, there is no substantial evidence available in support of the efficacy of this drug in the treatment of CAP due to PRSP or ERSP isolates. There were limited numbers of bacteremic patients with relatively low success rates.

b. Acute Bacterial Sinusitis

In this review of efficacy, *Streptococcus pneumoniae* isolates resistant to penicillin G and/or erythromycin A (macrolides) were analyzed based on the previously submitted studies (studies 3002, 3005 and 3011). All the isolates are pooled together and the results are as follows:

In the bacteriological PP population, there were 13 isolates with Penicillin G-resistant S. pneumoniae, of which 11/13 (84.6%, 95% CI:54.6,98.1) were clinical and bacteriological cures and in the MITT population, there were 16 isolates with Penicillin G-resistant S. pneumoniae, of which 14/16 (87.5%, 95%CI:61.7, 98.4) were clinical and bacteriological cures. The cure rates among the subjects with both PRSP and ERSP isolates in the PP and MITT were 9/11(73%) and 11/13 (85%) respectively.

Among the 21 isolates in the PP population with macrolide- (erythromycin A-) resistant S. pneumoniae, 18/21 (85.7%, 95%CI: 63.7, 97.0), were clinical and microbiological cures. Among the 26 isolates in the MITT population, 21/26 (80.8%, 95% CI:60.6, 93.4) were cures.

Overall, based on the data submitted, there is not enough evidence to support the claim for PRSP or ERSP. Since the applicant has requested for 5-day treatment of sinusitis with telithromycin, there were only 10 patients with PRSP and 14 patients with ERSP. In the PP population, the clinical cure rate was 8/10 (80%) for PRSP and 12/14 (86%) for ERSP. The evidence is substantially low due to smaller number of isolates and it is difficult to draw any statistically meaningful conclusion.

III. Acute Exacerbation of Chronic Bronchitis (AECB)

There were three studies (3003, 3007 and 3013) submitted in the treatment of patients with acute bacterial exacerbation of chronic bronchitis (AECB) and this review was focused on study of 3013 and the results are as follows:

The clinical cure rates in the PPc population at posttherapy/TOC were 193/225 (85.8%) in the telithromycin 5-day group and 206/231(89.2%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-10.0, 3.1) demonstrated that Tel 5-day group was equivalent to the clarithromycin (CLA) 10-day group using a non-inferiority margin of 10%.

The clinical cure rates in the mITT population at posttherapy/TOC were 224/270(83.0%) in the telithromycin 5-day group and 236/282(83.7%) in the clarithromycin 10-day group. The 95% CI for the difference in clinical cure rates (-7.3, 5.9) demonstrated that Tel 5-day group was equivalent to the CLA 10-day group using a non-inferiority margin of 10%. The ITT results were similar and concur with the MITT conclusions.

The bacteriological cure rates in the PPb population at posttherapy/TOC were 59/72(81.9%) in the telithromycin 5-day group and 63/76(82.9%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-14.5, 12.7) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%. Note that the number of subjects in each group is small.

The bacteriological cure rates in the mITT population at posttherapy/TOC were 65/90(72.2%) in the telithromycin 5-day group and 68/88(77.3%) in the clarithromycin 10-day group. The 95% CI for the difference in bacteriological eradication rates (-18.9, 8.8) demonstrated that Tel 5-day group was not equivalent to the CLA 10-day group using a non-inferiority margin of 10%.

In the PPb population at TOC, the eradication rates for Clarithromycin arm was higher than Telithromycin arm for *Haemophilus influenzae:* telithromycin 5-day 77.1% (27/35) and clarithromycin 10-day 83.3% (30/36), *Moraxella catarrhalis:* telithromycin 5-day 89.5% (17/19) and clarithromycin 10-day 94.4% (17/18), and *Streptococcus pneumoniae:* telithromycin 5-day 76.9% (10/13) and clarithromycin 10-day 100% (7/7), although the number of isolates were small.

Comparing all three AECB trials, in the Clinical PP test of cure population, the clinical cure rates were; Study 3003: 86.1% in the Ketek group and 82.1% in the amoxicillin/clavulanic acid 500/125 group with a 95% CI of (-6.4;14.3); Study 3007: 86.4% in the Ketek group and 83.1% in the cefuroxime axetil 500mg group with a 95% CI of (-5.8;12.4); Study 3013: 85.8% in the Ketek group and 89.2% in the clarithromycin 500mg group with a 95% CI of (-10.0;3.1). Based on these results, it can be concluded that the clinical efficacy of Ketek was at least as good as the comparators (amoxicillin/clavulanic acid, cefuroxime axetil, and clarithromycin) given for 10 days in patients with mild to moderate AECB infections, using a non-inferiority margin of 10%.

In the Modified MITT population, the clinical cure rates were; Study 3003: 81.3% in the Ketek group and 78.1% in the amoxicillin/clavulanic acid 500/125 mg group with a 95% CI of (-6.3;12.6); Study 3007: 78.0% in the Ketek group and 72.3% in the cefuroxime axetil 500mg group with a 95% CI of (-3.5;15.1); Study 3013: 83.0% in the Ketek group and 83.7% in the clarithromycin 500mg group with a 95% CI of (-7.3;5.9). Based on these results, it can be concluded that Ketek was equivalent to its comparators (amoxicillin /clavulanic acid, cefuroxime axetil,and clarithromycin), using a non-inferiority margin of 10%.

The clinical efficacy of Telithromycin was at least as good as the comparators (amoxicillin /clavulanic acid, cefuroxime axetil, and clarithromycin) in patients with mild to moderate AECB infections. However, for the major respiratory pathogens leading to AECB including S.

*Pneumonia*, H. *Influenzae* and M. *Catarrhalis,* the evidence was not strong enough to make any statistically meaningful conclusion.

Overall, the approval of this drug should depend upon the evidence provided on Safety and efficacy. However, this review is only focused in detail on the efficacy of the treatment based on study 3013. For a detailed safety review, refer to reviews from Dr. George Rochester and other medical officers.

## 2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 2.1 Introduction and Background

The applicant, Aventis Pharmaceuticals Inc. initially submitted NDA 21-144 to the Division on 28 February 2000 for telithromycin drug substance formulated as tablets for the indications of Community Acquired Pneumonia(CAP), Acute Exacerbation of Chronic Bronchitis (AECB), Acute Bacterial Sinusitis (ABS), and tonsillitis/pharyngitis. Additional studies have been submitted for the indications of CAP and AECB in response to the points raised in the FDA Approvable Letter. A Not Approvable Letter was sent on 1 June 2001 for the indication tonsillitis/pharyngitis

This review focused on the efficacy for the indications of CAP (new studies 4003, 3012), AECB (new study 3013) and also on the overall efficacy due to drug-resistant *S. pneumoniae* isolates (penicillin G and/or erythromycin A) in CAP (studies 3000, 3001, 3006, 3009OL, 3010, 3012 and 4003) and ABS (studies 3002, 3005, 3011). Two Japanese studies, 3107 (new) and 2105 were separately evaluated for efficacy due to *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A (macrolides) in CAP.

### 2.2 Data Analyzed and Sources

The data was electronically submitted and available at \\CDSESUB1\N21144\N_000. The datasets for the recently submitted trials for CAP and AECB are available in the folder dated July 24, 2002 and the remaining datasets are available in the earlier submissions (years 2000-2001)

#### 2.2.1 Community Acquired Pneumonia (CAP)

Under this section, the review was only focused on 2 new additional studies (4003 and 3012) in subjects with CAP to provide further efficacy data. However, the decision to approve this drug would depend upon the overall efficacy and safety for all the CAP trials (including the previous trials).

### 2.2.2 Infections due to Drug-Resistant Streptococcus pneumoniae

This review for the drug-resistant *Streptococcus pneumoniae* was performed for the indications of Community Acquired Pneumoniae (CAP) and Acute Bacterial Sinusitis (ABS), although the decision to approve for PRSP or ERSP claim for ABS will depend upon the evidence provided for the CAP indication.

#### 2.2.2.1 Community Acquired Pneumonia (CAP)

In this review of the efficacy due to drug-resistant *S. pneumoniae* isolates in CAP was performed based on Western and Japanese Trials. The Western trials included all the studies 3000, 3001, 3006, 3009OL, 3010, 3012(new) and 4003 (new). The two Japanese studies, 3107 (new) and 2105 were evaluated separately from the Western trials due to various issues as discussed in the corresponding section of the review.

#### 2.2.2.2 Bacterial Sinusitis (ABS)

In this review of efficacy, *Streptococcus pneumoniae* isolates resistant to penicillin G and/or erythromycin A (macrolides) were analyzed based on the previously submitted studies (studies 3002, 3005 and 3011).

### 2.2.3 Acute Exacerbation of Chronic Bronchitis (AECB)

The applicant submitted a total of three randomized, double-blind, controlled studies (Studies 3003, 3007 and 3013) of telithromycin in the treatment of patients with acute bacterial exacerbation of chronic bronchitis (AECB). This review was mainly focused on study 3013 although the results from the other two trials would be provided for corroborative evidence.

## 2.3 Statistical Evaluation of Evidence on Efficacy/Safety

### 2.3.1 Community Acquired Pneumonia

#### 2.3.1.1 Study 4003

**Design and Objectives**

This study was a multicenter, double-blinded, active-controlled, three-arm parallel-group (1:1:1) comparative study of telithromycin (800 mg given once daily) for 5 days versus 7 days versus 10 days of oral clarithromycin (500 mg given twice daily).

There were five visits: a pretherapy/entry visit (day 1), an on-therapy visit (days 3 to 5), an end-of-therapy visit (days 11 to 13), a posttherapy/test of cure (TOC) visit (days 17 to 21) and a late posttherapy visit (days 31 to 36).

Population: Adult subjects with clinical findings and chest x-ray findings compatible with a diagnosis of CAP, presumably due to common or atypical and intracellular bacterial pathogens.

Primary objective:

To demonstrate equivalence in clinical efficacy at the posttherapy/test of cure (TOC) visit and assess the safety of 5 days and 7 days of oral telithromycin (800 mg given once daily) and 10 days of oral clarithromycin (500 mg given twice daily) for treating CAP due to common or atypical and intracellular pathogens in adults.

Secondary objective:

To compare bacteriological efficacy of 5 days and 7 days of oral telithromycin and 10 days of oral clarithromycin for treating CAP due to common or atypical and intracellular pathogens in adults.

Clinical outcome:

The primary efficacy analysis variable for this study was the clinical outcome at the TOC visit analyzed on days 17 to 24. The clinical outcome at TOC (days 17 to 24) was evaluated by the investigator based on the following definitions:

Cure:

- Return to preinfection state: all pneumonia-related signs and symptoms had disappeared or had returned to the preinfection state and chest x-ray findings showed improvement.

OR

- Improved or postinfectious stigmata: residual symptoms that did not warrant any treatment and that represented the normal clearance of the inflammatory process; residual mild pneumonia-related signs and symptoms, residual signs and symptoms related to underlying condition/disease and not related to pneumonia, chest x-ray findings showed improvement or lack of progression, and no subsequent antibiotic therapy was started for treatment of the disease under investigation.

Failure:

- All pneumonia-related signs and symptoms had remained unchanged or had worsened and/or chest x-ray findings had worsened.

OR

- One or more antibiotics or subsequent treatment was added to the study treatment for the pneumonia due to lack of clinical improvement.

OR

- The subject developed new clinical findings consistent with active infection.

OR

- The subject died due to the infectious disease.

OR

- A new antibiotic treatment was started up to the end of day 21 for the treatment of CAP, bronchitis, any other lower RTI or an infection at another relevant site that could have indicated a complication of CAP (e.g., meningitis, sepsis).

OR

- An adverse event other than CAP, bronchitis, any other lower RTI or an infection at another relevant site that could have indicated a complication of CAP (e.g., meningitis, sepsis) occurred on therapy, leading to discontinuation of study drug, and a subsequent antibiotic was started for treatment of pneumonia because the investigator considered the improvement insufficient.

Bacteriological outcome:

At the TOC, the bacteriological outcome was determined for each pathogen found to be responsible for infection (i.e., causative) at pretherapy/entry.

According to the sponsor, there were a total of 581 subjects were enrolled and 575 subjects were randomized to one of the three treatment groups. The primary reason for enrolled subjects not being randomized was lack of chest x-ray findings consistent with CAP. All of the 575 randomized subjects received at least one dose of study medication as follows: telithromycin 5-day group: 193 subjects, telithromycin 7-day group: 195 subjects, and clarithromycin 10-day group: 187 subjects. The total number of subjects evaluable for each analysis population is provided in the table below.

Table 1: Disposition of Patients by Treatment

| Population | TEL 5-day | TEL 7-day | CLA 10-day |
|---|---|---|---|
| Total treated | 193 | 195 | 187 |
| Safety | 193 | 195 | 187 |
| mITT | 187 | 191 | 181 |
| PPc | 159 | 161 | 146 |
| bmITT | 111 | 123 | 102 |
| PPb | 65 | 65 | 54 |

**Sponsor's Table:**
PPc=All mITT subjects excluding those with major protocol violations
PPb=All PPc subjects with bacteriologically proven infection
bmITT=All mITT subjects containing at least one pathogen responsible for infection

## Statistical Reviewer's Comments

*Testing the equivalence of treatment differences with respect to the efficacy variables were assessed based on a two-tailed 97.5% confidence interval of the difference in clinical and microbiological cure rates adjusting for multiplicity. The primary efficacy analysis would be evaluated using a non-inferiority margin (delta) of 10%. The robustness of the primary efficacy analysis will be assessed using the Evaluable and the ITT and/or the MITT populations.*

## Demographics and Baseline Characteristics

Demographic information for mITT patients according to treatment group is presented below.

Table 2: Demographics and pretherapy/entry characteristics – mITT population

| | Number of subjects (%) | | |
|---|---|---|---|
| **Characteristic** | **TEL 5-day** | **TEL 7-day** | **CLA 10-day** |
| Total treated | 187 | 191 | 181 |
| Sex | | | |
| Male N (%) | 118 (63.1) | 102 (53.4) | 94 (51.9) |
| Female N (%) | 69 (36.9) | 89 (46.6) | 87 (48.1) |
| Age (years) | | | |
| Median (range) years | 43 (18-79) | 42 (19-87) | 41 (15-88) |
| <65 years N (%) | 157 (84.0) | 162 (84.8) | 144 (79.6) |
| ≥65 years N (%) | 30 (16.0) | 29 (15.2) | 37 (20.4) |
| BMI ($kg/m^2$) N | 187 | 190 | 179 |
| Mean ± SD | 26.2 ± 6.9 | 25.1 ± 5.7 | 25.3 ± 6.0 |
| Weight (kg) N | 187 | 190 | 179 |
| Mean ± SD | 75.6 ±21.5 | 70.6 ± 17.6 | 71.1 ± 19.1 |
| Race | | | |
| White N (%) | 134 (71.7) | 130 (68.1) | 122 (67.4) |
| Black N (%) | 34 (18.2) | 42 (22.0) | 47 (26.0) |
| Asian/Oriental N (%) | 5(2.7) | 1(0.5) | 3(1.7) |
| Multiracial N (%) | 14 (7.5) | 17 (8.9) | 8 (4.4) |
| Other N (%) | 0 (0.0) | 1 (0.5) | 1 (0.6) |

**Sponsor's Table**

## Statistical Reviewer's Comments:

*Based on the demographic information in Table 2, there were no significant differences among the treatment groups in gender, race, age and weight in the MITT patients. In each treatment group (Tel-5, Tel-7 and CLA), there were 63.1%, 53.4%, 51.9% of the patients were males and 36.9%, 46.6% and 48.1% were females. Overall, 69% of the patients were White and 22% were Black.*

## Efficacy and Safety Results

Clinical and Microbiological Responses

Table 3: Clinical Response at the Follow-Up Visit (PP-Clinical Population)

| Clinical Response | TEL 5-day n/N (%) | | TEL 7-day n/N (%) | | CLA 10-day n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 142/159 | (89.3%) | 143/161 | (88.8%) | 134/146 | (91.8%) |
| Failure | 17/159 | (10.7%) | 18/161 | (11.2%) | 12/146 | (8.2%) |

| Comparison of Cure Rates | 97.5% CI for Difference in Cure Rate[a] |
|---|---|
| TEL 5-day vs Clarithromycin 10-day | [-10.0, 5.0] |
| TEL 7-day vs Clarithromycin 10-day | [-10.5, 4.6] |

n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] The 97.5% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

*Clinical cure rates at the Follow-Up Visit among evaluable patients (PPc) were; Telithromycin 5-day: 89.3% (142/159 subjects); Telithromycin 7-day: 88.8% (143/161 subjects); and Clarithromycin 10-day: 91.8% (134/146 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days) and Telithromycin 800 mg once daily (for 7 days) was marginally equivalent to Clarithromycin 500 mg, using a non-inferiority margin of 10%.*

Table 4: Clinical Response at the Follow-Up Visit (MITT-Clinical Population)

| Clinical Response | TEL 5-day n/N (%) | | TEL 7-day n/N (%) | | CLA 10-day n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 154/187 | (82.4%) | 157/191 | (82.2%) | 147/181 | (81.2%) |
| Failure | 33/187 | (17.6%) | 34/191 | (17.8%) | 34/181 | (18.9%) |

| Comparison of Cure Rates | 97.5% CI for Difference in Cure Rate[a] |
|---|---|
| TEL 5-day vs Clarithromycin 10-day | [-7.9, 10.2] |
| TEL 7-day vs Clarithromycin 10-day | [-8.5, 10.5] |

n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] The 97.5% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

*Clinical cure rates at the Follow-Up Visit among Clinical MITT patients (MITTc) were;*

*Telithromycin 5-day: 82.4% (154/187 subjects); Telithromycin 7-day: 82.2% (157/191 subjects); and Clarithromycin 10-day: 81.2% (147/181 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.*

Table 5: Clinical Response at the Follow-Up Visit (ITT-Clinical Population)

| Clinical Response | TEL 5-day n/N (%) | | TEL 7-day n/N (%) | | CLA 10-day n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 154/193 | (79.8%) | 157/195 | (80.5%) | 147/187 | (78.6%) |
| Failure | 39/193 | (20.2%) | 38/195 | (19.5%) | 40/187 | (21.4%) |

| Comparison of Cure Rates | 97.5% CI for Difference in Cure Rate[a] |
|---|---|
| TEL 5-day vs Clarithromycin 10-day | [-8.2, 10.5] |
| TEL 7-day vs Clarithromycin 10-day | [-7.3, 11.2] |

n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] The 97.5% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

*Clinical cure rates at the Follow-Up Visit among ITT patients were; Telithromycin 5-day: 79.8% (154/193 subjects); Telithromycin 7-day: 80.5% (157/195 subjects); and Clarithromycin 10-day: 78.6% (147/187 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.*

APPEARS THIS WAY
ON ORIGINAL

Table 6: Bacteriological Response at the Follow-Up Visit (PP-Bacteriological Population)

| Bacteriological Response | TEL 5-day n/N (%) | | TEL 7-day n/N (%) | | CLA 10-day n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 57/65 | (87.7%) | 52/65 | (80.0%) | 45/54 | (83.3%) |
| Failure | 8/65 | (12.3%) | 13/65 | (20.0%) | 9/54 | (16.7%) |

| Comparison of Cure Rates | 97.5% CI for Difference in Cure Rate[a] |
|---|---|
| TEL 5-day vs Clarithromycin 10-day | [-11.9, 20.6] |
| TEL 7-day vs Clarithromycin 10-day | [-20.9, 14.3] |

n/N = number of evaluable patients with bacteriological response/total number of evaluable patients

[a] The 97.5% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

*Bacteriological cure rates at the Follow-Up Visit among evaluable patients (PPb) were; telithromycin 5-day: 87.7% (57/65 subjects); telithromycin 7-day: 80.0% (52/65 subjects); and clarithromycin 10-day: 83.3% (45/54 subjects). The 97.5% CI for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was not equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%. Note that the number of subjects were small in each treatment group.*

Table 7: Bacteriological Response at the Follow-Up Visit(Bact-MITT Population)

| Bacteriological Response | TEL 5-day n/N (%) | | TEL 7-day n/N (%) | | CLA 10-day n/N (%) | |
|---|---|---|---|---|---|---|
| Cure | 89/111 | (80.2%) | 94/123 | (76.4%) | 75/102 | (73.5%) |
| Failure | 22/111 | (19.8%) | 29/123 | (23.6%) | 27/102 | (26.5%) |

| Comparison of Cure Rates | 97.5% CI for Difference in Cure Rate[a] |
|---|---|
| TEL 5-day vs Clarithromycin 10-day | [ -7.2, 20.5 ] |
| TEL 7-day vs Clarithromycin 10-day | [-11.0, 16.8] |

n/N = number of evaluable patients with bacteriological response/total number of evaluable patients

[a] The 97.5% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

Statistical Reviewer's Comments:

*Bacteriological cure rates at the Follow-Up Visit among bacteriological mITT patients were; telithromycin 5-day: 80.2% (89/111 subjects); telithromycin 7-day: 76.4% (94/123 subjects); clarithromycin 10-day: 73.5% (75/102 subjects). The 97.5% CI for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent and Telithromycin 800 mg once daily (for 7 days) was not equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.*

Table 8: Eradication rates for the main causative pathogens at posttherapy/TOC – PPb and bmITT populations

| Pathogen [a] | Pathogens eradicated/Total pathogens (eradication rate [b]%) TEL 5-day | | TEL 7-day | | CLA 10-day | |
|---|---|---|---|---|---|---|
| **PPb population** | | | | | | |
| **Total pathogens** | 82 | | 95 | | 77 | |
| All pathogens-posttherapy/TOC | 74/82 | (90.2%) | 83/95 | (87.4%) | 67/77 | (87.0%) |
| *S. pneumoniae* | 23/24 | (95.8%) | 29/30 | (96.7%) | 23/26 | (88.5%) |
| *H. influenzae* | 22/25 | (88.0%) | 21/25 | (84.0%) | 15/17 | (88.2%) |
| *M. catarrhalis* | 1/1 | (100%) | 4/5 | (80.0%) | 3/4 | (75.0%) |
| *S. aureus* | 5/5 | (100%) | 4/5 | (80.0%) | 3/3 | (100%) |
| **bmITT population** | | | | | | |
| **Total pathogens** | 139 | | 165 | | 142 | |
| **Evaluable pathogens** *c* | 127 | | 146 | | 130 | |
| All pathogens-posttherapy/TOC | 111/127 | (87.4%) | 130/146 | (89.0%) | 111/130 | (85.4%) |
| *S. pneumoniae* | 31/33 | (93.9%) | 35/37 | (94.6%) | 31/35 | (88.6%) |
| *H. influenzae* | 32/37 | (86.5%) | 34/39 | (87.2%) | 25/29 | (86.2%) |
| *M. catarrhalis* | 1/1 | (100%) | 6/7 | (85.7%) | 5/7 | (71.4%) |
| *S. aureus* | 9/10 | (90.0%) | 8/9 | (88.9%) | 9/9 | (100%) |

[a] Single and multiple pathogen infections
[b] Eradication includes both documented and presumed eradication
[c] Denominators based on pathogens from posttherapy/TOC evaluable subjects in bmITT population (i.e., excludes subjects with indeterminate bacteriological outcome).
**Sponsor's Table**

**Statistical Reviewer's Comments:**

*Based on the above table, the Eradication rates at the posttherapy/TOC visit for Streptococcus pneumoniae and Haemophilus influenzae were comparable across the 3 treatment groups in PPb population. In the PPb population the eradication rates for Streptococcus pneumoniae were; telithromycin 5-day: 95.8%, telithromycin 7-day: 96.7%, and clarithromycin 10-day: 88.5%. The eradication rates for Haemophilus influenzae in the PPb population were; telithromycin 5-day: 88.0%, telithromycin 7-day: 84.0%, and clarithromycin 10-day: 88.2%. In the mITT population the eradication rates*

*for Streptococcus pneumoniae were; telithromycin 5-day: 93.9%, telithromycin 7-day: 94.6%, and clarithromycin 10-day: 88.6%. The eradication rates for Haemophilus influenzae in the mITT population were; telithromycin 5-day: 86.5%, telithromycin 7-day: 87.2%, and clarithromycin 10-day: 86.2%.*

## SAFETY

Table 9: All TEAEs in ≥2% of subjects

| Adverse event | Number of subjects (%) | | | | | |
|---|---|---|---|---|---|---|
| | TEL 5-day | | TEL 7-day | | CLA | |
| Total subjects in safety population | 193 | | 195 | | 187 | |
| Total subjects with TEAEs | 83 | (43.0) | 90 | (46.2) | 84 | (44.9) |
| Diarrhea NOS | 12 | (6.2) | 15 | (7.7) | 10 | (5.3) |
| Headache NOS | 13 | (6.7) | 13 | (6.7) | 5 | (2.7) |
| Nausea | 8 | (4.1) | 7 | (3.6) | 5 | (2.7) |
| Abdominal pain NOS | 6 | (3.1) | 2 | (1.0) | 3 | (1.6) |
| Flatulence | 4 | (2.1) | 2 | (1.0) | 0 | (0.0) |
| Pharyngolaryngeal pain | 2 | (1.0) | 4 | (2.1) | 1 | (0.5) |
| Dysgeusia | 4 | (2.1) | 1 | (0.5) | 8 | (4.3) |
| Herpes simplex | 3 | (1.6) | 1 | (0.5) | 6 | (3.2) |
| Pneumonia aggravated | 1 | (0.5) | 0 | (0.0) | 4 | (2.1) |
| Alanine aminotransferase increased | 4 | (2.1) | 2 | (1.0) | 3 | (1.6) |
| Aspartate aminotransferase increased | 2 | (1.0) | 2 | (1.0) | 4 | (2.1) |
| Fatigue | 4 | (2.1) | 1 | (0.5) | 1 | (0.5) |
| Chest pain | 2 | (1.0) | 4 | (2.1) | 2 | (1.1 |

Sponsor's Table

### Statistical Reviewer's Comments:

*According to the sponsor, Treatment-emergent adverse events (TEAEs, those reported in ≥2% of subjects) were reported in a total of 257 subjects (44.7%) and among these subjects who experienced at least one TEAE, the occurrence rates by treatment group were; telithromycin 5-day: 43.0% (83/193 subjects), telithromycin 7-day: 46.2% (90/195 subjects), clarithromycin 10-day: 44.9% (84/187 subjects). A detailed safety review can be found in the Medical Officer's review.*

### Conclusions and Recommendations

Among the PPc patients, the clinical cure rates at the Follow-Up Visit were; Telithromycin 5-day: 89.3% (142/159 subjects); Telithromycin 7-day: 88.8% (143/161

subjects); and Clarithromycin 10-day: 91.8% (134/146 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days) and Telithromycin 800 mg once daily (for 7 days) was marginally equivalent to Clarithromycin 500 mg, using a non-inferiority margin of 10%.

Among the MITT patients, the clinical cure rates at the Follow-Up Visit were; Telithromycin 5-day: 82.4% (154/187 subjects); Telithromycin 7-day: 82.2% (157/191 subjects); and Clarithromycin 10-day: 81.2% (147/181 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.

Among the ITT patients, clinical cure rates at the Follow-Up Visit were; Telithromycin 5-day: 79.8% (154/193 subjects); Telithromycin 7-day: 80.5% (157/195 subjects); and Clarithromycin 10-day: 78.6% (147/187 subjects). The 97.5% CI for the difference in clinical cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.

Bacteriological cure rates at the Follow-Up Visit among evaluable patients (PPb) were; telithromycin 5-day: 87.7% (57/65 subjects); telithromycin 7-day: 80.0% (52/65 subjects); and clarithromycin 10-day: 83.3% (45/54 subjects). The 97.5% CI for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days and 7 days) was not equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%. Note that the number of subjects were small in each treatment group.

Bacteriological cure rates at the Follow-Up Visit among bacteriological mITT patients were; telithromycin 5-day: 80.2% (89/111 subjects); telithromycin 7-day: 76.4% (94/123 subjects); clarithromycin 10-day: 73.5% (75/102 subjects). The 97.5% CI for the difference in microbiological cure rates demonstrated that Telithromycin 800 mg once daily (for 5 days) was equivalent and Telithromycin 800 mg once daily (for 7 days) was not equivalent to Clarithromycin 500 mg (twice daily for 10 days), using a non-inferiority margin of 10%.

### 2.3.1.2 Study 3012

**Design and Objectives**

Primary objective:

The primary objective of this open-label study was to evaluate the clinical and bacteriological efficacy of 7 days of oral telithromycin in the treatment of CAP due to penicillin G- and/or erythromycin A- (macrolide-) resistant *S. pneumoniae* in adolescents and adults (enrollment of subjects in France and Korea was limited to adults ≥18 years).

Secondary objective:

The secondary objective of this study was to evaluate the clinical and bacteriologic efficacy of 7 days of oral telithromycin in the treatment of CAP due to both susceptible and penicillin- or erythromycin- (macrolide-) resistant strains of *S. pneumoniae* in adolescents and adults (enrollment of subjects in France and Korea was limited to adults ≥18 years by amendments 1 and 5). An additional secondary objective of the study was to evaluate the clinical and bacteriological efficacy and safety of 7 days of oral telithromycin in the treatment of CAP in all adolescents and adults (enrollment of subjects in France and Korea was limited to adults ≥18 years by amendments 1 and 5).

In this study, subjects were enrolled at a total of 68 investigational sites from Argentina (9 sites), France (9 sites), Mexico (3 sites), South Africa (17 sites), Spain (4 sites), and the US (26 sites).

At the pretherapy/entry visit (day 1), subjects were enrolled and treated with telithromycin 800-mg orally once daily for 7 days. An on-therapy visit was to be performed at days 3 to 5. Subjects were to complete further visits at end-of-therapy (days 8 to 10) and posttherapy/test of cure (TOC) (days 17 to 21).

Based on the sponsor's description, all subjects in the study were dispensed telithromycin and were instructed to take 800 mg (400 mg tablets x 2) once daily for 7 days. However, in subjects with a history of severe renal impairment 30 mL/min [ 0.5 mL/sec]), the dose should be halved to 400 mg once daily for 7 days. In hemodialysis subjects, telithromycin tablets were to be taken after the dialysis session on dialysis days. Telithromycin was to be taken orally without specific regard to timing around meals. The first dose of telithromycin 800 mg was to be, if possible, taken by the subject while at the study site for the pretherapy/entry visit.

**Statistical Reviewer's Comments:**

*In this open label trial, the clinical cure rates and the bacteriological eradication rates for the PPb and bmITT population at posttherapy/TOC (days 17-24) in subjects with CAP due to penicillin G- or erythromycin A- (macrolide-) resistant strains of S. pneumoniae will be evaluated.*

Table 10: Number of subjects in each analysis population

| Population | TEL 7-day |
|---|---|
| Total treated | 550 |
| Safety | 550 |
| mITT | 538 |
| PPc | 473 |
| bmITT | 265 |
| PPb | 179 |

**Demographics and Baseline Characteristics**

Table 11: Demographics and pretherapy/entry characteristics – mITT population

| Characteristic | Number of subjects (%) TEL 7-day |
|---|---|
| Total mITT subjects | 538 |
| Sex | |
| Male | 291 (54.1) |
| Female | 247 (45.9) |
| Age (years) | |
| Median (range) years | 42.5 (13 to 90) |
| <65 years | 460 (85.5) |
| ≥65 years | 78 (14.5) |
| Body Mass Index (BMI) (kg/m$^2$) | |
| Mean ± SD | 25.4 ± 6.4 |
| Weight (kg) | |
| Mean ± SD | 71.1 ± 20.1 |
| Race | |
| White | 311 (57.8) |
| Black | 176 (32.7) |
| Asian/Oriental | 4 (0.7) |
| Multiracial | 47 (8.7) |

Sponsor's Table

**Statistical Reviewer's Comments:**

*Based on the sponsor's table, demographic and pre-therapy/entry characteristics of the mITT population, there were more males (54%) than the females (46%). Median age of the study population was 43 years and ranged from 13 to 90 years. There were 58% whites and 33% blacks in the study population.*

APPEARS THIS WAY ON ORIGINAL

**Efficacy and Safety Results**

Table 12: Clinical Response at the TOC (PPc Population)

| Clinical Response | TEL 7-day n/N (%) | 95% CI [a] |
|---|---|---|
| Cure | 424/473 (89.6) | (86.8, 92.4) |
| Failure | 49/473 (10.4) | |

n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] Two-sided 95% CI.

Table 13: Clinical Response at the TOC(mITT Population)

| Clinical Response | TEL 7-day n/N (%) | 95% CI [a] |
|---|---|---|
| Cure | 447/538 (83.1) | (79.9, 86.3) |
| Failure | 91/538 (16.9) | |

[a] Two-sided 95% CI.

**Statistical Reviewer's Comments:**

*In the PPc population, clinical outcome at posttherapy/TOC showed a cure rate of 89.6% (424/473 subjects) with a two-sided 95% confidence interval CI of (86.8, 92.4). In the mITT population, the clinical cure rate was 83.1% (447/538 subjects with a 95% CI of (79.9, 86.3). There is a 6.5% drop in clinical cure rate in the mITT compared to PPc even though there were 65 more subjects in the mITT.*

| Table 14: Bacteriological Response at the TOC | | |
|---|---|---|
| Bacteriological Response | TEL 7-day n/N (%) | 95% CI [a] |
| PPb Population | | |
| Eradication [2] | 161/179 (89.9) | (85.5, 94.3) |
| Failure [3] | 18/179 (10.1) | |
| bMITT Population | | |
| Eradication [2] | 229/265 (86.4) | (82.2, 90.5) |
| Failure [3] | 36/265 (13.6) | |

1 Two-sided 95% CI.
2 Includes eradication, presumed eradication, colonization.
3 Includes reinfection, superinfection, recurrence, presumed persistence and persistence.

**Statistical Reviewer's Comments:**

*The microbiologic cure (eradication) rates at the posttherapy/TOC Visit among the PPb patients were 89.9% (161/179 subjects) and in the bmITT population, microbiological eradication rate was 86.4% (229/265 subjects).*

| Table 15: Eradication rates for the main causative pathogens at posttherapy/TOC – PPb and bmITT populations | |
|---|---|
| | **Pathogens eradicated/Total pathogens (eradication rate [b] %)** |
| **Pathogen [a]** | **TEL 7-day** |
| **PPb population** | 212 |
| **Total pathogens** | |
| All pathogens-posttherapy/TOC | 194/212 (91.5%) |
| *S. pneumoniae* | 87/90 (96.7%) |
| *H. influenzae* | 67/74 (90.5%) |
| *M. catarrhalis* | 12/14 (85.7%) |
| *S. aureus* | 13/15 (86.7%) |
| **bmITT population** | |
| **Total pathogens** | 315 |
| **Evaluable pathogens** *c* | 294 |
| All pathogens posttherapy/TOC | 272/294 (92.5%) |
| *S. pneumoniae* | 99/103 (96.1%) |
| *H. influenzae* | 97/106 (91.5%) |
| *M. catarrhalis* | 19/21 (90.5%) |
| *S. aureus* | 22/24 (91.7%) |

[a] Single and multiple pathogen infections
[b] Eradication includes both documented and presumed eradication
[c] Denominators based on pathogens from posttherapy/TOC evaluable subjects in bmITT population (i.e., excludes subjects with indeterminate bacteriological outcome).
Sponsor's Table

**Statistical Reviewer's Comments:**

*Based on the table above, for Streptococcus pneumoniae, the eradication rate at the posttherapy/TOC visit in the PPb population was 96.7% and the eradication rate for Haemophilus influenzae was 90.5%. Similar rates were reported in the bMITT population.*

## SAFETY

Table 16: TEAEs possibly related to study medication in ≥2% of subjects

| Adverse event | Number of subjects (%) TEL 7-day | |
|---|---|---|
| Total subjects in safety population | 550 | |
| Total subjects with TEAEs | 159 | (28.9) |
| Diarrhea NOS | 18 | (3.3) |
| Nausea | 16 | (2.9) |

Sponsor's Table

**Statistical Reviewer's Comments:**

*Among the 159 subjects experienced TEAEs, a total of 18 subjects (3.3%) experienced diarrhea and 16 subjects (2.9%) experienced nausia. More details on safety can be obtained from Medical Officer's review.*

According to the sponsor, there were a total of 5 subjects who experienced an adverse event leading to death during this study. One of the 5 subjects had concurrent AIDS-related complex and experienced worsening of pneumonia that led to death on day 17 during the posttreatment period. The events leading to death during the on-treatment period were sepsis on day 1, worsening cardiac failure on day 3 (subject with chronic obstructive pulmonary disease, heart failure, and cor pulmonale; was in heart failure on day 1 and was given furosemide, heart failure worsened on day 3), worsening pneumonia on day 8 (subject was HIV seropositive), and lobar pneumonia on day 12 (subject with immunocompromised state and oral thrush).

Based on the sponsor's safety summary, there were 2 subjects who experienced TEAEs of blurred vision. Both events were assessed as mild in intensity and possibly related to study medication. Please refer to the safety review for more information.

**Conclusions and Recommendations**

In this open label trial, clinical outcome at posttherapy/TOC in the PPc population showed a cure rate of 89.6% (424/473 subjects) with a two-sided 95% confidence interval CI of (86.8, 92.4). In the mITT population, the clinical cure rate was 83.1% (447/538 subjects with a 95% CI of (79.9, 86.3). A 6.5% drop in clinical cure rate can be observed in the mITT population compared to PPc even though there were 65 more subjects.

The microbiologic cure (eradication) rates at the posttherapy/TOC Visit among the PPb patients were 89.9% (161/179 subjects) and in the bmITT population, microbiological eradication rate was 86.4% (229/265 subjects).

For Streptococcus pneumoniae, the eradication rate at the posttherapy/TOC visit in the PPb population was 96.7% and the eradication rate for Haemophilus influenzae was 90.5%. Similar rates were reported in the bMITT population.

### 2.3.2 Infections due to Drug-Resistant *Streptococcus pneumoniae* (FDA Analyses)

#### 2.3.2.1 Community Acquired Pneumonia

In this review, the efficacy of infections due to drug resistant *S. pneumoniae* isolates in CAP was performed based on Western and Japanese Trials. Clinical and bacteriological outcome data assessed at the TOC were used in the analyses.

There were a total of 9 studies submitted (western and Japanese included) for CAP for drug-resistant *S. pneumoniae*. Of which, four studies were submitted in the initial NDA including studies 3000, 3001, 3006 and 3009OL (this study was submitted in the 4-month safety update). Study 3010 was submitted as an Amendment-1 and three additional new studies, two performed in Western countries (studies 3012 and 4003) and one performed in Japan (Study 3107). A previously submitted Japanese study 2105 was also included in the review data.

Studies 3000, 3009OL, 3010 and 3012 were open label trials and studies 3001 and 3006, 4003 and 3107 were double-blind, randomized, active control trials. Study 2105 was a double-blind, randomized, 2-arm parallel group trial comparing 600mg and 800mg of Telithromycin.

**Statistical Reviewers Comments:**

*The overall efficacy due to S. pneumoniae isolates resistant to penicillin G and/or erythromycin A (macrolides) in CAP were assessed based on data from Western and Japanese studies. Japanese data would be evaluated separately for evidence without combining with the western trials. Combining the results is not appropriate since the two populations are different.*

Japanese Study (3107)

This was a randomized, double-blind study performed in Japan, comparing the efficacy and safety of 600 mg once daily of telithromycin to 100 mg tid of levofloxacin both administered for 7 days.

The design of this study is different from those of Western studies.

- The 600 mg qd dose for telithromycin was used. According to the sponsor, the drug levels obtained with this dose in respiratory tissue in Japanese subjects (evaluated in a previous study) did not show a major difference with data obtained in Western subjects with an 800 mg dose.
- The main endpoint analysis was performed at the end of treatment (7 days) to comply with Japanese guidelines for evaluating the efficacy of anti-infective agents. A second endpoint was an evaluation 7 days after the end of treatment, corresponding to a time window of 14 to 28 days after commencing treatment, which approximated the time window used for TOC evaluation in Western studies (Days 17 to 24).
- Difference in the inclusion/exclusion criteria. In Western protocols, subjects requiring intravenous treatment according to American Thoracic Society or British Thoracic Society

criteria were excluded, whereas in Study 3107 subjects were only to be included if three of the following four symptoms were present: body temperature <38.6°C [101.2°F]; elevated total peripheral white blood cell count <20,000/mm$^3$; chest X-ray score <6 points; C-reactive protein <20 mg/dL.

In this study, the minimum inhibitory concentrations (MICs) were determined at a central laboratory in Japan for the clinical study report according to NCCLS criteria for *S. pneumoniae* (Mitsubishi Kagaku Bio-Clinical Laboratories Inc., Tokyo, Japan). *S. pneumoniae* isolates were re-tested at CMI (Wilsonville, OR) and the retest values will be used in this integrated summary of efficacy.

According to the sponsor, only data for isolates of S. pneumoniae resistant to the macrolides (erythromycin A) (Ery-R) and/or penicillin G (Pen-R) using the end point of 14 to 28 days (corresponding to the main end point used in Western-country studies) will be presented and integrated with data obtained in Western studies.

**Japanese Study 2105:**

Study 2105 was a double blind, multicenter, randomized study of the evaluation of difference of efficacy and safety between oral telithromycin (HMR 3647) 600 mg and 800 mg once daily dose given for 7 days in the treatment of community-acquired pneumonia in adolescents and adults.

Table 17: Phase III studies submitted to NDA 21-144 (Sponsor's Table)

| Indication/ Study No. | Study Design | Treatment Regimen | | |
|---|---|---|---|---|
| **Community-acquired pneumonia** | | | | |
| 3000[a] | Open label | 7 to 10 d | TEL | 800 mg qd |
| 3001[a] | Double-blind, randomized, active controlled, 2-arm, parallel group | 10 d | TEL | 800 mg qd |
| | | 10 d | AMX | 1000 mg tid |
| 3006[a] | Double-blind, randomized, active controlled, 2-arm, parallel group | 10 d | TEL | 800 mg qd |
| | | 10 d | CLA | 500 mg bid |
| 3009OL[b] | Open label | 7 to 10 d | TEL | 800 mg qd |
| 3010[c] | Open label | 7 d | TEL | 800 mg qd |
| 3012[d] | Open label | 7 d | TEL | 800 mg qd [e] |
| 4003[d] | Double-blind, randomized, active controlled, 3-arm, parallel group | 5 d | TEL | 800 mg qd |
| | | 7 d | TEL | 800 mg qd |
| | | 10 d | CLA | 500 mg bid |
| 3107[d] (Japan) | Double-blind, randomized, active controlled, 2-arm, parallel group | 7 d | TEL | 600 mg qd |
| | | 7 d | LVF | 100 mg tid |
| 2105 (Japan) | Double-blind, randomized, 2-arm parallel group | 7 d | TEL | 600 mg qd |
| | | 7 d | TEL | 800 mg qd |

TEL = telithromycin; AMX = amoxicillin; CLA = clarithromycin; TVA = trovafloxacin; LVF = levofloxacin, AMC = amoxicillin-clavulanic acid (Augmentin); CXM = cefuroxime axetil.

[a] Study presented in the original NDA submission (February, 2000).

[b] Study presented in the safety update (June, 2000).

[c] Study presented in Amendment 1 (February, 2001).

[d] Study presented in Amendment 2.

[e] In subjects with severe renal impairment (creatinine clearance <30 mL/min), the dose was reduced to 400 mg qd.

| Table 18: All CAP Studies: All Penicillin and/or Erythromycin Resistant Cases in the MITT population (n=49) | |
|---|---|
| Resistance | N |
| Penicillin | 12 |
| Erythromycin | 21 |
| Penicillin and Erythromycin | 16 |

**Statistical Reviewer's Comments:**

*In the MITT population, based on FDA analysis of the western trials with the single or mixed pathogen infections, there were a total of 49 isolates with Penicillin G-resistant S. pneumoniae (PRSP) and macrolide- (erythromycin A-) resistant S. pneumoniae (ERSP). Of which, 28 PRSP (regardless of Erythromycin resistance) and 37 ERSP (regardless of Penicillin resistance) were identified.*

*In this section, all the 95% confidence limits were calculated using exact probabilities and no normal approximation was used.*

| Table 19: All CAP Studies: PP Population | | |
|---|---|---|
| | n/N | |
| | Clinical Response | Bacteriological Response |
| Penicillin Resistant only | 8/8 | 8/8 |
| Erythromycin Resistance only | 17/18 | 17/18 |
| Penicillin and Erythromycin | 8/11 | 8/11 |

**Statistical Reviewer's Comments:**

*In the PP population among the single or mixed pathogen infections, there were 19 isolates with Penicillin G-resistant S. pneumoniae, of which 16/19 (84.2%, 95% CI:60.4, 96.6) were clinical cures and 29 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, 25/29 (86.2%, 95% CI: 68.3, 96.1) were clinical cures. The clinical cure rates dropped among the subjects with both PRSP and ERSP isolates (8/11; 73%). Similar bacteriological cure rates were observed in the PP population.*

| Table 20: All CAP Studies: MITT Population | | |
|---|---|---|
| | n/N | |
| | Clinical Response | Bacteriological Response |
| Penicillin Resistant only | 9/12 | 9/12 |
| Erythromycin Resistance only | 19/21 | 19/21 |
| Penicillin and Erythromycin | 10/16 | 10/16 |

**Statistical Reviewer's Comments:**

*In the MITT population, there were 28 isolates with Penicillin G-resistant S. pneumoniae, of which 19/28 (67.9%, 95% CI: 47.6, 84.1) were clinical cures and 37 isolates with macrolide- (erythromycin A-) resistant S. pneumoniae, 29/37 (78.4%, 95% CI:61.8, 90.2) were clinical cures. The clinical cure rates dropped among the subjects with both PRSP and ERSP isolates (10/16; 62.5%).*

| Table 21: All CAP Studies: Bacteriological Responses (Pen-Resistant patients) PP Population | | | |
|---|---|---|---|
| | n/N | (%) | 95% CI |
| Bacteriological PP (n=19) | 16/19 | (84.2%) | (60.4, 96.6) |
| Blood | 5/7 | (71.4%) | (29.0, 96.3) |
| Sputum | 11/12 | (91.7%) | (61.5, 99.8) |
| Bacteriological MITT(n=28) | 19/28 | (67.9%) | (47.6, 84.1) |
| Blood | 5/10 | (50.0%) | (18.7, 81.3) |
| Sputum | 14/18 | (77.8%) | (52.4, 93.6) |

Statistical Reviewer's Comments:

*In the Bacteriological PP, the clinical cure rate was 16/19 (84.2%; 95% CI: 60.4. 96.6) and in the Bacteriological MITT, 19/28 (67.9%; 95% CI: 47.6, 84.1) of the isolates were clinical cures.*

*In the PPb population with PRSP isolates, there were a total of 7 subjects with resistant S. Ppneumoniae isolates that were cultured from blood and 12 isolates that were cultured from sputum at pretherapy/entry. Of the isolates cultured from blood, the eradication rate was 5/7 (71.4%) subjects. The numbers of isolates among bacteremic*