EXECUTIVE SUMMARY

This FDA briefing document contains a summary of New Drug Application (NDA) 21-144 for telithromycin tablets (Ketek™, Aventis Pharmaceuticals; development name HMR 3647). Telithromycin is the first in a new class of antimicrobials, ketolides, within the macrolide-lincosamide streptogramin (MLS_B) family. The original NDA for this drug was submitted on February 28, 2000 and discussed at an Anti-Infective Drug Advisory Committee Meeting on April 26, 2001. Issues discussed at that meeting included:

- potential hepatotoxicity of telithromycin;
- potential for telithromycin to affect cardiac repolarization;
- pharmacokinetic variability of telithromycin
- potential interactions between telithromycin and CYP 3A4 substrates;
- evidence for resistance claims for *S. pneumoniae* (penicillin and macrolides).

Following this meeting, the FDA issued an approvable letter for telithromycin on June 1, 2001, requesting that the Applicant perform a large safety study in examining the potential toxicities of telithromycin with regard to cardiac, hepatic, visual, and vascular safety. The Agency also requested that the Applicant submit additional data regarding the efficacy of telithromycin in the treatment of community-acquired pneumonia due to penicillin- or erythromycin-resistant *S. pneumoniae*. Finally, the Agency requested clinical pharmacology studies examining the pharmacokinetics and electrophysiologic effects of telithromycin in subjects with impaired clearance of this drug, as well as clinical pharmacology studies of the visual effects of telithromycin.

The Applicant amended the NDA for telithromycin on July 24, 2002, submitting new studies intended to address the issues described above. The applicant has requested approval for telithromycin in adults for the following indications:

- acute exacerbation of chronic bronchitis (AECB);
- acute sinusitis;
- community-acquired pneumonia (CAP)

Included among the requested pathogens are *S. pneumoniae* resistant to penicillin and erythromycin in CAP, AECB, and sinusitis.

Requests to the FDA regarding marketing claims for infections due to resistant *S. pneumoniae* are increasing. Levofloxacin is currently approved for the treatment of pneumonia caused by *S. pneumoniae* resistant to penicillin. No agents are approved for the treatment of *S. pneumoniae* resistant to erythromycin.

Summary:

Given the concerns raised regarding the safety of telithromycin, we ask the Advisory Committee to focus on the risk-benefit ratio of this new agent. Important considerations in this discussion, in addition to safety considerations, include *in vitro* evidence; potential for cross-resistance; clinical efficacy; overall weight of evidence; and public health benefit.

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I.   Regulatory History

A. Original NDA

The original New Drug Application (NDA) for Ketek™ (telithromycin) was submitted on February 28, 2000. The Applicant requested approval for marketing of telithromycin in the United States for the following indications in adults:

- tonsillopharyngitis;

- acute exacerbation of chronic bronchitis (AECB);

- acute bacterial sinusitis (ABS);

- community-acquired pneumonia (CAP)

In support of this NDA, the Applicant submitted efficacy and safety data from 13 Phase 3 trials. There were two comparative trials for each indication requested (three for CAP), as well as four supportive studies of telithromycin (three uncontrolled studies of telithromycin in the treatment of CAP and an uncontrolled study of two different doses of telithromycin in the treatment of acute sinusitis). In these trials, 3265 patients were treated with telithromycin (2045 in comparative trials and 1220 in non-comparative trials), while 1672 patients received a comparator drug[1]. The Applicant also submitted data on cases of CAP associated with erythromycin-resistant isolates of *S. pneumoniae* from a comparative study conducted in Japan.

In addition, the Applicant submitted data from 566 subjects receiving telithromycin in Phase 1 studies examining the drug's safety profile and clinical pharmacology. After the original NDA submission, the Applicant submitted additional Phase 1 clinical pharmacology data from 84 subjects receiving telithromycin. In addition, the Applicant submitted results from 14 drug interaction studies enrolling 261 subjects who received multiple oral doses of 800 mg telithromycin[2]. Subjects in these studies were healthy adults, generally less than 50 years old.

Finally, the Applicant submitted toxicologic, microbiologic, chemistry, and manufacturing data in support of the NDA.

Data were submitted to the NDA with the original application on February 28, 2000, as part of a 4 month safety update submitted June 30, 2000, and with a major clinical amendment submitted February 27, 2001.

B. April 2001 Anti-Infective Drugs Advisory Committee Meeting[3]

The Anti-Infective Drugs Advisory Committee (AIDAC) met on April 26, 2001 to discuss safety and efficacy data for telithromycin. (The FDA briefing package for that meeting is presented in Appendix A of this document.) The Committee heard

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[1] Comparators in these trials consisted of amoxicillin, amoxicillin/clavulanic acid, cefuroxime, penicillin VK, clarithromycin, and trovafloxacin.

[2] Concomitant medications or foods included ketoconazole, itraconazole, oral contraceptives, cisapride, sotalol, midazolam, digoxin, warfarin, simvastatin, theophylline, ranitidine, antacid, paroxetine, or grapefruit juice.

[3] Full meeting transcript is available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3746t1.html

presentations by the Applicant, FDA, and cardiology and hepatology consultants. Safety discussions focused on telithromycin's effects on cardiac repolarization (increased QT interval), hepatic adverse events, and blurred vision, while efficacy centered on patients with community acquired pneumonia due to drug-resistant *Streptococcus pneumoniae*. The Committee provided advice to the FDA, through discussion and formal vote, on telithromycin's overall risk/benefit profile in the treatment of outpatients with mild to moderate respiratory infections. On balance, the Committee recommended additional studies to delineate safety, particularly in "at risk" populations, and efficacy in patients with drug-resistant *S. pneumoniae and Haemophilus influenzae*. Highlights of the efficacy and safety discussions are reviewed below, followed by a summary of the Committee vote on FDA questions.

Efficacy analyses performed by the Applicant and FDA were in general agreement with regard to pneumonia, sinusitis, and bronchitis. The Agency presented its view of telithromycin's performance in eradicating *Streptococcus pyogenes* in tonsillopharyngitis (84% success for telithromycin versus 89% for pen VK [-14.3, 4.8]), and the Committee "tabled" discussion on this indication since efficacy criteria were not met. The body of evidence for patients with community-acquired pneumonia (CAP) due to drug-resistant *S. pneumoniae* was presented. A total of 174 telithromycin-treated CAP patients with any *S. pneumoniae* isolate were identified, with a clinical success rate of 96%. Of these 174, 17 patients had penicillin-resistant *S. pneumoniae* (PRSP) isolates, with a cure rate of 82%. Telithromycin-treated CAP patients with concurrent bacteremia included 38 patients with penicillin-sensitive *S. pneumoniae*, with a success rate of 89%, and 6 patients with PRSP and a cure rate of 67%. Experience with telithromycin in the treatment of CAP due to erythromycin-resistant *S. pneumoniae* (ERSP*)* was similar: a total of 17 telithromycin-treated ERSP CAP patients were identified, with a success rate of 14/17 (82%) concurrent bacteremia was present in 6 patients, of whom 4 (67%) were cured. The set of 17 ERSP patients overlapped with, but was not identical to, the set of 17 PRSP patients. Of note, of the 17 ERSP CAP cases, the 3 cases of treatment failure all had concurrent penicillin resistance. In general, the Committee felt that the data did not support a claim for PRSP or ERSP, citing insufficient numbers of patients, few bacteremic patients, relatively low success rates in bacteremic patients, and some concern about the clinical significance of erythromycin resistance in community-acquired pneumonia.

Discussion of telithromycin safety data and analyses focused primarily on cardiac repolarization, hepatotoxicity in animals and man, and complaints of blurred vision. There was general agreement that telithromycin has an effect on cardiac repolarization. This effect is concentration-dependent, and given the pharmacokinetic variability of telithromycin, concerns arose for "at risk" patients who may have greater exposure to the drug (e.g., elderly, patients with hepatic and/or renal impairment, etc.). When telithromycin is administered alone, the effect on prolongation of QT appears to be modest. FDA experience with other non-cardiac drugs (e.g., terfenadine) that increase the QT interval has emphasized that malignant ventricular arrhythmias such as torsades de pointes rarely result from use of a single drug by itself in a normal patient. Rather, the risk discussed was that of telithromycin with its modest effect on QT, together with one or more amplifying factor (e.g., concomitant medications that increase drug exposure by via cytochrome P450 metabolic pathways, hypokalemia, congestive heart failure, etc.)

The Committee considered the data in patients with multiple risk factors to be very limited and specifically recommended additional safety and pharmacokinetic studies in the elderly, patients with hepatic and/or renal impairment, and those on multiple concomitant medications, to allow for analysis of drug-drug interactions.

Hepatic effects were noted in both preclinical and clinical studies. In animals, all species tested (dogs, rats, and monkeys) showed evidence of hepatotoxicity. In comparing the effects in animals given telithromycin versus clarithromycin, the FDA reviewer noted that the hepatotoxic effects of telithromycin were greater. In Phase 1 studies that included 8 elderly subjects administered a single 2.0 gram dose of telithromycin, 3 patients had elevated liver transaminase values (ALT and AST levels ranging from 100-300, ALT > AST). Phase 1 data showed no clear dose-response for hepatic adverse events. In Phase 3 studies, 2 patients experienced serious hepatic adverse events possibly associated with telithromycin. One patient underwent a liver biopsy, read by Agency consultants as consistent with drug-induced liver injury. A second biopsy nine months later was consistent with autoimmune hepatitis. Further details on this patient may be found in Section IVB4 (b) of this document.

Visual complaints were noted in telithromycin-treated patients in Phase 3 studies of pneumonia, sinusitis, and pharyngitis. Blurred vision possibly related to study drug occurred in 11 (0.3%) telithromycin-treated patients and 0 comparator-treated patients. Patients were typically < 40 years of age and female. Duration of blurred vision ranged from hours to 10 days.

The Committee addressed FDA questions and voted as follows[4]:

I.   Given the risks of cardiac and hepatic toxicity of telithromycin, does the efficacy for telithromycin in respiratory infections support its use for:

- Community-acquired pneumonia   **Yes 7**   **No 3**
- Acute exacerbation of chronic bronchitis   **Yes 0**   **No 10**
- Acute sinusitis   **Yes 2**   **No 8**

A. Has the Applicant provided sufficient data to warrant a claim for the treatment of community-acquired pneumonia due to penicillin-resistant S. pneumoniae (PRSP)?

- **Yes 3   No 7**
- If NO, what additional studies should be conducted?

Members of the Committee expressed a need for more studies and more patient information, particularly in treating bacteremic patients and also resistant organisms.

B. Should the drug, if approved, have a specific indication to treat infections due to erythromycin-resistant S. pneumoniae.

Yes 3   No 7

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[4] Summary meeting minutes available at http://www.fda.gov/ohrms/dockets/ac/01/minutes/3746m1.htm

The Committee additionally expressed the following points:

The numbers of patients studied is small, particularly for patients with bacteremic pneumonia. They would like to see more data on cross-resistance.

C. If the committee recommends approval, should this approval involve restrictions? For example, restrictions in the label for use in special populations only, limitations in access or distribution.

The following issues were discussed in reference to community acquired pneumonia:

- *Concern for the emergence of telithromycin-resistant pneumococci during therapy*

- *The Committee did not believe there are sufficient data on risk factors for toxicity currently to enable preparation of guidelines for safe use.*

- *More data on safety from pre-marketing studies of older patients are needed to define drug interactions.*

- *Additional pre-marketing studies are preferred to post-marketing surveillance alone to better assess safety.*

- *Mandate large studies to better define Cmax and AUC in the elderly, and to enumerate drug risks and side effects, particularly for hepatotoxicity.*

- *Describe potential drug / drug interactions.*

- *Drug should not be indicated for prolonged use.*

- *Patient labeling should be provided as in a medication guide.*

- *Use in patients not requiring hospitalization.*

- *Risk groups should be noted to ensure caution is exercised.*

- *Note the potential for prolongation of the QT interval.*

II. If the committee has not recommended approval, please provide recommendations for additional studies if appropriate.

The Committee recommended that a drug safety profile be established to describe toxicity. Larger numbers of patients need to be enrolled to determine safety. In addition, patients with isolates of penicillin-resistant **S. pneumoniae** *and* **H. influenzae** *should be targeted.*

C. Regulatory Action

After considering the results of the FDA review of this NDA and the recommendations made by the AIDAC, the FDA issued an approvable letter on June 1, 2001 for the indications of AECB, ABS, and CAP (see Appendix C). The letter requested that the Applicant perform a large safety study to gather data on cardiac, hepatic, visual, and vasculitic adverse events in a patient population representative of that likely to be seen in usual clinical practice. Additional data was requested on the efficacy of telithromycin in the treatment of infections due to PRSP and ERSP. In addition, the Applicant was asked to a) characterize drug exposure and cardiac repolarization effects in

patients at risk for multiple perturbations of drug elimination pathways; b) study the visual effects of telithromycin; and c) study the *in vitro* effects of a major telithromycin metabolite (RU 76363) on electrophysiologic factors related to cardiac repolarization.

A nonapprovable letter was issued for the indication of tonsillopharyngitis.

D. NDA Amendment

In response to the approvable letter, the Applicant submitted an amendment to the NDA for telithromycin on July 24, 2002, containing the following new studies and data:

Safety

Study 3014 – A randomized, open-label multi-center trial of the safety and effectiveness of telithromycin versus amoxicillin-clavulanic acid in outpatients with respiratory tract infections in usual care setting.

Study 3014 was intended to address the request for a large safety study to examine adverse events of special interest (cardiac, hepatic, visual, and vasculitic). A detailed discussion of this study may be found in Section IV of this briefing document (Safety Analysis).

Periodic Safety Update Report covering the period July 9, 2001 to January 9, 2002

Line listing of adverse events reported between January 9, 2002 and April 24, 2002

A discussion of post-marketing events in countries where telithromycin is currently marketed may be found in Section IV of this briefing document (Safety Analysis).

Efficacy in PRSP and ERSP infections

Study 4003 – A double-blind active-controlled study of the efficacy and safety of oral telithromycin (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 – An open label, multicenter, multinational, uncontrolled, noncomparative study of the efficacy and safety of 7 days of oral telithromycin 800 mg once daily in the treatment of community-acquired pneumonia due to *S. pneumoniae* in adolescents and adults.

Study 3107 (performed in Japan) – A double-blind, randomized, drug-controlled, noninferiority, comparative study of the efficacy and safety of telithromycin 600 mg qd and levofloxacin 100 mg tid against community-acquired pneumonia. This study had significant differences in design from studies conducted in Western countries. By agreement with the Agency, the Applicant integrated data on outcomes involving infections due to PRSP and ERSP with data from other studies.

Studies 4003, 3012, and 3107 were intended to address the request for additional data on the efficacy of telithromycin in the treatment of infections due to PRSP and ERSP. Detailed discussions of these studies may be found in Section IIIB of this briefing document.

The Applicant also submitted data from a new study of telithromycin in the treatment of acute exacerbation of chronic bronchitis (Study 3013); detailed discussion of this study may be found in Section IIIC of this briefing document.

Clinical Pharmacology

Study 1063 - A multicenter, multinational, randomized, open-label, 3-treatment parallel group, multiple oral dose study. The primary objective was to determine the effect of cytochrome P450 3A4 (CYP3A4) inhibition by ketoconazole on the pharmacokinetics of telithromycin in elderly subjects with diminished renal function. The study included assessment of QT interval changes in study subjects.

Study 1062 – A study of multiple-dose telithromycin pharmacokinetics in renally impaired patients. This study included assessment of QT interval changes in study subjects.

Studies 1063 and 1062 were intended to address the request to characterize drug exposure and cardiac repolarization effects in patients at risk for multiple perturbations of drug elimination pathways. A detailed discussion of these studies may be found in Sections IIC and IVC of this briefing document.

Study 1059 – A single dose, randomized, placebo-controlled, double-blind, crossover study conducted in healthy young subjects with normal vision and older subjects (50 to <65 years old) with presbyopia. Telithromycin was administered as single 800 and 2400 mg doses. Extensive ophthalmologic evaluations were performed, along with measurements of telithromycin concentrations in plasma and tears.

Study 1064 – A single dose, randomized, placebo-controlled, double blind, 2-way crossover study conducted in healthy subjects 18 to <65 years old. Telithromycin was administered as a single supraclinical 2400 mg dose. Ophthalmologic and pharmacokinetic evaluations were similar to those in Study 1059.

Both studies 1059 and 1064 were intended to address the request to study the visual effects of telithromycin. A detailed discussion of these studies may be found in Sections IIC and IVD of this briefing document.

Study 1060 - A multiple-dose study of telithromycin pharmacokinetics in hepatically impaired patients. Detailed discussion of this study may be found in section IIC of this document.

Studies of interactions between telithromycin and rifampin (Study 1058), as well as between telithromycin and metoprolol (Study 1061). Detailed discussion of these studies may be found in Section IIC of this briefing document.

After the approvable letter was issued, agreement was reached between the FDA and the Applicant that sufficient data would be available regarding the potential electrophysiologic effects of RU 76363 (a major telithromycin metabolite) from existing data in the original and amended NDA, and that no additional specific studies need be conducted regarding these effects.

II. Summary of preclinical and clinical pharmacology information

A. Microbiology

Telithromycin is a semisynthetic antibacterial belonging to the ketolide family of antimicrobials, within the macrolide-lincosamide streptogramin (MLS_B) class. It inhibits bacterial protein synthesis by action at the 23S ribosomal RNA.

Telithromycin has *in vitro* activity against Gram-positive bacteria, fastidious Gram-negative bacteria, some anaerobes, and atypical pathogens (*Chlamydia pneumoniae*, *Legionella pneumonia*, and *Mycoplasma pneumoniae*). It is bacteriostatic against *Staphylococcus aureus* and *Streptococcus pyogenes*. Telithromycin is bactericidal against penicillin– or erythromycin-susceptible and -resistant *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. It has little or no activity against methicillin-resistant *S. aureus* or methicillin-resistant coagulase-negative staphylococci.

MIC_{90} ranges for target pathogens are as follows:

S. pneumoniae (including penicillin- and erythromycin-resistant stains): 0.25 µg/mL

H. influenzae (β-lactamase-negative: 2 µg/mL; β-lactamase-positive: 4 µg/mL)

M. catarrhalis (including β-lactamase-positive strains): 0.5 µg/mL

S. pyogenes (erythromycin-susceptible: 0.06 µg/mL; erythromycin-resistant: 8 µg/mL)

Telithromycin has *in vitro* activity against some strains of *S. pneumoniae* that carry the *mef*E and *erm*B genes, as well as against strains of *S. pyogenes* that do not carry *erm*B. Increased MIC_{90}s have been observed in strains of *S. pyogenes* that carry *erm*B.

No data are available with regard to synergism or antagonism with other antimicrobials. Telithromycin has been shown to have a post-antibiotic effect ranging from approximately 1 to 8 hours at 10x MIC against the pathogens of interest. A decrease in pH from 7 to 5.5 increases the telithromycin MIC for *S. pneumoniae* by approximately 15-fold. Increasing inoculum size from 10^4 to 10^5 cfu/mL does not affect the MIC. If the inoculum size is 10^7 or greater, the telithromycin MIC for *S. pneumoniae* goes up approximately 2 to 4-fold.

B. Pre-clinical Pharmacology/Toxicology

The pre-clinical pharmacology/toxicology review of the telithromycin NDA submission included a side-by-side comparison with pre-clinical data for clarithromycin. The review evaluated the original source data submitted to the FDA in support of all clarithromycin applications, since the NDA for telithromycin compares its hepatic and cardiac effects to those of clarithromycin. Summary comments are listed below, and additional data regarding potential hepatic and cardiac toxicities are included in the Sections IVB and IVC of this briefing document.

Dr. John Koerner of the Division of Cardio-Renal Drug Products has reviewed the preclinical electrophysiologic data for telithromycin. He concluded that "[Telithromycin] demonstrated a potential to affect ventricular repolarization . . . The absence of an effect on absolute QT interval in the presence of a heart rate increase strongly supports the conclusion of a drug-related effect on ventricular repolarization since, in the absence of drug, a heart rate increase should shorten the QT. All of the above mentioned effects were concentration- or dose-related."

As the Applicant has suggested that telithromycin has a risk profile no worse than that of clarithromycin, it is critical to consider the effects of each drug in each species evaluated. The applicant for clarithromycin considered the monkey the most appropriate animal model for toxicologic studies. After 2 weeks of dosing with telithromycin or clarithromycin, increased LFTs were seen with both compounds. In addition, telithromycin elicited renal tubular atrophy and increased total bilirubin levels. After 4 weeks of dosing in the monkey, both compounds elicited increased LFTs, but more significant increases were seen with telithromycin. Telithromycin-treated monkey showed increased total bilirubin levels during this entire dosing period.

In the rat, after 4 weeks of dosing, although both drugs increased LFTs (clarithromycin 2-3x; telithromycin 2-15x), the qualitative and quantitative effects were quite different. Clarithromycin primarily affected multinucleated hepatocytes (significance to humans unknown) with minimal to mild hepatic necrosis at >50 mg/kg/d. Telithromycin caused moderate to severe hepatic necrosis with steatosis/phospholipidosis at >50 mg/kg/d (lowest dose tested). After 13 weeks of dosing, multinucleated hepatocytes were reported for clarithromycin while telithromycin elicited increased LFTs, increased N-acetyl-ß-glucosamidase (3x) in urine, and phospholipidosis.

In dogs, LFTs were increased with both compounds (clarithromycin 4-5x; telithromycin 6x) but telithromycin elicited one premature decedent with acute liver and renal failure, and phospholipidosis in mid- and high-dose groups. EKGs showed no drug-related differences from controls/baseline with clarithromycin, while telithromycin caused a markedly increased heart rate and increased QTc interval (27-30 msec). In the only comparative study performed, clarithromycin and erythromycin each increased the QTc interval by 17 msec while telithromycin increased it by 30 msec.

The applicant for clarithromycin stated that dogs are exquisitely sensitive to the toxicologic effects of clarithromycin. Of note, it appears that the incidence and severity of significant changes in LFTs, histopathology, and QT intervals were increased in telithromycin-treated dogs when compared to clarithromycin-treated dogs. In addition, more species appeared to be adversely affected by telithromycin treatment than by clarithromycin treatment.

C. Clinical Pharmacology

To address issues of pharmacokinetic variability and potential for increased telithromycin exposure in patients with impaired drug clearance, two clinical pharmacology studies were recommended by the FDA in the June 2001 approvable letter for telithromycin:

(1) To investigate the steady-state pharmacokinetics (PK) of telithromycin following administration of telithromycin 400 mg, 600 mg, and 800 mg QD in patients with mild, moderate, and severe renal impairment.

(2) To investigate the effects of co-administration of ketoconazole on the steady-state pharmacokinetics (PK) of telithromycin following administration of telithromycin 800 mg QD to elderly subjects with mild to moderate renal impairment.

In addition, a third study was recommended because of reports of unexplained blurred vision in Phase 3 studies in the original NDA:

(3) To address the effects of telithromycin on visual acuity, refraction, accommodation, anterior chamber angle, lens/pupil dilation, tear film stability, visual field testing, and color vision.

The intent of studies (1) and (2) was to (a) provide a greater understanding of the pharmacokinetics (PK) and safety of telithromycin in individuals who may experience higher systemic drug exposure due to perturbations of the pathways for telithromycin elimination, and (b) determine if adjustment of the telithromycin dosage was needed under such conditions. The intent of study (3) was to characterize and provide a better understanding of the visual adverse effects (i.e., blurring of vision) that were associated with telithromycin in the review of the NDA.

The Applicant submitted a total of 7 clinical pharmacology studies to the July 2002 NDA Amendment, 4 of which were those recommended by the FDA in the June 2001 approval letter. The following is a summary of the clinical pharmacology / PK results from these studies. Please refer to Section IV of this document for discussion of the safety aspects of these clinical pharmacology studies, including effects on the QT interval.

1. General aspects of clinical pharmacology

For a summary of clinical pharmacology studies submitted in the original NDA, please refer to Section III of the FDA briefing document for the April 2001 AIDAC meeting, which is provided in Appendix A.

2. Clinical pharmacology in special populations

a) Study 1062: Pharmacokinetics and Safety of Telithromycin in Patients with Renal Impairment after Multiple Doses of 400 mg, 600 mg, or 800 mg QD for 5 Days

The effect of renal impairment on telithromycin PK was evaluated following single oral dose administration of 800mg in the original NDA submission. The mean C_{max} and AUC of telithromycin were increased by 33% and 42%, respectively, in subjects with moderate renal impairment (Creatinine Clearance (CLcr) range: 40-79 mL/min). In subjects with severe renal impairment (CLcr range: 10-39 mL/min), the mean C_{max} and AUC were increased by 44% and 59%, respectively.

The higher systemic exposure in subjects with renal impairment following single dose administration suggested that dose adjustment may be needed for this sub-group of patients. Since the PK of telithromycin exhibits non-linear characteristics, systemic exposure in renally impaired subjects may be greater than expected after multiple dose administration, as compared to single dose administration. Thus, for a drug that exhibits non-linear PK, a single dose study will not be able to accurately predict the PK following multiple doses.

In order to adequately determine if dose adjustment in individuals with renal impairment is needed, a multiple dose pharmacokinetic study in renal impairment subjects was conducted. Study 1062 was an open-label crossover trial employing multiple oral doses of 400 mg, 600 mg, and 800 mg telithromycin given daily for 5 days to the following 3 groups of renally impaired subjects:

Mild Impairment: CLcr[5] 50 to 80 mL/min
Moderate Impairment: CLcr 30 to 49 mL/min
Severe Impairment: CLcr <30 mL/min

A fourth group of healthy subjects (CLcr >80 mL/min) also received multiple oral doses of 800mg telithromycin given daily for 5 days.

The steady state AUC (0-24 hr) and Cmax for the various renal function groups at the dose levels of 400 mg, 600 mg, and 800 mg are shown in Figures 1 and 2.

Figure 1

Steady State AUC(0-24 hr) for Telithromycin Following Multiple Oral Doses of

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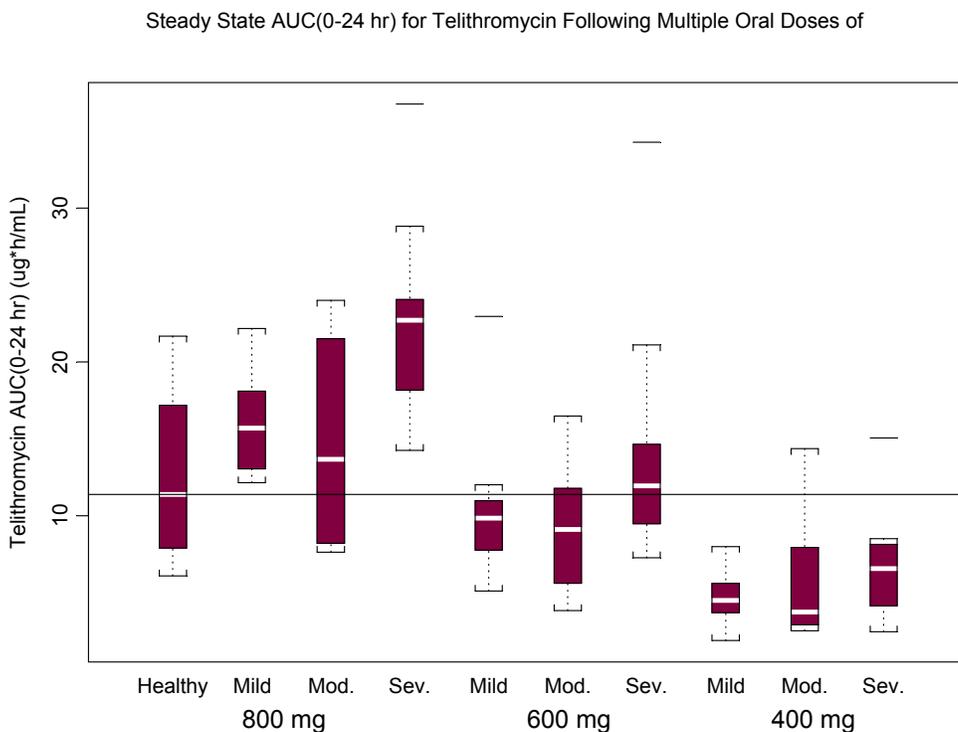
[5] CLcr = creatinine clearance

Figure 2

Steady State Cmax for Telithromycin Following Multiple Oral Doses of
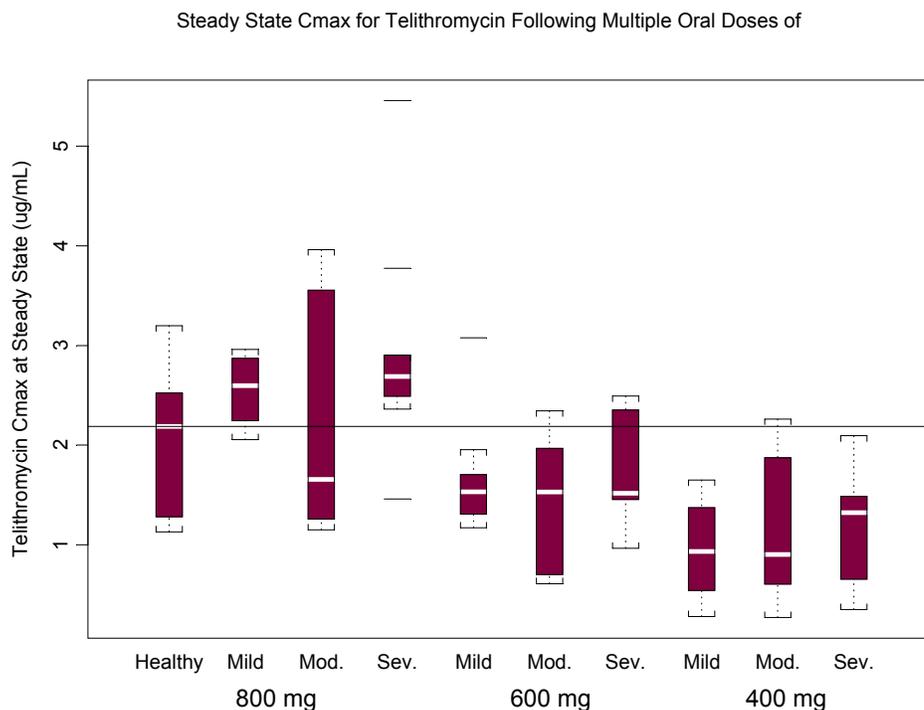
There were no significant changes in the Cmax estimates for telithromycin for all three renal impairment groups when compared to the healthy subjects following 800 mg QD for 5 days. The steady-state AUC (0-24 hr) estimates following multiple 800mg doses were not significantly increased in the mild and moderate renal impairment subjects as compared to healthy subjects. However, steady state AUC (0-24 hr) was increased approximately 2-fold in the severe renal impairment subjects as compared to the healthy subjects following 800 mg QD for 5 Days.

Following multiple 400 mg doses of telithromycin, steady-state AUC (0-24 hr) estimates were reduced by approximately 40% to 60% in all three groups of renally impaired subjects.

The results from this study indicate that in order to obtain comparable exposure (i.e., AUC) to healthy subjects given the clinical regimen of 800 mg QD, a regimen of 600 mg QD should be administered to individuals with severe renal impairment (CLcr <30 mL/min). No dose adjustment is necessary in individuals with mild to moderate renal impairment (CLcr 30 to 80 mL/min, inclusive).

The results from this study also indicate that a telithromycin dosage regimen of 400 mg QD in individuals with severe renal impairment, as suggested by the Applicant, may result in lower systemic exposure to telithromycin that may be sub-therapeutic in this subgroup.

b) <u>Study 1063:</u> Effects of Ketoconazole on the Pharmacokinetics of Telithromycin after Multiple Oral Doses of 800mg Once Daily for 5 Days in Subjects 60 Years of Age and Older with Diminished Renal Function

In the original NDA submission, the Phase 1 studies showed that factors such as renal impairment and drug interactions with telithromycin can increase the systemic exposure / plasma concentrations of telithromycin. In the ketoconazole drug interaction study in the original NDA, ketoconazole increased telithromycin mean C_{max} and AUC by 52% and 95%, respectively, in healthy subjects. The mechanism for this interaction is inhibition of CYP3A4-mediated metabolism of telithromycin by ketoconazole.

Study 1063 was designed to examine the PK of telithromycin in the situation where the two factors mentioned above are simultaneously invoked, i.e., renal impairment and co-administration of the CYP3A4 inhibitor, ketoconazole. The rationale for this study was to characterize drug exposure in patients that are potentially at greater risk (e.g., taking concurrent interacting drugs, elderly, renal impairment) due to multiple perturbations of the elimination pathways for telithromycin, namely renal and hepatic. Due to the concern about unacceptable adverse events potentially resulting from high telithromycin plasma exposure in individuals with severe renal impairment, only subjects with mild (CLcr 50-80 mL/min) and moderate (CLcr 30-49 mL/min) renal impairment were to be included in this study (N = 10). Although subjects with severe renal impairment (CLcr <30 mL/min) were to be excluded, two subjects each with CLcr <30 mL/min were studied (i.e., CLcr 24 and 28 mL/min). This study also only included subjects 60 years of age and older.

Figures 3 and 4 show steady state Cmax and AUC (0-24 hr) estimates across the following groups of subjects from several Phase 1 studies: (1) ≥60 years of age with mild to moderate renal impairment and ketoconazole co-administration (Study 1063); (2) healthy young subjects; (3) renal impairment (Study 1062); (4) ketoconazole co-administration to healthy young subjects.

The results of these comparisons indicate the following:

In healthy young subjects, the mean steady state AUC and C_{max} estimates after multiple doses of 800 mg telithromycin are 12.4 μg·h/mL and 2.27 μg/mL, respectively.

In healthy young subjects co-administered ketoconazole, the telithromycin mean AUC and C_{max} estimates were 28.6 μg·h/mL and 3.31 μg/mL, respectively, which represented increases of 2-fold and 1.4-fold, respectively, as compared with administration of telithromycin alone.

In the 10 older subjects ≥60 years of age with mild to moderate renal impairment and ketoconazole co-administration (Study 1063), the mean steady state AUC and C_{max} estimates of telithromycin were increased 2.7-fold and 1.6-fold, respectively, as compared to the healthy young subjects.

From limited data in the 2 subjects included in Study 1063 with severe renal impairment (CLcr 24 and 28 mL/min), the steady state telithromycin AUC estimates were increased 4-fold and 5-fold, and the telithromycin C_{max} estimates were increased 2.4-fold and 4-fold, as compared to the healthy young subjects.

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Figure 3

Telithromycin Steady State AUC Estimates following Multiple Oral Dose Administration
to Subjects from Various Phase 1 Studies
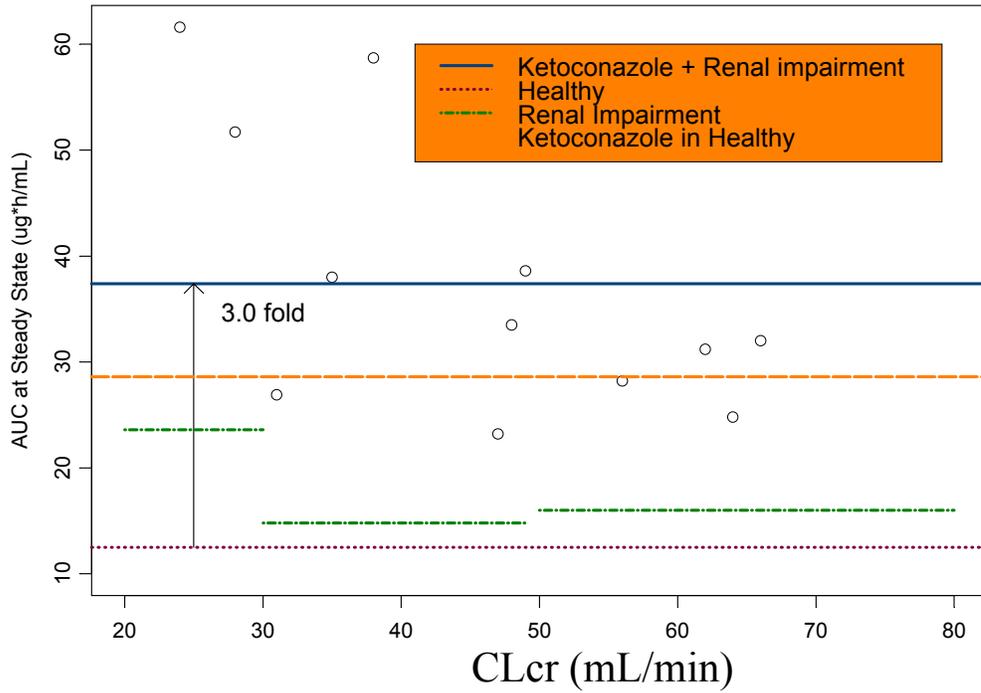
Figure 4

Telithromycin Steady State Cmax following Multiple Oral Dose Administration
to Subjects from Various Phase 1 Studies

16
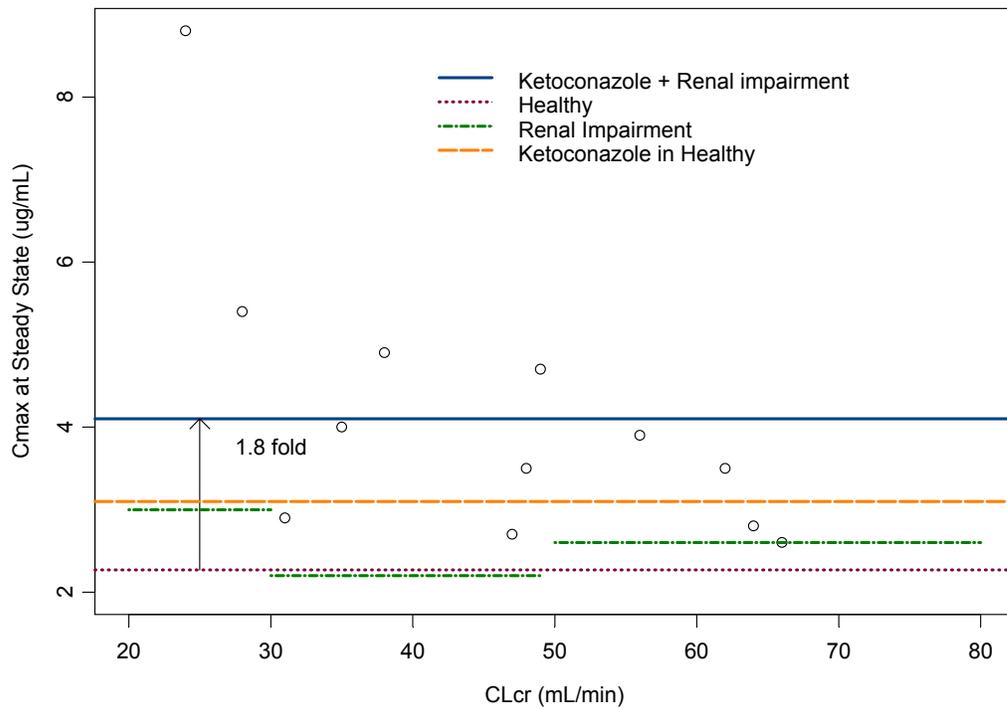
Overall, the results from Study 1063 indicated that the systemic plasma exposure to telithromycin is increased to a greater extent in older individuals with renal impairment who are concomitantly taking the CYP3A4 inhibitor, ketoconazole, with telithromycin, as compared to the effect of either factor alone (i.e., renal impairment or co-administration with ketoconazole). A reduction in the telithromycin daily dosage is recommended in patients with severe renal impairment (CLcr <30 mL/min). Dosage reduction may be needed with co-administration of ketoconazole with telithromycin in patients with normal renal function. In addition, the telithromycin dosage may also need to be reduced in patients with both renal impairment and taking a CYP3A4 inhibitor, such as ketoconazole.

c) Study 1060: Pharmacokinetics and Safety of Telithromycin after Multiple Oral Dose Administration of 800mg QD for 7 Days in Patients with Hepatic Impairment and Healthy Subjects

In the original NDA submission, the AUC and C_{max} of telithromycin following a single oral dose of 800mg to subjects with hepatic impairment (Child-Pugh scores 5-12; median score 9) and healthy subjects were similar between the two groups. However, the half-life ($t_{1/2}$) was increased from 10 hours in healthy subjects to 14 hours in the hepatic impairment subjects. There was concern that a longer half-life in the hepatic impairment subjects could result in more significant accumulation of telithromycin in plasma after multiple doses as compared to healthy subjects.

Therefore, Study 1060 was a multiple-dose study conducted in 13 subjects with varying degrees of hepatic impairment (Child-Pugh score 5-11; median score 7) and 13 healthy subjects. The results showed that the mean C_{max}, AUC, $t_{1/2}$, and plasma accumulation of telithromycin were comparable for the hepatically impaired and healthy subjects after multiple doses. The mean renal clearance of telithromycin was 27% higher in the hepatic impairment subjects as compared to healthy subjects, indicating that renal elimination becomes a compensatory pathway when liver function is impaired.

3. Visual effect studies

Two studies were conducted to investigate the mechanism of blurred vision associated with telithromycin administration. Please refer to Section IV of this document for a more detailed discussion of the ophthalmologic findings and the safety data generated from these two studies. Only the relevant clinical pharmacology/PK data will be discussed in this section.

a) Study 1064: Assessment of the Ophthalmologic Safety of Telithromycin after Administration of a Supraclinical Single Dose (2400mg) to Healthy Subjects

In this study telithromycin concentrations in plasma and the amount of drug excreted in tears were to be determined following single oral dose administration of 2400 mg to 24 healthy young subjects from pre-dose to 6 hr post-dose. However, only plasma concentration data were reported and no data for telithromycin in tears was provided.

Since the PK of telithromycin in plasma has already been characterized at this dose in previous NDA studies, no discussion of this data will be presented here.

b) Study 1059: Mechanism of Blurred Vision Induced by Telithromycin following a Single Supraclinical Dose (2400mg) vs. a Single Therapeutic Dose (800mg) to Younger and Older Healthy Subjects

Study 1059 was a randomized, double blind, placebo controlled, 3-period cross over design in 15 young (18-40 years) and 15 older (50- <65 years) male and female subjects. All subjects received a single dose of placebo, 800mg telithromycin, and 2400mg telithromycin. Plasma concentrations of telithromycin and the amount of drug excreted in tears were determined at pre-dose to 24 hr post-dose. The results showed a proportional increase in telithromycin mean Cmax in plasma with the increase in dose within the two age groups. The maximal amount of drug excreted in tears was also proportional to the increase in dose within the two age groups. After both doses the plasma Cmax was slightly higher in the older group compared to the younger subjects. However, although plasma exposure was higher in the older subjects, the mean maximal amount of telithromycin excreted in tears was lower by approximately 40% to 50% in the older subjects compared to the younger group following administration of both doses. The clinical implication of the differences in the amount of drug excreted in tears in older versus younger adults is not known.

4. Drug interaction studies

a) Study 1058: Effect of Rifampicin on the Pharmacokinetics of Telithromycin in Healthy Men

Telithromycin has been shown to be a CYP3A4 substrate and inhibitor. The interaction of multiple doses of telithromycin 800 mg QD with rifampicin 600 mg QD, a potent CYP3A4 inducer, was assessed in this crossover study conducted in 12 healthy young men. The study showed that co-administration with rifampicin decreased telithromycin C_{max} and AUC by 5- and 7-fold, respectively, as compared to when telithromycin was given without rifampicin. As suggested by the Applicant, co-administration of rifampicin and telithromycin should be considered contraindicated.

b) Study 1061: Effect of Telithromycin on the Pharmacokinetics of Metoprolol in Healthy Subjects

In vitro studies in the original NDA submission suggested that telithromycin was an inhibitor of hepatic CYP2D6. In Study 1061, the effect of telithromycin on the PK of metoprolol, a CYP 2D6 substrate, was assessed in healthy subjects. Co-administration of repeated 800 mg doses of telithromycin increased metoprolol C_{max} and AUC after a single 100 mg dose by approximately 40%. No adjustment of metoprolol dosage is needed when this drug is co-administered with telithromycin.

Two studies were conducted to investigate the mechanism of blurred vision associated with telithromycin administration. Please refer to Section IVD of this document for a more detailed discussion of the ophthalmologic findings and the safety data generated.

Results of an additional interaction study (Study 1067), examining the effect of telithromycin on the pharmacokinetics of simvastatin, are presented in the Applicant's briefing package. As of the date of this briefing document, data from this study have not been submitted to the FDA for review.

III. Efficacy Analysis

A. Labeling Claims

In this resubmission, the applicant has requested labeling of oral telithromycin for the treatment of the following infections (indications) in adults:

- **Community-acquired pneumonia** due to *S. pneumoniae*, including strains resistant to penicillin G and/or the macrolides, *H. influenzae* (including ß-lactamase producing strains), *M. catarrhalis* (including ß-lactamase producing strains), *S. aureu*s, *C. pneumoniae*, *L. pneumophila*, and/or *M. pneumoniae*.

- **Acute bacterial exacerbation of chronic bronchitis** due to *S. pneumoniae* including strains resistant to penicillin G and/or the macrolides, *H. influenzae* (including ß-lactamase producing strains), *M. catarrhalis* (including ß-lactamase producing strains), and/or *S. aureus*.

- **Acute sinusitis** due to *S. pneumoniae,* including strains resistant to penicillin G and/or the macrolides, *H. influenzae* (including ß-lactamase producing strains), *M. catarrhalis* (including ß-lactamase producing strains), and/or *S. aureu*s.

This section will focus on the results of efficacy studies for indications being sought in the current application. For each indication, the FDA analyses of pivotal and supportive Phase 3 trials contained in the original NDA submission are summarized, followed by newly submitted data. The briefing package provided to the Anti-Infective Drugs Advisory Committee in April of 2001 gives more detailed information on the original NDA submission, and is presented in Appendix A.

B. Community-Acquired Pneumonia (CAP)

1. Summary of Original NDA Submission for CAP

The original NDA submission included both blinded, comparative studies and open-label, non-comparative studies of telithromycin for the treatment of CAP. These trials were designed to include patients with mild-to-moderate CAP. There were specific exclusion criteria to limit the enrollment of patients with characteristics of severe CAP or other risk factors for serious infection(e.g., neoplastic disease, HIV infection) in most trials. The length of treatment varied from 7 to 10 days, depending on the design of the trial. Table E1 provides summary information about the pivotal and supportive trials for CAP in the original NDA.

Table E1. Study Information for Pivotal and Supportive CAP Trials in the original NDA

STUDY	DESIGN	TREATMENT	DAYS	N	GEOGRAPHIC REGION
Pivotal Comparative Studies					
3001	Multicenter, double-blind, randomized, active-controlled, comparative, 2-arm parallel group	Telithromycin 800 mg po qd Amoxicillin 1000 mg po tid	10 d 10 d	404	Argentina, Australia, Austria, Finland, France, Germany, Hungary, New Zealand, South Africa, Spain, Sweden, UK, Uruguay
3006	Multicenter, double-blind, randomized, active-controlled, comparative	Telithromycin 800 mg po qd Clarithromycin 500 mg po bid	10 d 10 d	449	USA, Canada, Argentina, Chile
3009*	Multicenter, double-blind, randomized, active-controlled, comparative	Telithromycin 800 mg po qd Trovafloxacin 200 mg po qd	7 - 10 d 7 - 10 d	204	USA, Canada, South Africa
Supportive Non-Comparative Studies					
3000	Multicenter, open-label, non-comparative	Telithromycin 800 mg po qd	7 - 10 d	240	Argentina, Australia, Austria, Belgium, Finland, France, Germany, Hungary, Israel, New Zealand, Norway, South Africa, Sweden
3009OL	Multicenter, open-label, non-comparative	Telithromycin 800 mg po qd	7 - 10 d	221	South Africa
3010	Multicenter open-label, non-comparative	Telithromycin 800 mg po qd	7 d	432	USA, South America, South Africa, Canada

This study was terminated prematurely because of safety concerns with the comparator, trovafloxacin.

The dose of amoxicillin used in Study 3001 is based on treatment recommendations in Europe. This amoxicillin dose is higher than the FDA labeled dose for lower respiratory tract infections. Study 3009 was converted to an open-label trial,

study 3009OL, when restrictions were placed on the use of trovafloxacin. Study 3010 was submitted in a major amendment to the original NDA, in order to increase the number of CAP patients with drug-resistant *S. pneumoniae*.

The clinical response (cure, fail, or indeterminate) was generally assigned at a test-of-cure (TOC) visit, usually 7-10 days after the end of treatment. Patients who failed treatment at an earlier visit were assigned an outcome of failure at the TOC visit. Table E2 summarizes the FDA analysis of clinical outcomes at the TOC visit for the pivotal and supportive studies:

Table E2. FDA Analysis of CAP Clinical Responses at the TOC Visit

	Telithromycin				Comparators[1]				2-sided 95% Confidence Interval
	Regimen	N	Cure	%	Regimen	N	Cure	%	
PPc Population*									
Study 3001	TEL 10 d	149	141	94.6	AMX 10 d	152	137	90.1	(-2.1%, 11.1%)[2]
Study 3006	TEL 10 d	162	143	88.3	CLA 10 d	156	138	88.5	(-7.9%, 7.5%)[2]
Study 3009	TEL 7-10 d	80	72	90.0	TVA 7-10 d	86	81	94.2	(-13.6%, 5.2%)[2]
Study 3000**	TEL 7-10 d	197	183	92.9	-	-	-	-	
Study 3009OL**	TEL 10-d	187	175	93.6	-	-	-	-	
Study 3010**	TEL 7 d	357	332	93.0	-	-	-	-	
MITT Population*									
Study 3001	TEL 10 d	199	171	85.9	AMX 10 d	205	161	78.5	(-0.5%, 15.3%)[2]
Study 3006	TEL 10 d	204	161	78.9	CLA 10 d	212	171	80.7	(-9.9%, 6.5%)[2]
Study 3009	TEL 7-10 d	100	82	82.0	TVA 7-10 d	104	89	85.6	(-14.7%, 7.5%)[2]
Study 3000**	TEL 7-10 d	240	191	79.6	-	-	-	-	
Study 3009OL**	TEL 7-10 d	212	182	85.8	-	-	-	-	
Study 3010**	TEL 7 d	418	357	85.4	-	-	-	-	

* PPc = Clinical Per-protocol Population, MITT = Modified Intent-to-treat Population; See Appendix A for definitions

** Studies which did not include an <u>active control</u> arm

[1] TEL = telithromycin, AMX = amoxicillin, CLA= clarithromycin, TVA = trovafloxacin,

[2]Confidence interval for the difference of the two cure rates.

Table E3 provides the FDA analysis of bacteriological eradication and clinical cure rates for patients whose baseline culture(s) grew the reported pathogen. In general, the bacteriological responses are determined based on clinical outcome. Most subjects reported as clinical cures no longer produce sputum samples, and most clinical failures are categorized as having presumed persistence of the baseline pathogen.

Table E3. FDA Analysis of CAP Bacteriological Eradication and Clinical Cure Rates at the TOC Visit for Telithromycin-Treated Patients in the PPb* Population

Causative pathogen	Bacteriological eradication			Clinical cure		
	N	Cure	(%)	N	Cure	(%)
S. pneumoniae	174	166	(95.4)	174	165	(94.8)
H. influenzae	105	94	(89.5)	105	95	(90.5)
M. catarrhalis	30	27	(90.0)	30	26	(86.7)
S. aureus	19	15	(78.9)	19	15	(78.9)

* *PPb = Bacteriological Per-protocol Population; See Appendix A for definitions*

The original NDA briefing package in Appendix A describes the data available in April of 2001 regarding telithromycin treatment of CAP due to drug-resistant *S. pneumoniae*. This information is not repeated here. This briefing document will integrate old and new data regarding telithromycin treatment of CAP due to drug-resistant *Streptococcus pneumoniae*.

Table E4 provides the FDA analysis of clinical outcomes in CAP patients meeting specific serologic criteria for these atypical pathogens. Comparator patients received either clarithromycin or trovafloxacin.

Table E4. FDA Analysis of Clinical Cure Rates at the TOC Visit for Atypical Pathogens Based on Serologic Diagnosis

Pathogen	Telithromycin 7-10 Days			Comparators 7-10 Days		
	N	Cure	%	N	Cure	%
Chlamydia pneumoniae	34	32	(94.1%)	18	17	(94.4%)
Mycoplasma pneumoniae	31	30	(96.8%)	19	18	(94.7%)
*Legionella pneumophila***	12	12	(100.0%)	3	2	(66.7%)

* *Includes controlled CAP studies 3006, 3009 and uncontrolled CAP studies 3000, 3009OL and 3010.*
** *Only five cases were documented by urinary antigen; the remainder were diagnosed by serum antibody titers.*

2. New CAP Studies

In the NDA resubmission, three new CAP studies were submitted with the objective of increasing the number of CAP patients with drug-resistant *S. pneumoniae* treated with telithromycin. Table E5 provides summary information about the new CAP trials.

Table E5. Study Information for New CAP Trials

Study	Design	Treatment Regimen	Duration	N	Geographic Region/ No. of Study Sites
4003	Multicenter, Double-blind, Randomized, Active-controlled, Comparative, 3-arm parallel group	Telithromycin 800 mg qd Telithromycin 800 mg qd Clarithromycin 500 mg bid	5 days 7 days 10 days	187 191 181	Argentina, Brazil, Canada, Chile, Germany, South Africa, Spain, United Kingdom, USA
3012	Multicenter, Open-label, Non-comparative	Telithromycin 800 mg qd	7 days	538	Argentina, France, Mexico, South Africa, Spain, USA
3107	Multicenter, Double-blind, Randomized, Active-controlled, Comparative,2-arm parallel group	Telithromycin 600 mg qd Levofloxacin 100 mg tid	7 days 7 days	126 111	Japan

* N = number of patient in MITT population

The overall clinical outcomes for these new trials were reported in the Applicant's briefing package, but have not been independently reviewed by FDA. The results reported by the Applicant are generally consistent with those of the CAP trials in the original NDA submission. The FDA review has focused on the assessment of outcome in patients with CAP due to drug-resistant *S. pneumoniae*.

3. CAP due to Drug-Resistant *Streptococcus pneumoniae*

The Applicant has requested a claim for treatment of CAP due to penicillin-resistant and erythromycin-resistant *Streptococcus pneumoniae* (PRSP and ERSP, respectively). To address these claims, all available cases in the NDA database of CAP with isolates of PRSP or ERSP were identified. The main body of evidence to support PRSP and ERSP claims comes from studies conducted in Western countries ("Western studies"). These are studies 3000, 3001, 3006, 3009, 3009OL, 3010, 3012, and 4003. Although the studies varied in the duration of telithromycin treatment and blinding, the selection criteria, timing of visits, outcome definitions, and other study methods were fairly similar.

Additional cases of CAP due to PRSP and ERSP from two Japanese studies (studies 3107 and 2105) were provided as supportive evidence for these claims. These data are described separately for several reasons. First, these studies were conducted in Japanese patients, a more homogeneous population different from the "Western Studies" population in many respects. Most patients in the Japanese trials received a different, though lower, dose of telithromycin (600 mg qd) than that proposed for US patients. Finally, there were differences in the design of the Western and Japanese studies, including selection criteria and timing of the protocol-specified test of cure visit.

The following breakpoints were used to define penicillin and erythromycin resistance in *S. pneumoniae* strains:

Penicillin		**Erythromycin**	
Sensitive	< 0.06 µg/ml	Sensitive	< 0.25 µg/ml
Intermediate	0.12 < MIC < 1 µg/ml	Intermediate	0.25 < MIC < 1 µg/mL
Resistant	≥ 2 µg/ml	Resistant	> 1 µg/ml

Table E6 provides the FDA analysis of clinical cure rates for telithromycin-treated CAP patients from all Western Studies with drug-resistant *Streptococcus pneumoniae* isolated from baseline cultures (sputum and/or blood). Clinical outcome was assessed at the TOC visit. A total of 49 cases (MITT population) were identified where PRSP and/or ERSP were isolated. The table separates patients by resistance patterns. Results are shown for both the per-protocol and modified intent-to-treat populations. Of note, 16/28 (57.1%) PRSP isolates were also resistant to erythromycin.

Table E6. FDA Analysis of Clinical Cure Rates in Patients with Drug-Resistant *Streptococcus pneumoniae* by Resistance Pattern (Western Studies)

Study Population/ Resistance mechanism	Telithromycin 800 mg qd		
	N	Cure	%
PPb Population			
PRSP Only*	8	8	100
ERSP Only**	18	17	94.4
Both PRSP and ERSP***	11	8	72.7
MITT Population			
PRSP Only*	12	9	75.0
ERSP Only**	20	18	90.0
Both PRSP and ERSP***	16	11	68.8

* Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC ≤ 1 µg/ml
** Patients with isolates whose penicillin MIC ≤ 2 µg/ml and erythromycin MIC > 1 µg/ml
*** Patients with isolates whose penicillin MIC ≥ 2 µg/ml and erythromycin MIC > 1 µg/ml

In cases with PRSP isolates (regardless of erythromycin resistance), the clinical cure rate was 16/19 (84.2%) in the per-protocol group and 20/28 (71.4%) in the MITT population. For cases with ERSP isolates (regardless of penicillin resistance), the clinical cure rate was 25/29 (86.2%) in the per-protocol group and 29/36 (80.6%) in the MITT population.

In the comparative studies (3001, 3006, 3009, and 4003), there were 7 comparator-treated patients with drug-resistant *S. pneumoniae* identified in baseline cultures. One amoxicillin-treated CAP patient had ERSP isolated from sputum. The isolate was susceptible to penicillin. She was considered cured at the TOC visit. One clarithromycin-treated CAP patient had PRSP identified in baseline cultures. The isolate was susceptible to erythromycin. He was considered cured at the TOC visit.

Five CAP patients with ERSP were treated with clarithromycin in the comparative trials. At the TOC visit, 4/5 were considered cured. However, one of the clinical cures was noted to have a recurrence of pneumonia at a later follow-up visit.

The FDA analysis of outcomes for CAP patients with pneumococcal bacteremia due to drug-resistant strains is shown in the following table. In CAP patients with bacteremia due to PRSP (regardless of erythromycin resistance), the clinical cure rate was 5/7 in the per protocol group and 5/10 in the MITT population. For bacteremia due to ERSP (regardless of penicillin resistance), the clinical cure rate was 8/10 in the per protocol group and 8/11 in the MITT population.

Table E7. FDA Analysis of **Clinical Cure Rates in CAP Patients with Bacteremia** due to Drug-Resistant *Streptococcus pneumoniae* by Resistance Pattern (Western Studies)

Study Population/ Resistance mechanism	Telithromycin 800 mg qd	
	N	Cure
PPb Population		
PRSP Only*	3	3
ERSP Only**	6	6
Both PRSP and ERSP***	4	2
MITT Population		
PRSP Only*	5	3
ERSP Only**	6	6
Both PRSP and ERSP***	5	2

Patients with isolates whose penicillin MIC $\geq$ 2 µg/ml and erythromycin MIC $\leq$ 1 µg/ml
*** Patients with isolates whose penicillin MIC $\leq$ 2 µg/ml and erythromycin MIC > 1 µg/ml*
**** Patients with isolates whose penicillin MIC $\geq$ 2 µg/ml and erythromycin MIC > 1 µg/ml*

Table E8 provides the FDA analysis of clinical cure rates for telithromycin-treated CAP patients from Japanese studies with drug-resistant *Streptococcus pneumoniae* isolated from baseline sputum cultures. None of the patients in these trials had blood cultures. Although the Japanese protocols use the end-of-therapy visit for the TOC, clinical outcome was also assessed at a later visit (days 17-24).

Table E8. FDA analysis of Clinical Cure Rates in Patients with Drug-Resistant *Streptococcus pneumoniae* by Resistance Pattern (Japanese Studies)

Study Population/ Resistance mechanism	Telithromycin	
	N	Cure
PPb Population		
PRSP Only*	0	0
ERSP Only**	13	11
Both PRSP and ERSP***	8	8

Patients with isolates whose penicillin MIC $\geq$ 2 µg/ml and erythromycin MIC $\leq$ 1 µg/ml
*** Patients with isolates whose penicillin MIC $\leq$ 2 µg/ml and erythromycin MIC > 1 µg/ml*
**** Patients with isolates whose penicillin MIC $\geq$ 2 µg/ml and erythromycin MIC > 1 µg/ml*

Table E9 shows the distribution of telithromycin MIC's for clinical isolates of *S. pneumoniae* from the Western studies. The table presents the MIC distribution for ERSP separately from erythromycin susceptible or intermediate strains. The heavy line indicates the recommended FDA breakpoint for telithromycin susceptibility for *S. pneumoniae*. Of note, the telithromycin MICs for ERSP strains appear to be higher than for most *S. pneumoniae* strains. However, the clinical impact of this shift is unknown.

Table E9. Distribution of Telithromycin MIC's for CAP clinical isolates of *Streptococcus pneumoniae* from Western Studies – PPb Population

Telithromycin MIC (µg/mL)	Erythromycin Susceptible and Intermediate Strains	ERSP
	N	N
N/A	32	--
0.004	4	
0.008	125	
0.016*	112	1
0.03	14	9
0.06	1	5
0.12	1	5
0.25	--	1
0.5	--	3
1	--	5
Total	289	29

* Data for MIC values of 0.015 and 0.016 µg/mL have been pooled.

C. Acute Exacerbation of Chronic Bronchitis (AECB)

1. Summary of Original NDA Submission for AECB

The original NDA submission included two pivotal studies of AECB. Table E10 provides summary information about the pivotal trials for AECB.

Table E10. Study Information for Pivotal AECB Trials

Study	Design	Treatment Regimen	Duration	N*	Geographic Region/ No. of Study Sites
3003	Multicenter, double-blind, randomized, active-controlled, comparative, 2-arm parallel group	Telithromycin 800 mg qd Amoxicillin 500 mg/ Clavulanate 125 mg tid	5 days 10 days	163 161	Argentina , Australia, Belgium, France, Germany, Ireland, South Africa, United Kingdom
3007**	Multicenter, Double-blind, randomized, active-controlled, comparative,2-arm parallel group	Telithromycin 800 mg qd Cefuroxime axetil 500 mg bid	5 days 10 days	183 193	USA, Canada

N = number of randomized subjects
**For Study 3007, FDA excluded data from the two US sites from overall analyses (a total of 124 patients). The number of randomized subjects reflects this exclusion.

The primary efficacy variable in these studies was clinical response at the TOC visit, 17 to 21 days after the start of therapy. Table E11 provides the FDA analysis of clinical response rates in different study populations in the two AECB studies. The protocol definition for AECB and the population definitions are provided in Section IV B (pp. 20-22) of the briefing document for the April 2001 AIDAC meeting (Appendix A).

Table E11. FDA Analysis of AECB Clinical Responses at the TOC Visit

	Telithromycin 5-Days			Comparators 10-Days				2-sided 95% Confidence Interval
	N	Cure	%		N	Cure	%	
PPc Population								
Study 3003	115	99	86.1	AMC[1]	112	92	82.1	(-6.4%, 14.3%) (−10.8%; 17.0%)[2]
Study 3007	140	121	86.4	CXM[1]	142	118	83.1	(-5.8%, 12.4%)
MITT Population								
Study 3003	160	130	81.3	AMC	160	125	78.1	(-6.3%, 12.6%) (− 9.3%,14.3%)[2]

| Study 3007 | 182 | 142 | 78.0 | CXM | 191 | 138 | 72.3 | (-3.5%, 15.1%) |

[1]*AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil*
[2]*A 97.5% Confidence Interval was calculated by FDA for this study to adjust for an interim analysis.*

Bacteriological success (eradication or presumed eradication) was a secondary endpoint of the AECB studies. Bacteriological success rates in the per-protocol bacteriological population were calculated at the TOC visit. In Study 3003, bacteriological success was reported in 69.2% (27/39) for telithromycin, compared to 70% (21/30) for amoxicillin/clavulanate. In Study 3007, bacteriological success was reported in 80% (20/25) for telithromycin, compared to 78.6% (22/28) for amoxicillin/clavulanate. Bacteriological success rates for telithromycin varied between trials.

The bacteriological success rates at the TOC visit by pre-therapy pathogen are provided in the following table. This table combines results from Study 3003 and 3007. Of note, the bacteriological success rate for telithromycin against *H. influenzae* is lower than for comparator. The small numbers available do not allow for statistically meaningful conclusions regarding efficacy against individual pathogens.

Table E12. FDA Analysis of Bacteriological Success at TOC Visit by Pre-Therapy Pathogen from Combined Studies 3003 and 3007

All Pathogens	Telithromycin n/N %	Comparators n/N %
TOTAL	**54/70 (77.0%)**	**53/68 (77.9%)**
S. pneumoniae	13/14 (92.8%)	9/12 (75.0%)
H. influenzae	15/25 (60.0%)	15/17 (88.2%)
H. parainfluenzae	5/6 (83.3%)	0/1 (0.0%)
M. catarrhalis	10/10 (100.0%)	14/16 (87.5%)
S. aureus	2/2 (100.0%)	2/3 (66.6%)
Other	9/13 (69.2%)	13/19 (68.4%)

2. New AECB Data

The Applicant provided the results of an additional AECB study in the NDA resubmission. Study 3013 was a double-blind, comparative trial of telithromycin and clarithromycin in the treatment of AECB, summarized in the following table.

Table E13. New AECB Trial

Study	Design	Treatment Regimen	Duration	N	Geographic Region/ No. of Study Sites
3013	Multicenter, Double-blind, randomized, active-controlled, comparative, 2-	Telithromycin 800 mg qd Clarithromycin 500 mg bid	5 days 10 days	272 282	Argentina, Australia, Belgium, Brazil, Canada, Chile, Germany,

				Italy, Mexico, South Africa, Spain, Turkey, USA
arm parallel group				

The primary objective was to demonstrate equivalence in clinical outcomes at the TOC visit. There were five visits in the study: a pre-therapy/entry visit (Day 1); an on-therapy visit (Days 3 to 5), an end-of-therapy visit (Days 11 to13), a post-therapy/ TOC visit (Days 17 to 21) and a late post-therapy visit (Days 31 to 36). The study population consisted of adult outpatients with a documented history of chronic bronchitis; clinical findings of dyspnea, increased sputum volume, and increased purulence; and a chest X-ray excluding pneumonia.

The following table summarizes the clinical outcome rates by treatment group for the clinical per-protocol and modified intent-to-treat populations in the new study.

Table E14. FDA Analysis of AECB Clinical Responses at the TOC Visit

	Telithromycin 5-Days				Comparator 10-Days			2-sided 95% Confidence
	N	Cure	%		N	Cure	%	Interval
PPc Population								
Study 3013	225	193	85.8	CLA[1]	231	206	89.2	(-10.0%, 3.1%)
MITT Population								
Study 3013	270	224	83.0	CLA[1]	282	236	83.7	(-7.3%, 5.9%)

[1] *CLA= Clarithromycin*

Bacteriological success rates (eradication or presumed eradication) are reported by pre-therapy pathogen in Table E15. The bacteriological success rate for telithromycin against *H. influenzae* is higher than that seen in the original NDA submission. It also increases the number of *S. pneumoniae* and *M. catarrhalis* isolates.

Table E15. FDA Analysis of Bacteriological Success at TOC Visit by Pre-Therapy Pathogen from Study 3013

All Pathogens	Telithromycin n/N %	Comparators n/N %
S. pneumoniae	10/13 (76.9%)	7/7 (100%)
H. influenzae	27/35 (77.1%)	30/36 (83.3%)
M. catarrhalis	17/19 (89.5%)	17/18 (94.4%)
S. aureus	2/4 (50.0%)	4/6 (66.6%)

D.   Acute Bacterial Sinusitis (ABS)

The following section summarizes ABS data submitted with the original NDA application, as amended. No new studies of ABS were provided in the NDA resubmission.

Two studies, 3002 and 3005, were included in the original NDA submission as pivotal trials for the treatment of acute bacterial sinusitis (ABS). Study 3002 compared two different durations of telithromycin in a trial primarily designed to gather outcome data in subjects with microbiologically confirmed ABS. There was no comparator in this trial. Study 3005 was a comparative study in subjects with a clinical diagnosis of sinusitis. Study 3011 was submitted in a major amendment to the original NDA. It was submitted in order to bolster the number of patients with ABS due to drug-resistant *S. pneumoniae*. This study employed sinus puncture in US patients for microbiological diagnosis.   Table E16 summarizes pivotal ABS trials in the original NDA

Table E16. Study Information for Pivotal ABS Trials

Protocol	Study Type	Dose/Frequency/Duration	Patients Randomized	
Study 3002[1]	Multicenter, randomized, double-blind, uncontrolled trial including sinus puncture	Telithromycin 800 mg qd for 5 d Telithromycin 800 mg qd for 10 d	170 171	Austria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Sweden
Study 3005[2]	Multicenter, randomized, controlled, three-arm trial	Telithromycin 800 mg qd for 5 d Telithromycin 800 mg qd for 10 d Amox/Clav 500/125 mg tid for 10 d	245 257 251	Argentina, Canada, Chile, S. Africa, US *(US patients 64.3%)*
Study 3011[1,2,3]	Multicenter, randomized (2:1), double-blind, controlled trial including sinus puncture in US	Telithromycin 800 mg qd for 5 days Cefuroxime axetil 250 mg bid for 10 d	252 122	France, S. America, S. Africa, US *(US patients 56.4%)*

[1]*These studies were primarily intended to capture patients who had maxillary sinus punctures for bacteriologic studies.*
[2] *Patients from two investigative sites were excluded from the FDA analyses due to concerns about data integrity.*
[3] *Submitted to the NDA as part of a major amendment on February 20, 2001. Additional case-report forms were submitted on March 05, 2001.*

All three studies enrolled patients based on clinical signs and symptoms as well as radiological findings. The studies differed in the radiological criteria used for enrollment. Patients in all three studies could be enrolled with total opacification or air fluid levels on sinus X-ray. Patients with mucosal thickening of ≥ 6 mm could be enrolled in Study 3005. Patients with mucosal thickening of ≥ 10 mm could be enrolled in Study 3011. All three studies employed placebo dummy capsules to maintain blinding.

Table E17 summarizes the FDA analysis of clinical outcomes at the TOC visit for the defined populations. The TOC visit was scheduled for days 17 to 24. Clinical outcomes (cure, fail, or indeterminate) at the TOC visit were assigned based on resolution

or improvement in clinical findings, no worsening of radiological findings, and no need for subsequent antimicrobial treatment during the study.

Table E17. FDA Analysis of ABS Clinical Responses at the TOC Visit

	Telithromycin 5-Days			Comparators 10-Days				2-sided 95% Confidence Interval
	N	Cure	%		N	Cure	%	
PPc Population								
Study 3002 [1]	123	112	91.1	TEL 10-D [2]	133	121	91.0	(-7.7%, 7.9%%)
Study 3005	146	110	75.3	AMC [2]	137	102	74.5	(-9.9%, 11.7%)
Study 3011	189	161	85.2	CXM [2]	89	73	82.0	(-7.1%, 13.4%)
PPb Population								
Study 3002	70	65	92.9	TEL 10-D	69	63	91.3	(-10.3%, 7.4%)
Study 3005	7	5	87.5	AMC	8	6	66.7	(-48.5%, 41.4%)
Study 3011	100	84	84.0	CXM	49	38	77.6	(-8.8%, 21.0%)
MITT Population								
Study 3002	167	138	82.6	TEL 10-D	168	147	87.5	(-13.1%, 3.3%)
Study 3005 [3]	201	140	69.7	AMC	202	138	68.3	(-8.2%, 10.9%)
Study 3011	240	193	80.4	CXM	116	84	72.4	(-2.2% , 18.2%)

[1] Study 3002 compared two dosing regimens of TELITHROMYCIN (5 days vs. 10 days).

[2] TEL 10-D = telithromycin 10-Days, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil

[3] The results for MITT patients in Study 3005 have been corrected; they differ from the numbers in Appendix A

In the PPc population, efficacy rates differed between studies for telithromycin treatment. The higher clinical response rates in Study 3002 may be related to treatment bias, since it was known that all subjects received telithromycin (whether for 5 or 10 days). On the other hand, the lower response rates in Study 3005 are more difficult to assess without microbiological confirmation of ABS. However, the lower rates were seen in both the telithromycin and comparator patients.

Reasons for excluding patients in the mITT population from the PPc populations were: previous antibiotic therapy, insufficient treatment duration, incorrect entry diagnosis, lost to follow-up, no X-ray within 2 days of entry into study, baseline laboratory abnormality followed by treatment discontinuation.

Table E18 shows the FDA analysis of bacteriologic outcome in these studies.

Table E18. FDA Analysis of Bacteriologic Outcome (Cure) in subjects with pathogens of importance in ABS – PPb population at posttherapy/TOC (single and mixed isolates)

Pathogen	Telithromycin 5 d	Telithromycin 10 d	Amox/Clav	Cefuroxime
S. pneumoniae	49/55 (89.1%)	24/26 (92.3%)	2/4 (50%)	12/12 (100%)
H. influenzae	36/42 (85.7%)	12/12 (100%)	1/1 (100%)	12/14 (85.7%)
M. catarrhalis	12/13 (92.3%)	3/4 (75%)	1/1 (100%)	6/6 (100%)

The Applicant has requested the indication of acute sinusitis due to *S. pneumoniae,* including penicillin- and erythromycin-resistant strains. Table E19 shows the FDA analysis of telithromycin efficacy across the three ABS studies in the PPb population for drug-resistant *S. pneumoniae*.

The definition of the breakpoints for *S. pneumoniae* follows:

Penicillin		Erythromycin	
Sensitive	< 0.06 µg/ml	Sensitive	< 0.25 µg/ml
Intermediate	0.12 < MIC < 1 µg/ml	Intermediate	0.25 < MIC < 1 µg/mL
Resistant	≥ 2 µg/ml	Resistant	> 1 µg/ml

Table E19. FDA Analysis of Outcomes in ABS due to *S. pneumoniae* by resistance pattern in telithromycin-treated patients (PPb population, 3 studies combined)

Study #	Outcome - Cured					
	Pen-S	**PRSP**	**Ery-S**	**Ery-R**	**Pen-S + Ery-S**	**PRSP+ Ery-R**
3002	32/37 (86.5%)	**3/3 (100%)**	30/34 (88%)	**7/8 (87.5%)**	30/34 (88%)	**3/3 (100%)**
3005	2/2 (100%)	**1/1 (100%)**	2/2 (100%)	**1/1 (100%)**	2/2 (100%)	**1/1 (100%)**
3011	10/12 (83%)	**7/9 (77.8%)**	9/11 (82%)	**10/12 (83.3%)**	9/11 (82%)	**5/7 (71.4%)**
TOTAL	44/51 (86.3%) *12 mixed* (10/12, 83%)*	**11/13 (84.6%)** *2 mixed (2/2, 100%)*	41/47 (87%) *12 mixed 9/12 (75%)*	**18/21 (85.7%)** *5 mixed (5/5, 100%)*	41/47 (87%) *11 mixed (10/11, 91%)*	**9/11 (82%)** *2 mixed (2/2, 100%)*

* mixed - cultures which contained bacterial pathogens in addition to S. pneumoniae

The applicant requested an indication for 5-day treatment of sinusitis with telithromycin. Across sinusitis studies, there were 10 patients with PRSP isolated in the 5-day treatment groups. The clinical success rate in this group was 80% (8/10). There were 4 patients with PRSP isolates in the cefuroxime axetil group in study 3011, and all were considered cures.

IV. Safety Analysis

A. Overall safety analysis

1. Phase 1 studies

a) Extent of exposure

In the original NDA submission, the Applicant presented safety data on 566 subjects receiving telithromycin in single and multiple PO dose studies and single dose IV studies. Doses of telithromycin in these studies ranged from 50 mg to 2400 mg. The vast majority of subjects (>95%) were white; most (>80%) were men. There were 55 subjects aged 65 years or older; 12 subjects with hepatic impairment; and 30 with renal impairment.

After the original NDA submission, the Applicant submitted data from additional clinical pharmacology studies comprising 84 patients. Most of these involved administration of single or multiple oral 800 mg doses of telithromycin. One study, designated 1049, enrolled 24 subjects (age range 53 – 77 years) with underlying cardiovascular disease, who received single telithromycin doses ranging from 800 – 1600 mg.

In 14 drug interaction studies, there were an additional 261 subjects who received multiple oral doses of 800 mg telithromycin. Concomitant medications or foods included ketoconazole, itraconazole, oral contraceptives, cisapride, sotalol, midazolam, digoxin, warfarin, coumadin, simvastatin, theophylline, ranitidine, antacid, paroxetine, or grapefruit juice. Subjects in these studies were healthy adults, generally less than 50 years old.

In the resubmitted NDA, the Applicant submitted data from eight additional single and multiple dose clinical pharmacology studies comprising 147 subjects; telithromycin doses ranged from 400 mg to 2400 mg The vast majority of subjects (>95%) were white; most (>75%) were men. Of subjects receiving telithromycin in these studies, 30 (20%) were 65 years of age or older. There were 48 patients with renal impairment in these studies and 12 with hepatic impairment.

b) Deaths and nonfatal serious adverse events (SAEs)

There were no deaths in Phase 1 studies. There were four SAEs in Phase 1 studies; none of these were felt to be related to telithromycin.

2. All Phase 3 studies other than 3014

a) Overview of safety database

The safety analysis contained in this section includes all Phase 3 studies submitted to date. This does not include data from the large safety study 3014. The new Integrated Summary of Safety includes all previous Phase 3 studies in addition to three new Phase 3 studies. The safety data from the three new studies was combined with the previous

Phase 3 studies and is presented together. The three new studies include Study 3012, Study 3013, and Study 4003. Details regarding these studies are contained in Table S1.

Table S1. New Phase 3 studies.

Study	Indication	Study Design	Treatment Duration	Treatment Regimen	Number of Patients
3012	Community Acquired Pneumonia	Open Label, non-comparative	7 days	800 mg qd telithromycin	550
4003	Community Acquired Pneumonia	Double Blind, randomized, active controlled, 3-arm parallel group	5 days	800 mg qd telithromycin	193
			7 days	800 mg qd telithromycin	195
			10 days	500 mg bid clarithromycin	187
3013	Acute Exacerbation of Chronic Bronchitis	Double- blinded, randomized, active controlled, 2-arm, parallel group	5 days	800 mg qd telithromycin	269
			10 days	500 mg bid clarithromycin	280

The three new Phase 3 clinical trials contributed an additional 37% to the total number of patients exposed to telithromycin during Phase 3 studies. Table S2 details the number of patients contained in the original NDA and in the new submission.

Table S2. Numbers of patients in initial and new studies by study design (uncontrolled vs. controlled)

Treatment Arm	Original NDA		New Studies		Integrated		Total
	Uncontrolled	Controlled	Uncontrolled	Controlled	Uncontrolled	Controlled	
Telithromycin	1,400	1,865	550	657	1,950	2,522	4,472
Comparator	-	1,672	-	467	-	2,139	2,139
Total	4,937		1,674		6,611		6,611

b) Patient demographics

The safety population in Phase 3 clinical studies (11 controlled and 5 uncontrolled studies) included 4472 telithromycin-treated subjects and 2139 comparator-treated subjects. Demographic and baseline characteristics for All Integrated Phase 3 studies are summarized in Table 3. There was a small increase in the proportion of elderly subjects (> 65 years) in the safety population; from 372 (11.4%) to 624 (14.0%) telithromycin-treated subjects and from 260 (15.6%) to 416 (19.4%) comparator-treated subjects. The majority of these new elderly subjects were enrolled in Studies 3012 (81 telithromycin-treated subjects) and 3013 (109 telithromycin-treated subjects and 117 comparator-treated subjects). Table S3 summarizes the demographics for the original NDA and all integrated studies (original NDA studies with new studies integrated).

Table S3. Demographic characteristics for safety population in all Phase 3 studies (controlled and uncontrolled): comparison between previous studies (original NDA) and all integrated studies (combined new studies with previous studies)

	Number (%) of subjects/characteristics					
	Previous Studies[a]			All Integrated Studies[b]		
Demographic variable	TEL 5 d N=1429	TEL 7-10 d [c] N=1836	Comparator 7-10 d N=1672	TEL 5 d N=1891	TEL 7-10 d [c] N=2581	Comparator 7-10 d N=2139
Sex						
Male	648 (45.3)	983 (53.5)	785 (46.9)	913 (48.3)	1383 (53.6)	1031 (48.2)
Female	781 (54.7)	853 (46.5)	887 (53.1)	978 (51.7)	1198 (46.4)	1108 (51.8)
Race						
White	1282 (89.7)	1409 (76.7)	1438 (86.0)	1678 (88.7)	1858 (72.0)	1830 (85.6)
Black	85 (5.9)	313 (17.0)	163 (9.7)	128 (6.8)	535 (20.7)	220 (10.3)
Asian/Oriental	28 (2.0)	32 (1.7)	26 (1.6)	34 (1.8)	37 (1.4)	30 (1.4)
Other [d]	34 (2.4)	82 (4.5)	45 (2.7)	51 (2.7)	150 (5.8)	58 (2.7)
Age (years)						
13 to 18	57 (4.0)	38 (2.1)	69 (4.1)	58 (3.1)	55 (2.1)	73 (3.4)
>18 to <65	1219 (85.3)	1579 (86.0)	1343 (80.3)	1539 (81.4)	2196 (85.1)	1650 (77.1)
≥65	153 (10.7)	219 (11.9)	260 (15.6)	294 (15.5)	330 (12.8)	416 (19.4)
N	1429	1836	1672	1891	2581	2139
Mean ± SD	41.2 ± 16.1	43.8 ± 16.0	43.7 ± 17.6	44.3 ± 17.1	44.1 ± 16.2	46.0 ± 18.1
Median	38.0	42.0	41.0	42.0	42.0	44.0
Range	13-86	13-99	13-97	13-92	13-99	13-97

[a] Includes all studies in the NDA Amendment 1; [b] Previous Studies plus 3 new studies; [c] telithromycin 7 to 10-day and 10-day regimens were pooled; [d] includes multiracial and other races (excludes those for whom race was unknown)

c) **Extent of exposure**

Of the 4,472 telithromycin-treated safety evaluable subjects in controlled and uncontrolled Phase 3 studies, 1,891 subjects participated in 5-day studies, 1,175 participated in 7-day studies and 1,406 subjects in 7- to 10-day studies. A 5-day dosing regimen of telithromycin was administered to 193 subjects in CAP studies, 609 subjects in AECB studies, 662 subjects in AS studies, and 427 subjects in tonsillitis/pharyngitis studies. A 7- to 10-day dosing regimen of telithromycin was administered to 2,160 subjects in CAP studies and a 10-day regimen to 421 subjects in AS studies.

d) **Deaths**

There were 26/6611 (0.4%) deaths in all Phase 3 studies. Of the 4472 telithromycin- treated patients, there were 17 (0.4%) deaths and of the 2139 comparator-treated patients, there were 9 (0.4%) deaths. Of the 17 telithromycin-treated patients who died, 10 (0.5%) were from uncontrolled studies and 7 (0.3%) were from controlled studies. Thirteen of the telithromycin-treated patients died while on-treatment and 4 died post-treatment. Of the 9 deaths in the comparator-treated subjects, 3 occurring while on-treatment and 6 during post-treatment.

There were no deaths in Phase 3 studies which were considered possibly related to study drug and in all deaths, the cause was identified. The majority of deaths (15 of the telithromycin exposed deaths and 5 of the comparator exposed patients) occurred in CAP studies. Causes of death in the telithromycin-treated patients included multi-organ failure, heart failure, leptospirosis, Gram-negative septicemia, aspiration, acute myocardial infarction, cardiac arrest, convulsions, AIDS, and pneumonia. Causes of death in the comparator group included asthma, lung carcinoma, pneumonia, acute lymphoid leukemia, myocardial infarction, cardiac arrest, and cardiac dysrrhythmia. None of the deaths were assessed as being related to study drug.

d) Serious Adverse Events

In the safety database combining all controlled phase 3 trials, there were a total of 59/2,522 (2.4%) serious treatment emergent adverse events (TEAEs[6]) in the telithromycin arm as compared to 61/2,139 (2.9%) in the comparator arm. There was no significant change in the rates or types of serious adverse events before and after integration of the new Phase 3 studies.

Table S4 shows a comparison between previous studies and all integrated studies with regard to all possibly related treatment emergent serious adverse events in controlled studies.

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[6] TEAE is a Treatment Emergent Adverse Event, defined as any on-treatment adverse event that was not present before treatment and became more intense (increased in severity) or frequent during the treatment period as determined by the investigators. The treatment period encompassed the period from the first day of study medication to 7 days (or three days for clinical pharmacology trials) after the last day of study medication.

Table S4. Possibly related serious adverse events in all controlled Phase 3 studies: comparison between previous studies (original NDA) and all integrated studies (combined new studies with previous studies)

Serious adverse event preferred term	Number (%) of subjects			
	Previous Studies[a]		All Integrated Studies[b]	
	TEL	Comparator	TEL	Comparator
	(N=2045)	(N=1672)	(N=2702)	(N=2139)
Subjects with possibly related serious TEAEs [d]	**8 (0.4)**	**4 (0.2)**	**9 (0.3)**	**6 (0.3)**
Hepatocellular damage [e]	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Colitis pseudomembranous	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.0)
Hypersensitivity NOS	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.0)
AECB NOS	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Drug hypersensitivity	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Erythema multiforme	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Gastroenteritis NOS	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Vomiting NOS	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Dyspnea NOS	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
GI disorder NOS	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Mania	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Overdose NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
a Includes all controlled studies in NDA Amendment 1.				
b Previous Studies plus CAP Study 4003 and AECB Study 3013.				
c Based on a minimum of 2 subjects with all serious TEAE in telithromycin group in controlled studies.				
d All possibly related serious TEAEs in controlled studies are shown.				
e Asymptomatic transaminase elevation				
NOS = not otherwise specified				

The one additional possibly related nonfatal serious TEAE in the telithromycin treated population was a 51-year-old woman who was enrolled in an AECB study, Study 3013. She had worsening of her acute exacerbation of chronic bronchitis 10 days after completion of her study medication as the serious adverse event.

In the new uncontrolled study (Study 3012), there was one additional possibly related non-fatal serious TEAE. This patient was a 24-year-old with community acquired pneumonia who experienced a worsening pleural effusion requiring hospitalization for aspiration of the effusion. This patient had a sputum culture which was positive for *H. influenzae.*

c) Adverse Events

Table S5 shows the most common TEAE's in controlled Phase 3 studies. Rates of the most common TEAE's did not change significantly when the new studies were integrated with the previous studies.

Table S5. All TEAEs by decreasing frequency in <u>controlled </u>Phase 3 telithromycin studies: All Integrated Studies

Preferred term	Number (%) of subjects	
	All Integrated Studies[*]	
	TEL	Comparator
	N=2702	N=2139
Diarrhea NOS	292 (10.8)	184 (8.6)
Nausea	213 (7.9)	99 (4.6)
Headache NOS	148 (5.5)	125 (5.8)
Dizziness (excluding vertigo)	99 (3.7)	57 (2.7)
Vomiting NOS	79 (2.9)	48 (2.2)
Loose stools	63 (2.3)	33 (1.5)
Dyspepsia	46 (1.7)	31 (1.4)
Dysgeusia	43 (1.6)	77 (3.6)
Abdominal Pain **	65 (2.4)	32 (1.5)

*Previous Studies plus CAP Study 4003 and AECB Study 3013.
** Includes MedDRA preferred terms: Abdominal pain NOS, abdominal pain upper, and abdominal pain lower. Individual patients may have had more than one of these adverse events.

Because telithromycin is metabolized by CYP 3A4, and because telithromycin exposure is increased by concomitant administration of CYP 3A4 inhibitors, it was of interest to examine adverse event rates in patients receiving 3A4 inhibitors. Table S6 shows the rates of the most common TEAEs in patients who received or did not receive a 3A4 inhibitor. Although rates were higher in patients who received 3A4 inhibitors, this pattern was not consistent. Because patients were not randomized on the basis of 3A4 inhibitor administration, this analysis must be interpreted with caution.

Table S6. Frequency of TEAE's in All <u>Controlled</u> Studies by the Presence of CYP3A4 Inhibitors

Preferred Term	Received CYP 3A4 Inhibitor		Did not Receive CYP 3A4 Inhibitor	
	TEL N=484	Comparators N=424	TEL N=2218	Comparators N=1715
Diarrhea NOS	60 (12.4%)	33 (7.8%)	232 (10.5%)	151 (8.8%)
Nausea	45 (9.3%)	18 (4.2%)	168 (7.6%)	81 (4.7%)
Vomiting	19 (3.9%)	13 (3.1%)	60 (2.7%)	35 (2.0%)
Dyspepsia	12 (2.5%)	3 (0.7%)	34 (1.5%)	28 (1.6%)
Gastritis NOS	6 (1.2%)	2 (0.5%)	6 (0.3%)	9 (0.5%)
Liver Function Abnormality*	14 (2.9%)	7 (1.7%)	57 (2.6%)	48 (2.8%)
Headache	23 (4.8%)	22 (5.2%)	125 (5.6%)	103 (6.0%)
Dizziness (excluding vertigo)	19 (3.9%)	13 (3.1%)	80 (3.6%)	44 (2.6%)

* This includes all combined reports of the following preferred terms: LFT tests NOS abnormal, ALT increase, AST increase, Transaminase NOS increase, Alkaline Phosphatase NOS increase. Individual patients may have had more than one of these adverse events.

f) Discontinuations

In Phase 3 controlled trials, discontinuations due to adverse events occurred in 119/2702 (4.4%) of telithromycin-treated patients and 92/2139 (4.3%) of comparator-treated patients. Table S7 shows the most common reasons for discontinuation in <u>controlled</u> trials.

Table S7. All and possibly related TEAEs resulting in discontinuation of study medication in controlled Phase 3 telithromycin studies

Preferred term	Number (%) of subjects	
	TEL (N = 2702)	Comparator (N = 2139)
Subjects with TEAE resulting in discontinuation of study medication	**119 (4.4)**	**92 (4.3)**
Diarrhea NOS	23 (0.9)	13 (0.6)
Vomiting NOS	21 (0.8)	10 (0.5)
Nausea	19 (0.7)	10 (0.5)
Liver function tests NOS abnormal	5 (0.2)	5 (0.2)
Abdominal pain NOS	5 (0.2)	2 (0.1)
Dizziness (excl vertigo)	5 (0.2)	1 (0.0)
Headache NOS	2 (0.1)	7 (0.3)
Rash NOS	2 (0.1)	5 (0.2)
Subjects with possibly related TEAE resultingin discontinuation of study medication	**86 (3.2)**	**60 (2.8)**
Diarrhea NOS	22 (0.8)	13 (0.6)
Vomiting NOS	21 (0.8)	7 (0.3)
Nausea	19 (0.7)	9 (0.4)
Liver function tests NOS abnormal	3 (0.1)	3 (0.1)
Abdominal pain NOS	5 (0.2)	2 (0.1)
Dizziness (excl vertigo)	5 (0.2)	1 (0.0)
Headache NOS	2 (0.1)	5 (0.2)
Rash NOS	2 (0.1)	5 (0.2)
Note: The numbers in each column are not additive because a subject may have had more than one adverse event that resulted in discontinuation of study medication. NOS = not otherwise specified		

3. Study 3014

a) General background and design

Study 3014 was an open-label, randomized, comparative, multicenter, US clinical trial which was conducted primarily to provide additional safety information for telithromycin 800 mg taken orally once per day versus amoxicillin-clavulanic acid (AMC) 875/125 mg orally bid for 7 to 10 days. Subjects were enrolled on the basis of a clinical diagnosis for three community-acquired respiratory tract infections: community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), or acute sinusitis (AS). Subjects randomized to telithromycin received 7-10 days of treatment for either CAP or AECB and 5 days for AS. The treatment duration for AECB was increased in this study to provide more data on the longer treatment duration although the Applicant is requesting approval of a 5-day treatment regimen for AECB. All subjects randomized to AMC were treated for 7-10 days.

There were four pre-specified safety endpoints, otherwise referred to as adverse events of special interest (AESIs): hepatic, cardiac, visual and vasculitic. Telithromycin had been studied previously in 3265 subjects with CAP, AECB, AS and tonsillitis-pharyngitis due to *S. pyogenes*. There was one case of significant hepatic injury among those previously studied subjects. Study 3014 was therefore sized to detect adverse events (AEs) with an incidence of $\geq 1/4000$, with a possibility of observing other rare adverse events. Additional safety data on elderly subjects and subjects treated for CAP were particularly desirable because many of the hepatic-related adverse experiences were observed among those patients in previous studies. Subjects with concomitant illnesses and concomitant drug use were also targeted for enrollment, such as subjects with pre-existing cardiovascular disease, known hepatic impairment, and renal impairment.

Inclusion criteria were: males and females ≥ 18 years of age, and fulfillment of a clinical diagnosis based on investigator's judgment for one of the three respiratory infections. Subjects were to be excluded if they had a known history or congenital long-QT syndrome, were pregnant or breast feeding, were hypersensitive to telithromycin or beta-lactams or macrolides, had a previous history of cholestatic jaundice or hepatic dysfunction associated with AMC, and subjects who required treatment with ergot alkaloid derivatives, terfenadine, cisapride, astemizole or pimozide.

There were three scheduled visits:

- Visit 1 (Day 1, pretherapy/entry): Screening, including informed consent and clinical laboratory tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and alkaline phosphatase), randomization, dispense and start treatment with study medication.

- Visit 2 (Day 17 to 22, post-therapy): Document dates of first and last dose of study medication, conduct clinical laboratory tests, evaluate safety and effectiveness.

- Visit 3 (Day 30 to 35, late post-therapy): Evaluate safety and effectiveness.

Subjects were to be seen in the clinic at Visits 1 and 2, while Visit 3 could be performed either as a telephone visit or with the subjects attending the clinic (at the

investigator's discretion, or depending on whether an SAE or an AESI occurred at or before Visit 2). In order to increase ascertainment of potential hepatic AESI which could be missed if only clinically overt symptoms were relied upon, all subjects were required to have repeat laboratory tests at visit 2. All subjects who met a pre-defined threshold of increases in laboratory assays were then to be followed up until lab data were within normal ranges (for those who began with normal baseline values) or returned to baseline values (for those with abnormal baseline values). Follow-up for subjects with hepatic AESI was carried out for 6 months post-therapy.

Clinical evaluation committees/consultants (CEC) were set up by the Applicant as experts to adjudicate AESIs in a blinded fashion within 5 working days of the investigator's documentation of the AESI. Case files of all reported AESIs that were sent to the appropriate CEC for review and adjudication contained the entire CRF, AESI forms, SAE forms, the patient profile, a subject narrative, laboratory values, ECGs, and any available hospital records or office notes. All information identifying the study drug received was removed from the case file to maintain the blind for adjudication.

There were three major limitations of the design and conduct of this study. First, there was no explicit algorithm to guide investigators in the diagnostic evaluation of an AESI. Although follow-up procedures were listed on the CRF, tests were infrequently done, or done so long after the end of treatment, that the information obtained was potentially quite limited. Thus, data required to support documentation of the complete clinical experience of these subjects was not adequate. For example, one patient with a suspected drug-related hepatic AESI underwent liver biopsy, but not until three weeks after his treatment course had ended; this lag greatly decreased the sensitivity of the biopsy as far as detecting an eosinophilic infiltrate or other evidence of drug-associated hepatitis. Having an algorithm that each investigator followed during the trial would have greatly improved data collection, completeness, and usefulness in assessing AESIs. For example, there was no guidance given to the investigators as to when to involve a specialist such as a hepatologist, or when a liver biopsy might be desirable, or follow-up of subjects with visual disturbance lasting over several days by an ophthalmologist. The absence of a rational diagnostic algorithm resulted in missing data, leading to underestimation of drug-related events. Missing data would also decrease the power of the study to detect any differences between treatment arms.

Second, according to the Applicant's study report, "*While it was initially planned that cases would be reviewed in an ongoing fashion by the CECs, due to the nature of the follow-up process and data and record collection, the majority of cases were reviewed by the CECs in an aggregate at the end of the study.*" Since these subjects were not reviewed on an ongoing basis during the study, it was not possible for the CECs to request additional data in a timely fashion, which they were explicitly authorized to do. Lack of such data would again lead to underestimation of rates of drug-related events, and minimize differences between treatment arms.

Finally, hepatic and vasculitis endpoints were defined in the study protocol as positive if there was a possible relation to study drug. However, the adjudication form provided to the CECs explicitly provided that an AESI could be considered a positive endpoint only if alternative explanations had been excluded, effectively

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changing the endpoint to one of a definite, rather than possible, drug-related event.
Again, this aspect of the study would lead to underestimation of drug-related event rates,
and blur any differences between treatment arms.

b) Patient demographics

Twenty-four thousand and twenty-four (24,140) subjects were randomized in a
1:1 fashion to telithromycin or AMC. All but three subjects were evaluable for safety
(telithromycin: 12159; amoxicillin-clavulanic acid: 11978). Approximately 10% of
subjects were treated for CAP, 30% for AECB and 60% for AS. While the general target
of a combined enrollment of 40% of subjects with CAP or AECB was achieved, only
10% of the subjects were treated for CAP. Approximately 45% of all subjects were ≥50
years of age with about 18% of the study population of ≥65 years of age. About 1% of
subjects (telithromycin: 97, 0.8%; AMC: 119, 1.0%) had known hepatic impairment,
0.6% had renal impairment (telithromycin: 78, 0.6%; AMC: 76, 0.6%) although only
about 0.2% had known creatinine clearance of <30 mL/min (telithromycin: 23, 0.2%;
AMC: 17, 0.1%), about 33% of subjects in both treatment groups had underlying cardiac
disorders, and 9% of subjects had diabetes (telithromycin: 1126, 9.3%; AMC: 1075,
9.0%). A total of 13,435 subjects (telithromycin: 6852 ,56.4%; AMC: 6583 ,55.0%) took
selected concomitant non-antimicrobial medications of interest during treatment with
study medication are summarized in Table S8.

Table S8. Study 3014: Selected concomitant non-antimicrobial medication of interest in
the safety evaluable population irrespective of indication

Concomitant non-antimicrobial medication	Number (%) of subjects			
	TEL		AMC	
Total safety evaluable population	12159		11978	
Total subjects with non-antimicrobial concomitant medications of interest	6852	(56.4)	6583	(55.0)
Antiarrhythmic drugs	32	(0.3)	59	(0.5)
Class Ia	4	(0.0)	11	(0.1)
Class III	28	(0.2)	48	(0.4)
CYP3A4 inhibitors (as classified by Applicant)	353	(2.9)	377	(3.1)
Mild	139	(1.1)	116	(1.0)
Moderate	122	(1.0)	158	(1.3)
Strong	99	(0.8)	116	(1.0)
Drugs metabolized by CYP3A4	988	(8.1)	936	(7.8)
Drugs metabolized by CYP2D6	514	(4.2)	531	(4.4)
Diuretics (hypokalemic)	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	(6.8)	797	(6.7)
Central nervous system drugs	3649	(30.0)	3474	(29.0)
Acetaminophen (paracetamol)	1337	(11.0)	1295	(10.8)
HMG Co-A inhibitors of interest [a]	1420	(11.7)	1341	(11.2)

[a] Simvastatin, lovastatin, atorvastatin

c) Deaths

Deaths were categorized according to time of occurrence. There were a total of 35 deaths (telithromycin: 14; AMC: 21) which occurred during complete follow-up period. Three deaths were not included in the clinical database, but were noted by the Applicant in the study report and case report forms were provided. Table S9 shows all deaths which occurred during the study by indication. One case was not reported as a serious adverse event. The overall incidence of mortality was 0.15% (35/24,137). Review of source data showed that for subjects who died during the study, a relationship of death to study medication in both treatment arms was not highly probable.

Table S9. Study 3014: All deaths reported during the study irrespective of when the event occurred: By indication

All deaths reported [a]	Number of subjects	
	TEL[b]	AMC
All indications	14	21
CAP	1	6
AECB	8	9
AS	5	6

[a] Includes three deaths that were not included in the database but were acknowledged by Applicant and CRFs were available.
[b] TEL, Telithromycin, AMC, amoxicillin-clavulanic acid

All deaths among telithromycin-treated subjects by indication are shown Table S10. The average age of the deaths among telithromycin-treated subjects was approximately 63 years (range: 42 - 81 years). There were no deaths that were coded as possibly related to study drug by the investigator.

Table S10. Study 3014: Deaths among subjects treated with telithromycin: All indications irrespective of when the death occurred

Deaths among subjects treated with telithromycin: All indications irrespective of when the death occurred				
Subject Number	Age/Sex/ Race [a]	Last day on study drug	Day of Death [b]	Cause of death (Per investigator)
Telithromycin: Community-acquired pneumonia (N = 1)				
1814/086	48/ M/ White	4	17	Cardiac arrest
				Empyema
Telithromycin: Acute exacerbation of chronic bronchitis (N = 8)				
1766/018	52/ M/ White	3	3	Cerebrovascular accident NOS
2827/002	66/ M/ White	5	7	Cardiac arrest
				Pneumonia NOS
				Sepsis NOS
0211/004	81/ M/ White	unknown	17	Coronary artery disease aggravated
				Aortic aneurysm
0885/002	42/ M/ White	11	30	Cardiac arrest
1987/001	74/ F/ White	11	41	Cerebrovascular accident NOS
0136/025	63/ F/ White	11	44	Respiratory failure
1766/013	81/ F/ White	11	46	Pressure sore
				COPD exacerbated
0406/051	71/ M/ White	11	66	Respiratory failure
				Renal failure NOS
Telithromycin: Acute sinusitis (N = 5)				
0198/023	74/ M/ White	2	14	Myocardial infarction
				Hepatorenal failure
1305/006	56/ F/ White	11	14	COPD exacerbated
1760/029	56/ F/ White	11	31	Acute myocardial infarction
0403/062	57/ M/ White	unknown	32	Cardiac arrest
0639/056	67/ M/ White	11	33	Death NOS

[a] M = Male, F = Female, NOS₌Not otherwise specified
[b] Day of death relative to start of study drug

All deaths among AMC-treated subjects by indications are listed in Table S11. The average age of the deaths among AMC treated subjects was approximately 71 years (range: 37 - 90 years). There were no deaths which were coded as possibly related to study drug by the investigator.

Table S11. Study 3014: Deaths among subjects treated with amoxicillin-clavulanic acid: All indications irrespective of when the death occurred

Subject Number	Age/Sex/ Race [a]	Last day on study drug	Day of Death [b]	Cause of death (Per investigator)
**Deaths among subjects treated with amoxicillin-clavulanic acid: All indications irrespective of when the death occurred**
**Amoxicillin-clavulanic acid: Community-acquired pneumonia (N = 6)**
3168/003	88/ M/ White	1	15	Intestinal perforation NOS [a] Pneumonia NOS
0590/002	90 /M/ White	8	21	Pneumonia aggravated Pulmonary edema NOS
0427/004	82 /M/ White	11	26	COPD Sepsis NOS
1921/002	68/ M/ White	1	37	Metastatic carcinoma
1696/015	80/ F/ White	11	37	Aortic aneurysm
0249/070	80/ F/ White	3	78	COPD, pneumonia aggravated
**Amoxicillin-clavulanic acid: Acute exacerbation of chronic bronchitis (N = 9)**
1228/111	71/ F/ White	3	7	Respiratory failure
1302/002	73/ M/ White	11	13	Respiratory arrest
0098/011	72/ F/ White	11	23	Acute myocardial infarction
0728/008	62/ F/ Black	11	28	Myocardial infarction
1769/018	89/ M/ White	11	30	Acute respiratory failure Pneumonia pseudomonal
0050/015	46/ M/ White	8	31	Carcinoma NOS
0728/059	68/ M/ Black	unknown	32	Cardiac failure NOS
0443/002	82/ F/ White	8	42	Cerebrovascular accident NOS
0639/022	37/ M/ White	11	52	Cardiopulmonary arrest
**Amoxicillin-clavulanic acid: Acute sinusitis (N = 6)**
0074/014	62/ F/ White	11	21	Cardiac arrest
2792/019	82/ M/ White	11	27	Cerebral hemorrhage
0838/037	81/ M/ White	11	29	Myocardial infarction
0787/005	80/ M/ White	11	32	Sepsis NOS
0884/001	59/ M/ White	11	36	Metastatic tumors to lung
1339/034	47/ F/ White	11	52	Respiratory failure

[a] M = Male, F = Female, NOS Not otherwise specified
[b] Day of death relative to start of study drug

d) Discontinuation of study medication regardless of reasons

A total of 1639 (6.8%) subjects in the safety evaluable population discontinued the study medication before completion of the assigned treatment duration. The main reasons for discontinuing study medication are summarized Table S12. Approximately 93% of subjects in both treatment groups completed the course of therapy.

Table S12. Study 3014: Reasons for discontinuation of study medication irrespective of indication

Reason for discontinuation of study medication	Number (%) of subjects			
	TEL		AMC	
Total safety evaluable population	12159		11978	
Total with TEAEs leading to discontinuation of Study medication	725	(6.0)	914	(7.6)
Adverse event (TEAE or non-TEAE)	490	(4.0)	594	(5.0)
Other (loss to follow-up, withdrew consent, subject stopped taking medication on his own for various reasons)	170	(1.4)	237	(2.0)
Failure of study drug	72	(0.6)	83	(0.7)

TEL = telithromycin, AMC = amoxicillin-clavulanic acid
Note: Subjects may have more than one reasons for discontinuing study medication.

Within indications, reasons for discontinuation were largely balanced between treatment groups, with the exception of discontinuation due to failure of the drug in CAP subjects (telithromycin: 7/1092 ,0.6%; AMC: 16/1053, 1.5%) and AECB subjects (telithromycin 33/3786, 0.9%; AMC: 20/3668, 0.5%) and discontinuation due to adverse event in AS subjects (telithromycin: 223/7281, 3.1%; AMC: 335/7257, 4.6%).

e) Discontinuation of study medication due to TEAEs

In general there was a low rate of discontinuations from study medication in both treatment arms. Study medication was permanently discontinued due to TEAEs in 1024 subjects (telithromycin: 467/12159, 3.8%; AMC: 557/11978 , 4.7%). The majority of TEAEs leading to discontinuation of study medication were considered possibly related to treatment (telithromycin 369/12159, 3.0%; AMC 484/11978, 4.0%). There was slightly more discontinuations in the AMC treatment arm as whole due largely to diarrhea. In the telithromycin treatment group, the most common TEAE leading to discontinuation of study medication was nausea. The most common TEAEs leading to permanent discontinuation of study medication are summarized in Table S13. Telithromycin reported more discontinuations due to blurred vision and dizziness. There were no notable differences in the nature of TEAE leading to discontinuation of study medication between the different groups. The incidence of such events appeared greater in subjects >50 years in both treatment groups (telithromycin 247/5671, 4.4%; AMC 299/5536,5.4%) than in subjects <50 years (telithromycin 220/6481, 3.4%; AMC 257/6436, 4.0%).

Table S13. TEAEs leading to discontinuation of study medication in >0.2% subjects in either treatment group irrespective of indication

Reason for discontinuation of study medication due to TEAEs	Number (%) of subjects			
	TEL		AMC	
Total safety evaluable population	12159		11978	
Total with TEAEs leading to discontinuation of Study medication	467	(3.8)	557	(4.7)
Nausea	83	(0.7)	88	(0.7)
Diarrhea NOS	75	(0.6)	224	(1.9)
Vomiting NOS	40	(0.3)	57	(0.5)
Dizziness (excluding vertigo)	38	(0.3)	10	(0.1)
Headache NOS	36	(0.3)	21	(0.2)
Vision blurred	23	(0.2)	2	(0.0)
Abdominal pain NOS	22	(0.2)	29	(0.2)
Rash NOS	12	(0.1)	23	(0.2)
Urticaria NOS	10	(0.1)	18	(0.2)

TEL = telithromycin, AMC = amoxicillin-clavulanic acid, NOS = not otherwise specified

4. Post-Marketing Safety Data

Telithromycin was first approved in the European Union (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, and United Kingdom) through the Centralized Procedure for use in respiratory infections on 09 July 2001. The approved indications for use are as follows: CAP, AECB, AS, and tonsillitis/pharyngitis. Telithromycin was first launched in Germany in October 2001. Since that time, it has been marketed in five countries: Germany, Spain, Italy, Brazil and Mexico. In addition, there is one ongoing post-marketing observational survey conducted among general practitioners in Germany

During the period from 09 July 2001 through 24 April 2002, more than 500,000 courses of therapy of telithromycin have been sold worldwide for the four approved indications. Of these, about 63% were sold in Germany, 30% from the other European countries (Italy and Spain), and the remaining 7% from Latin American countries (Brazil and Mexico). This number can serve as a rough approximation of courses of treatment administered, where exact data for dispensed prescriptions are not available.

A single post-marketing survey (HMR3647A/5001) conducted with general practitioners in Germany was ongoing at the time of the NDA re-submission. This is an open, uncontrolled, observational survey in outpatients with CAP, AECB, AS, or tonsillitis/pharyngitis treated with telithromycin to collect safety and efficiency (efficacy in a real use setting) data under conditions of usual medical practice. Participating physicians were asked to report all adverse events seen, regardless of association to drug. All SAEs were to be reported within 24 hours, following the Applicant's standard operating procedure (SOP). Liver enzyme values were collected at the discretion of the treating physician as medically indicated (standard of care). Additionally, all adverse events that represented adverse events of interest (as identified by the Applicant's German Pharmacovigilance group) were actively followed up using the standardized AESI questionnaire designed for Study 3014 to attempt to capture maximal information

retrieval on these important events. However, following local regulations, there was no direct access to patient records and no office monitoring was performed.

A total of approximately 28,000 patient records from this survey have been received as of 24 April 2002 (approximately 86% of surveillance forms distributed).

B. Hepatic safety

1. Overview of hepatic safety

The hepatic risk profile of telithromycin is notable for the following:

- Toxicologic studies show the liver to be the main site of telithromycin toxicity.

- Telithromycin is metabolized by the 3A4 isoform of cytochrome P450, a potential pathway for generation of hepatotoxic metabolites

- In Phase 1 studies, a cluster of elderly subjects receiving a single 2 g dose of telithromycin showed elevations in serum transaminases.

- In the original NDA, a serious hepatic adverse event occurred in a telithromycin-treated patient with a liver biopsy showing centrilobular necrosis and eosinophilic infiltration, changes strongly suggestive of a hypersensitivity type drug-related liver injury and similar to those described in cases of trovafloxacin-associated hepatitis. Several months later this patient went on to have an episode of asymptomatic elevations in his ALT and AST and a second liver biopsy showing changes consistent with chronic hepatitis, probably autoimmune.

- Analyses of liver function tests from the comparative Phase 3 studies in patients who were normal at baseline show a greater proportion of patients with low level elevations of aspartate aminotransferase (AST) and to a lesser extent alanine aminotransferase (ALT) in the telithromycin-treated patients from the CAP studies. The AST and ALT elevations from patients in the CAP studies were present during the On-Therapy and Post-Therapy visits. Patients with concomitant transaminase and total bilirubin elevations were infrequent, but only found in telithromycin-treated patients and were categorized as low level elevations between 1x and 2x the upper limit of normal (ULN).

- Study 3014, the large safety study, compared telithromycin to amoxicillin/clavulanic acid; the latter agent is a recognized cause of cholestatic hepatitis.

- In Study 3014, there were five patients (three telithromycin and two amoxicillin-clavulanic acid) with hepatic endpoints (hepatic AESIs possibly related to study drug) adjudicated by the study's Clinical Evaluation Committee (CEC). The FDA medical reviewer agreed with the CEC's assessment of these cases. One telithromycin-treated patient in this group had a liver biopsy performed which showed cholestasis and " rare red dead hepatocytes" ; however, the biopsy was performed more than three weeks after telithromycin treatment had ended. The FDA medical reviewer assessed one other

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telithromycin-treated patient as having a possibly drug-
related hepatic AESI.
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- Analyses of liver function tests in Study 3014 showed a higher rate of high (>8x ULN) transaminase elevations in telithromycin-treated patients compared to amoxicillin/clavulanic acid-treated patients. In addition, there was a higher incidence of such elevations in patients receiving 7 to 10 days of telithromycin compared to patients receiving 5 days of telithromycin.

- As of the date of this briefing document, post-marketing safety reports received by the FDA regarding telithromycin-treated patients in countries where telithromycin has been approved have included 54 hepatic adverse events; 19 of these were considered serious.

2. Preclinical studies

FDA analyses of preclinical studies in the original NDA relevant to hepatic safety are presented in Section II of the FDA briefing document (presented as Appendix A of this briefing document) for the April 2001 AIDAC meeting. A brief synopsis is presented here.

In preclinical studies in rats, dogs, and monkeys, the main site of organ toxicity for telithromycin was the liver, with the kidney as a second target organ. Electron microscopic examination of selected tissues (hepatocytes, bile duct epithelium, and renal epithelium) found that telithromycin was stored in lysosomes. Telithromycin is primarily metabolized by the liver by cytochrome P450 3A4 (CYP 3A4) and to a lesser extent by cytochrome P450 1A.

3. Phase 1 studies

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In Phase 1 studies, several telithromycin-treated
patients experienced hepatic adverse events. There was a
clustering of events (elevated alanine aminotransferase
(ALT) and aspartate aminotransferase (AST)) in elderly
subjects receiving a single 2000 mg dose of telithromycin
(the highest dose received by elderly subjects). The
elevations occurred between 7 to 17 days after the last dose
of telithromycin. All three of these elderly patients had
negative serologic evaluations for Hepatitis A, B, and C.
These patients also underwent serologic testing at the time
of the event for cytomegalovirus (CMV), Epstein-Barr virus
(EBV), Herpes Simplex virus (HSV), and toxoplasmosis. One of
the subjects had a serology that was positive for CMV IgG
and IgM and another of the three had a serology positive for
EBV IgG and IgM. However, consideration of all of the
serologic information in the patient group in which these
events are occurring does not provide convincing evidence
that these events are due to either CMV or EBV. The
possibility remains that these may be drug-related events
with a one to two week latency period. In the single dose
studies of 2400 mg in young subjects, no hepatic adverse
events were reported. There was one hepatic adverse event in
the single dose studies of young subjects receiving 3200 mg.
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In the highest doses studied in multiple dose studies of
telithromycin (1600 mg qd and 1200 mg po qd), no hepatic
adverse events were noted. In examining these results it is
important to consider that the design of the Phase 1 studies
may limit the degree to which such studies can be expected
to provide evidence of drug-induced hepatic toxicity.
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Review of hepatic laboratory abnormalities in the new Phase 1 studies is ongoing. In Study 1060, one healthy control subject with a normal total bilirubin level at baseline developed an increase in total bilirubin to >1.5x the upper limit of normal by day 4 of telithromycin dosing, but without any increase in transaminase levels. The subject's bilirubin level returned to normal after the telithromycin course ended.

4. Phase 3 studies

a) Deaths and Serious Adverse Events due to hepatic disorders

There were no deaths attributed to hepatic causes in controlled Phase 3 studies. There were four serious hepatic adverse events in these studies (three in telithromycin-treated patients and one in a comparator-treated patient). Full case narratives for these patients are presented in Appendix E. Of these, two of the hepatic SAEs in telithromycin-treated subjects were plausibly related to telithromycin therapy, as described in the original Advisory Committee Briefing Document from April 26th, 2001. These SAEs were as follows.

A 53 year-old male with CAP from a study center in Finland was enrolled in the non-comparative CAP study. At baseline his ALT was slightly elevated [ALT=81 U/L (normal range (NR) <49)] and his peripheral eosinophil count was 774 cells/10^{-6}L (lab normal range not available). He completed 10 days of telithromycin at 800 mg po qd. Four days after completing therapy, he developed a gastroenteritis-like illness similar to other members of his family, except that the subject's fever persisted. Ten days after completing therapy he had laboratory studies drawn that demonstrated elevations of his ALT to 7x ULN and AST to 5x ULN with eosinophilia. His ALT increased to a peak of 31x ULN and his eosinophils peaked at 2856 cells/10^{-6}L. Serologic evaluations for hepatitis A, B, and C, were negative. Throughout the episode his T. Bili. was only mildly elevated (<1.6 x ULN). During this episode of hepatitis, he had a liver biopsy that showed centrilobular hepatic necrosis with eosinophilic infiltration. Other medications that the patient received around the time of this event included inhaled Atrovent, salbutamol, and fluticasone, Nasonex spray (mometasone furoate), six 500 mg acetaminophen tables over a one week time period. His ALT elevation almost completely resolved in the absence of specific therapy by 6-weeks after initial detection of the hepatic event (AST levels were only infrequently monitored).

Eight months later at a routine follow-up visit, the subject was noted to have an elevated ALT of 1331 U/L in the absence of eosinophilia. Prior to this second event there was no known antecedent exposure to a ketolide or macrolide class agent. Several weeks later he underwent a liver biopsy that showed chronic hepatitis with marked activity and extensive bridging fibrosis. Review of the pathology from the liver biopsy at the Armed Forces Institute of Pathology found the pathologic changes on the first biopsy strongly

suggestive of drug-induced liver disease and the second biopsy probably consistent with autoimmune hepatitis. This event is thus consistent with drug-induced immunologic hepatic injury due to generation of neoantigens[7].

The other event plausibly related to telithromycin therapy occurred in a 76 year-old female with community-acquired pneumonia (CAP) and a history of hypercholesterolemia and hyperuricemia, maintained chronically on pravastatin 20 mg po QD and allopurinol 20 mg po QD. She experienced isolated asymptomatic elevations of ALT to 13x Upper Limit of Normal (ULN)) and AST to 9x ULN on Day 5 of therapy with telithromycin 800 mg po QD in the absence of an elevated total bilirubin (T. Bili.). Telithromycin was discontinued on Day 6 of therapy. Her transaminase abnormalities had nearly resolved by Day 12.

There were no additional treatment-emergent serious hepatic adverse events in the three new Phase 3 studies (Studies 3012, 3013, 4003).

b) Hepatic Adverse Events

Table S14 shows hepatic adverse events in the controlled Phase 3 clinical studies. The proportion of subjects experiencing hepatic adverse events was similar between telithromycin and its comparators. This was true for both "All Treatment Emergent Adverse Events (TEAEs)" and for "Possibly-Related TEAEs". In the non-comparative studies on telithromycin, there were some hepatic TEAEs which were reported slightly more frequently than in the comparative studies. The absence of a comparator group in these studies limits the extent to which any conclusions regarding causality can be made.

Table S14. Hepatic TEAEs (MedDRA Preferred Terms) in all Completed Controlled Telithromycin Phase 3 studies (excluding 3014)

	Number (%) of Subjects			
	All TEAE's		Possibly Related TEAE's	
	N=2702	N=2139	N=2702	N=2139
Preferred Term	**TEL**	**Comparator**	**TEL**	**Comparator**
LFTs NOS abnormal	28 (1.0)	26 (1.2)	19 (0.7)	18 (0.8)
ALT increased	21 (0.8)	17 (0.8)	16 (0.6)	14 (0.7)
Transaminase NOS increased	6 (0.2)	3 (0.1)	6 (0.2)	3 (0.1)
AST increased	10 (0.4)	6 (0.3)	9 (0.3)	5 (0.2)
Alkaline Phosphatase increased	6 (0.2)	3 (0.1)	1 (0.0)	3 (0.1)
LDH increased	5 (0.2)	3 (0.1)	2 (0.1)	1 (0.0)
GGT increased	5 (0.2)	3 (0.1)	1 (0.0)	3 (0.1)
Hepatocellular damage	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Hepatic Function Abnormal NOS	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Jaundice NOS	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Bilirubinemia	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Hepatitis NOS	2 (0.1)	1 (0.0)	2 (0.1)	1 (0.0)
Hepatic pain	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)

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[7] Zimmerman HJ. *Hepatotoxicity: The adverse effects of drugs and other chemicals on the liver*, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1999: pp. 136-137.

Hepatomegaly	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Hepatic cyst	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Gallbladder pain	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Cholestasis	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Total number of hepatic events*	91 (3.4)	69 (3.2)	63 (2.3)	50 (2.3)

*A subject may have had more than one hepatic TEAE.

In the controlled studies, the proportion of subjects discontinuing study medication because of hepatic TEAEs was similar for telithromycin and comparator-treated subjects. The proportion of patients discontinued from the non-comparative studies because of hepatic TEAEs was similar to that observed in the controlled studies.

c) Hepatic Laboratory Findings

In the review of the original NDA, differences were seen in the rates of laboratory abnormalities between telithromycin and comparator-treated patients. In particular, for patients in comparative CAP studies with normal ALT, AST, and total bilirubin at baseline, there was a greater proportion of telithromycin treated patients than comparator treated patients with low-level (between 1x to 3x ULN) elevations in AST. This difference was present for analyses of On-Therapy and Post-Therapy visits and absent for analyses of Late Post-Therapy visit. In the comparative CAP studies, there was a slightly greater proportion of telithromycin-treated patients than comparator-treated patients with low-level ALT elevations at On-Therapy and Post-Therapy. For patients from the comparative CAP studies with normal ALT, AST, and total bilirubin at baseline, total bilirubin elevations were infrequent in both telithromycin and comparator-treated patients. The numbers of patients experiencing elevations in excess of 3x ULN were small in both treatment groups.

Tables S15A-C show analyses of laboratory abnormalities integrating data from the two new controlled studies (3013, 4003). The results of these analyses are similar to those of the analysis of the original NDA data. There were no real changes in the previously identified trends after incorporation of data from controlled studies 3013 and 4003.

Table S15A. Changes in ALT by Visit in Controlled Phase 3 CAP Studies in Subjects with Normal ALT, AST, and total bilirubin at Baseline, Integrated controlled database

	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
Changes in ALT	**TEL**		**Comp**		**TEL**		**Comp**		**TEL**		**Comp**	
	N= 544		N= 418		N= 378		N= 337		N= 295		N= 221	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
< ULN	478	87.9	376	90.0	328	86.8	304	90.2	272	92.2	203	91.9
> ULN to ≤ 2x ULN	55	10.1	38	9.1	45	11.9	29	8.6	19	6.4	15	6.8
> 2 to ≤ 3x ULN	7	1.3	3	0.7	5	1.3	3	0.9	3	1.0	3	1.4
> 3 to ≤ 5x ULN	4	0.7	0	0	0	0.0	1	0.3	1	0.3	0	0.0
> 5 to ≤ 8x ULN	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0
> 8x ULN	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Number of patients lacking lab data for visit	31		35		197		116		280		232	

ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Table S15B. Changes in AST by Visit in Controlled Phase 3 CAP Studies in Subjects with Normal ALT, AST, and total bilirubin at Baseline, Integrated controlled database

Changes in AST	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
	TEL		Comp		TEL		Comp		TEL		Comp	
	N=545		N= 418		N= 379		N= 337		N= 295		N= 221	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
< ULN	487	89.4	387	92.6	354	93.4	326	96.7	276	93.6	203	91.9
> ULN to ≤ 2x ULN	52	9.5	27	6.5	22	5.8	11	3.3	18	6.1	17	7.7
> 2 to ≤ 3x ULN	3	0.6	2	0.5	2	0.5	0	0.0	0	0.0	0	0.0
> 3 to ≤ 5x ULN	3	0.6	2	0.5	1	0.3	0	0.0	1	0.0	0	0.0
> 5 to ≤ 8x ULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5
> 8x ULN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Number of patients lacking lab data for visit	30		35		196		116		280		232	

ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Table S15C. Changes in total bilirubin by Visit in Controlled Phase 3 CAP Studies in Subjects with Normal ALT, AST, and total bilirubin at Baseline, Integrated controlled database

Changes in total bilirubin	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
	TEL		Comp		TEL		Comp		TEL		Comp	
	N= 521		N= 403		N= 359		N= 326		N= 281		N= 214	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
< ULN	517	99.2	401	99.5	355	98.9	320	98.2	280	99.6	212	99.1
> ULN to ≤ 2x ULN	3	0.6	2	0.5	4	1.1	4	1.2	1	0.4	1	0.5
> 2 to ≤ 3x ULN	0	0.0	0	0	0	0.0	0	0.0	0	0.0	1	0.5
> 3 to ≤ 5x ULN	1	0.2	0	0	0	0.0	1	0.3	0	0.0	0	0.0
> 5 to ≤ 8x ULN	0	0.0	0	0	0	0.0	1	0.3	0	0.0	0	0.0
> 8x ULN	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Number of patients lacking lab data for visit	54		50		216		127		294		239	

ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Similar analyses in subjects from the comparative Non-CAP studies found the proportion of subjects with elevations in AST, ALT, or total bilirubin to be similar between treatment groups, with the exception that at the Late Post-Therapy visit, there was a greater proportion of comparator-treated patients with low-level elevations in AST. This pattern was also present in the original analysis. Incorporation of data from studies

3013 and 4003 did not result in a change in the previous findings for LFT's in Non-Cap patients.

The combination of elevations in transaminase and bilirubin levels may represent a signal for the potential of a drug to induce hepatocellular jaundice; an entity associated with significant mortality and morbidity[8]. In the controlled Phase 3 studies in the original NDA, there were 3 telithromycin treated subjects [3/1349 (0.2%)] with elevations of ALT and total bilirubin occurring on the same day and zero in the comparator arms [0/1139 (0.0%)] (Table S16). From the uncontrolled studies in the original NDA population and study 3009OL, there were several additional telithromycin treated patients with low level elevations involving either or both transaminases and total bilirubin. Patients with concomitant transaminase and total bilirubin elevations were infrequent, but only found in telithromycin-treated patients and were categorized as low level elevations between 1x and 2x the upper limit of normal (ULN). There were no patients with combined elevations of transaminases and total bilirubin in the new controlled Phase 3 studies.

Table S16. Concomitant ALT and Total Bilirubin or AST and Total Bilirubin or ALT and AST and Total Bilirubin Elevations During Treatment in Patients with Normal AST, ALT, and Total Bilirubin at Baseline – Patients in Original NDA and Study 3009OL

	Controlled Phase 3 Studies				Uncontrolled Phase 3 Studies	
Analysis						
	TEL		**Comparator**		**TEL**	
	n/N	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Total number of patients with						
ALT and T. bilirubin > ULN & < 2x ULN	3/1349	(0.2)	0/1139	(0.0)	6/538	(1.1)
ALT and T. bilirubin > 2x ULN & < 3x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and T. bilirubin > 3x ULN & < 5x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and T. bilirubin > 5x ULN & < 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and T. bilirubin > 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
Total number of patients with						
AST and T. bilirubin > ULN & < 2x ULN	0/1349	(0.0)	0/1139	(0.0)	4/538	(0.7)
AST and T. bilirubin > 2x ULN & < 3x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
AST and T. bilirubin > 3x ULN & < 5x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
AST and T. bilirubin > 5x ULN & < 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
AST and T. bilirubin > 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
Total number of patients with						
ALT and AST and T. bilirubin > ULN & < 2x ULN	0/1349	(0.0)	0/1139	(0.0)	4/538	(0.7)
ALT and AST and T. bilirubin > 2x ULN & < 3x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and AST and T. bilirubin > 3x ULN & < 5x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and AST and T. bilirubin > 5x ULN & < 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and AST and T. bilirubin > 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)

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[8] Zimmerman HJ. *Hepatotoxicity: The adverse effects of drugs and other chemicals on the liver*, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1999: pp. 427-456.

In the original NDA analysis, the changes in alkaline phosphatase were similar between telithromycin and comparators in both the CAP and Non-CAP studies. This similarity between telithromycin and comparators was also seen after the incorporation of data from studies 3013 and 4003.

5. Study 3014

a) Background

Concerns about the potential for telithromycin to cause hepatotoxicity and serious liver injury were a major factor in the recommendation by the Anti-Infective Drugs Advisory Committee (AIDAC) in April 2001 to obtain additional safety information about this drug.

The Applicant conducted Study 3014 in part to address these concerns and to better characterize the hepatic risk profile of telithromycin in a usual care setting.

For an overview of the objectives and general design of Study 3014, see Section IVA3. In Study 3014, liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK), and total bilirubin (Tbili) were to be collected on all subjects at baseline (Study Day 1) and visit 2 (Day 17-22). There was adequate laboratory data (baseline and visit 2) available to assess hepatic safety in 12159/12277 randomized subjects (99.0%) in the telithromycin group and 11978/12147 randomized subjects (98.6%) in the amoxicillin/clavulanate group.

b) Hepatic Adverse Events of Special Interest

Investigator reports of hepatitis, jaundice, or worsening of pre-existing hepatic function, along with all cases of ALT ≥3 x upper limit of normal (ULN), were considered to be hepatic adverse events of special interest (HAESI). These events were referred to the Hepatic Clinical Expert Committee (CEC) for evaluation. The panel, blinded to treatment assignment, reviewed medical history, concomitant medications, and symptoms provided by the investigator on the case report form (CRF), along with laboratory data and additional pertinent medical records for determination of the relationship of event occurrence to administration of study drug, as well as possible drug-related significant hepatic injury events. Repeat liver function tests and additional laboratory data to assist in evaluation of hepatic events, such as hepatitis A, B, and C serology, white blood cell count with differential, and prothrombin time were to be performed by the investigator per usual medical practice. Other diagnostic studies, if performed by the investigator, such as autoimmune serologic studies or diagnostic studies (such as ultrasound, CT scan, or liver biopsy) were to be reported to the medical monitor and CEC.

Three important limitations of study design and conduct should be noted:

1. There was no prespecified algorithm for investigators to follow in assessing the etiology of HAESIs other than the protocol specifying "follow-up laboratory investigations will be conducted as recommended in general medical practice." The details of diagnostic evaluation, beyond verification of abnormal liver function studies, were left to the investigator's discretion. Thus, related information was not obtained in a consistent manner with regard to extent or timing of work-up, making it

difficult in some instances to determine the relation between study drug administration and occurrence of a HAESI.

2. According to the study report for 3014, most investigator reports of HAESI were sent to the CEC at the end of the study. This effectively prevented the CEC from requesting additional diagnostic evaluations, which they were explicitly authorized to do under the CEC charter.

3. Although the protocol definition of an endpoint for a hepatic AESI was a possibly drug-related significant injury, the adjudication form provided to the CEC by the Applicant required that all alternative explanations for a hepatic AESI be excluded in order for the event to be considered a positively adjudicated endpoint. This effectively changed the definition of the endpoint from a possibly related event to a definitely drug-related event.

These aspects of design and conduct limit the conclusions that can be drawn from the data in Study 3014.

In addition, in assessing the results of this study with regard to hepatic safety, the following two caveats should be kept in mind. First, the comparator used, amoxicillin/clavulanic acid, is a recognized cause of cholestatic hepatitis; most cases have a favorable prognosis[9]. The low rate of hepatotoxicity with amoxicillin alone suggests that the combination of amoxicillin with clavulanic acid or the clavulanate component alone is responsible for this toxicity. Although the incidence of amoxicillin/clavulanic acid-associated hepatotoxicity is often cited as being quite low (less than 1 case per 100,000 prescriptions), retrospective cohort studies have suggested that the true rate in some patient populations may be greater than 10 cases per 100,000 prescriptions[10]. Thus, assessment of hepatic risk via comparison of event rates in telithromycin-treated and amoxicillin/clavulanic acid-treated patients must take into account the hepatotoxicity of the latter agent.

It is also important to note that amoxicillin/clavulanic acid is thought to cause cholestatic, rather than hepatocellular, jaundice. It is unclear to what extent a hepatic AESI in this study was predictive of the type of drug-induced injury, especially given the issues in data collection discussed above. Thus, comparisons between amoxicillin/clavulanic acid and telithromycin with regard to event rates should be interpreted cautiously, since similarities in rates do not guarantee similar etiologies or outcomes.

Second, despite its size, the study is not powered to detect serious hepatic adverse events at the rate that might realistically be expected in a usual care setting. Although the study is powered to detect events at a rate of 1/4000, it is worth noting that the reported incidence of serious hepatic adverse events associated with trovafloxacin is 1/18,000 prescriptions. Thus, even a study of this size would have been unlikely to detect the hepatotoxicity of trovafloxacin. Although the Applicant correctly notes that this is the largest comparative antimicrobial trial ever conducted, it is important to remember that

[9] Zimmerman HJ. *Hepatotoxicity: The adverse effects of drugs and other chemicals on the liver*, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1999: pp. 597-598

[10] Rodriguez LA *et al*. Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. Arch Int Med 1996; **156:**1327-1332.

the number of patients receiving telithromycin in this trial (~12,000) is dwarfed by the number of courses of antimicrobial therapy prescribed annually in the United States for community-acquired respiratory tract infections (80,000,000 in 1992)[11].

The definition of possible drug-related significant hepatic injury used by the CEC required that all of the following conditions be met:

- Symptomatic liver damage (manifestations including nausea/vomiting, right upper quadrant pain, rash/pruritis, significant or unusual fatigue impacting daily activities, fever, dark urine, and jaundice).

- Associated ALT values of at least 3 x ULN occurring during observation in the absence of other causes.

- Temporal relationship, requiring new onset of symptoms on or later than Day 5 of treatment and a decrease in ALT ≥50% occurring within 30 days of drug cessation.

The distribution of subjects with HAESIs was balanced between treatment groups. There were 111 events in 12159 telithromycin-treated patients (0.91%) versus 98 events in 11978 amoxicillin/clavulanate-treated patients (0.82%). Of those events reported to the CEC, 72% (80/111) of the telithromycin group events and 64.2% (63/98) of the amoxicillin/clavulanate group events were considered to be possibly related to study medication as determined by the FDA medical reviewer. The numerators for these rates include two telithromycin cases and one amoxicillin/clavulanate case considered indeterminate due to inadequate baseline or missing visit 2 labs.

Assessment of the relation between study drug and occurrence of a HAESI made by the FDA medical reviewer differed from that of the CEC for 27 subjects, with 13 telithromycin and 14 amoxicillin/clavulanate subjects reclassified by the FDA reviewer as having had possible drug-related events. The majority of differences (13, of whom seven received telithromycin and six received amoxicillin/clavulanate) were in subjects with hepatitis C who had transaminase increases from baseline levels felt by the CEC to be consistent with hepatitis C, although the FDA medical reviewer felt that drug effect could not be discounted in these cases. The majority of HAESIs in both treatment groups were asymptomatic, with 82% (91/111) of subjects in the telithromycin group and 80.6% (79/98) in the amoxicillin/clavulanate group free from symptoms. In the 39 subjects with a clinically symptomatic HAESI, study drug had a possible relationship in 15/20 (75%) of the telithromycin treatment group and in 11/19 (55%) amoxicillin/clavulanate treatment group as determined by the FDA medical reviewer. The symptoms noted most commonly were fatigue and nausea.

c) HAESIs adjudicated as possibly drug-related
There were five CEC-adjudicated cases of possible significant drug-related hepatic injury, with three occurring in the telithromycin-treated group and two in the amoxicillin/clavulanate group. Brief narratives of these events follow:

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[11] McCaig LF and Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. J Am Med Assoc. 1995; **273:**214-9.

Telithromycin-treated patients with positive hepatic endpoints

- Patient #1567 009, a 58-year-old female was randomized to telithromycin 800 mg for 7-10 days for AECB and took the medication for 10 days. Baseline and visit 2 (Day 17) hepatic laboratory studies were within the normal range and are shown in the table below. On Day 21, the patient developed gross hematuria, along with fever and back pain, and was evaluated in the emergency room on Day 26 (discrepancy noted between investigator note in CRF indicating ER visit on Day 23 and ER letter and laboratory evaluation indicating visit on Day 26), with CBC notable for WBC 14.6 K/µL (ULN 11) with left shift (24 bands), urinalysis notable for positive leukocyte esterase, 1+ protein, 3+ blood, 2+ bilirubin, occasional RBCs, 10-20 WBCs/HPF, and many bacteria, although urine culture collected at the same time (difference of one minute on lab records) was $<10^5$ colonies/ml. The patient was treated with a 10 day course of ciprofloxacin 500 mg BID. Liver function tests on Day 26 showed mild elevation of transaminases with an elevated total bilirubin. Values for these laboratories and follow-up studies on Day 58 are shown in the table below. Hepatitis serologies were negative for hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis B IgM core antibody, and hepatitis C antibody.

	Analyte value/flag				
Analyte (units)	Normal Range	Baseline	Day 17	Day 26	Day 59
ALT (U/L) -C	6 - 34	14	16		22
ALT (U/L) - L	8 - 35			66 H	
AST (U/L) - C	9 - 34	19	21		19
AST (U/L) - L	8 - 37			86 H	
Alk Phos (U/L) - C	35 - 123	91	90		89
Alk Phos (U/L) - L	30 - 120			196 H	
Total Bili (µmol/L) – C	ULN 20.9*	3.0	9.0	78.2[#]	9.0
Total Bili (mg/dL) - L	0.1 – 1.0			4.6 H	
Direct Bili (µmol/L) – C	ULN 7.0*			21.0[#]	3.0
Direct Bili (mg/dL) - L	0.0 – 0.3			3.0 H	
C = central laboratory value, L= local laboratory value					
* Reference values not provided. Value extrapolated from ratio of patient value to reference value.					
[#] Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL = 17 µmol/L					

> *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.*

FDA Medical Reviewer Assessment: Agreed with the CEC, including the possibility that intercurrent illness (possible pyelonephritis) was also contributory.

- Patient #2004 002, a 72-year-old male with type II diabetes mellitus, hypertension, chronic left lower extremity lymphedema, congestive heart failure, coronary artery disease, chronic pleural effusion, and chronic anticoagulation, was randomized to treatment with telithromycin 800 mg for 7-10 days for CAP. Concomitant medications included Aceon, coumadin, glyburide, Lasix, and

spironazide. He completed 10 days of therapy and on visit 2 (Study Day 22) was noted to have liver function test abnormalities including transaminases, alkaline phosphatase, and total bilirubin as shown in the table below. These tests were repeated on study day 28, along with EBV titers, ANA, anti-DNA, hepatitis A, B, and C serologies, CBC with differential, and prothrombin time (PT). Lab tests were significant for a PT of 15.3 sec, a relative lymphocytosis with 54.9% lymphocytes on differential, and liver function tests as shown in the table below. Hepatitis serologies, ANA, and anti-DNA were negative. CT scan of the abdomen showed bilateral pleural effusions with segmental atelectasis at the right lung base, mild eventration of the right dome of the diaphragm, and a gallbladder with increased wall thickness and increased density, suggesting filling with stones and/or a significant amount of sludge. An ultrasound of the gallbladder demonstrated a contracted gallbladder with increased wall thickness with some sludge and very small low density calculi, with the largest being 5 mm. On Day 30, the patient was admitted to the hospital with jaundice, treated with Levaquin, and on Day 35 underwent a laparoscopic cholecystectomy with gallbladder pathology consistent with cholelithiasis and cholecystitis and a simultaneous liver biopsy showing cholestasis. He was treated with Unasyn post-operatively. One week post-operatively (study day 45), laboratory tests showed an absolute eosinophilia with 658 eosinophils/μL (ULN 200) and liver function studies as shown in the table below. The final diagnosis for this hepatic abnormality by the investigator was choledocholithiasis.

Analyte	Normal range	Analyte value/flag				
		Baseline	Day 23	Day 29	Day 45	Day 178
ALT (U/L)	6 – 35	17	270 H	158 H	36 H	25
AST (U/L)	11 – 36	19	162 H	100 H	50 H	25
Alk phos (U/L)	35 – 156	148	461 H	617 H	210 H	127
Total bili (μmol/L)	ULN 21.0*	17.0	104 H	79 H	23.94 H	9.0
Direct bili (μmol/L)	ULN 7.0*			46 H		
* Reference values not provided. Value extrapolated from ratio of patient value to reference value.						

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.

FDA Medical Reviewer Assessment: Agreed with the CEC assessment.

- Patient #3440 001, a 75-year-old female with a history of coronary artery disease, angina/myocardial infarction, cholecystectomy, gastroesophageal reflux, hyperlipidemia, hypertension, and hypothyroidism, was randomized to telithromycin 800 mg for 5 days for acute sinusitis. Concomitant medications

included Synthroid, Zestril, hydrochlorothiazide, Betapace, pravastatin, Nexium, vitamins D and E, calcium, and acetaminophen. On Study Day 17, the patient had complaints of severe abdominal (epigastric) pain associated with fatigue, nausea, fever, and jaundice. The patient was hospitalized on Day 18 with elevated temperature (T 101º), jaundice, and right upper quadrant and epigastric tenderness.   Laboratory studies showed transaminase and ALK elevations shown in the table below, normal amylase, and mildly elevated lipase 314 U/L (normal range: 114-286). The patient was kept npo and pravastatin was withheld. Transaminase and ALK levels had decreased over the next 24 hours as shown below. Serologic testing for acute hepatitis A and B was negative, as was hepatitis C testing. Anti-DNA, ANA, ASMA, and AMA were negative as well. An abdominal CT scan was notable for prior cholecystectomy and no dilatation of the common bile duct. The patient continued to improve and was discharged from the hospital on Study Day 21 with a diagnosis of hepatitis with possible etiologies being drug-related hepatitis (study drug versus pravastatin) and passed gallstone. By Study Day 29, laboratory studies were almost completely normal as shown below.

Analyte	Normal range	Analyte value/flag				
		Baseline	Day 18	Day 19	Day 29	Day 64
ALT (U/L)	6 – 32	9	969 H	629 H	33 H	18
AST (U/L)	9 - 34	16	1357 H	333 H	18	17
Alk phos (U/L)	35 – 164	74	285 H	282 H	103	71
Total bili (µmol/L)		7 ULN 21.2*	30.78 H ULN 17.1*	18.81 H ULN 17.1*	5.0 ULN 20.8*	7.0 ULN 21.2*
Direct bili (µmol/L)					2.0 ULN 6.9*	
* Reference values not provided. Value extrapolated from ratio of patient value to reference value.						

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.

FDA Medical Reviewer Assessment: Agreed with the CEC assessment.

Amoxicillin/clavulanic acid-treated patients with positive hepatic endpoints
- Patient #0604 004, a 43-year-old male, was randomized to receive amoxicillin/clavulanate 875/125 mg BID for 7-10 days for acute sinusitis and took medication for 10 days. At the time of study visit 2 (Day 18), the patient was experiencing rash or pruritis (one check-box for these two events on hepatic AE CRF) and was noted to have isolated elevation of transaminases, with normal ALK and Tbili levels as shown in the table below. The patient had completed therapy and withdrew from the study on Day 28 because he did not wish to continue, without further laboratory studies.

		Analyte value/flag	
Analyte	Normal range	Baseline	Day 18
ALT (U/L)	6 – 43	50 H	154 H
AST (U/L)	11 – 36	35	68 H
Alk phos (U/L)	31 - 129	67	66
Total bili (µmol/L)		7.0 ULN 21.2*	9.0 ULN 20.9*
* Reference values not provided. Value extrapolated from ratio of patient value to reference value.			

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.

FDA Medical Reviewer Assessment: Agreed with that of the CEC that this event was possibly related to amoxicillin/clavulanate administration; however, despite this event meeting the criteria established for clinically significant hepatic injury, it is more likely that the rash or pruritis were indicative of a hypersensitivity reaction rather than a clinically symptomatic hepatic event (hepatitis).

- Patient #2326 004, a 64-year-old female, was randomized to treatment with amoxicillin/clavulanate 875 mg BID for 7-10 days for AECB. However the patient was continued on amoxicillin/clavulanate for the primary infection beyond the 10 day treatment period for an additional 14 days of therapy. Visit 2 occurred on Study Day 17, at which time all hepatic laboratory analyses were normal. On Study Day 28, the patient experienced nausea, pruritis, dark urine, and jaundice associated with abnormal hepatic laboratory tests, with the following values as shown below. These lab abnormalities were accompanied by a relative eosinophilia, with 6.4% eosinophils noted on differential.
Amoxicillin/clavulanate was discontinued and the patient was treated with tapering doses of prednisone for hypersensitivity reaction and cholestasis (the reason given by the investigator was modified to cholestasis alone after medical monitor inquiry to investigator). On study day 33 (five days after discontinuing amoxicillin/clavulanate and starting prednisone), hepatic laboratory abnormalities had begun to resolve as shown below. By study day 69, hepatic laboratory values had decreased to normal values.

		Analyte value/flag				
Analyte	Normal range	Baseline	Day 17	Day 28	Day 33	Day 69
ALT (U/L)	6 - 34	19	21	571 H	384 H	24
AST (U/L)	9 - 34	18	22	348 H	162 H	25
Alk phos (U/L)	35 – 123	38	38	182 H	143 H	46
Total bili (µmol/L)		10.0 ULN 20.8*	10.0 ULN 20.8*	86. 7[#] H 5.1 mg/dL	44.0 ULN 21.0*	9.0 ULN 20.9*
Direct bili (µmol/L)					21.0 ULN 7.0*	3.0 ULN 7.0*
* Reference values not provided. Value extrapolated from ratio of patient value to reference value. [#] Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL = 17 µmol/L						

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.

FDA Medical Reviewer Assessment: Concur with CEC assessment. Cholestatic hepatitis has been associated with administration of amoxicillin/clavulanate, particularly prolonged courses of therapy.

There were four additional cases of possible significant hepatic injury as indicated by clinical symptoms and laboratory evidence, with three cases occurring in the telithromycin group and one case in the amoxicillin/clavulanate group. However, these events were not considered to be drug-related by the CEC because of alternative explanations based on existing hepatic pathology. The FDA medical reviewer disagreed with the CEC exclusion of one patient from the possible significant hepatic injury category as described above. A narrative of this event follows.

Patient #0363 015, a 68-year-old female, was treated for AECB for five days (randomized to a 7-10 day regimen) with telithromycin. Concomitant medications included Accupril, Premarin, multivitamin (along with calcium and vitamin E supplements), and ibuprofen (daily dose not specified). At study visit 2 (Day 19) the patient was noted to have fever (T 101.0°), cough, and nausea, was started on therapy with Levaquin and Flumadine for the primary infection (AECB) versus possible influenza, and had post-therapy hepatic laboratory studies performed. Significant elevations were noted at this visit in transaminase levels, with an increased ALT of 150 U/L (baseline 27 U/L) and an AST of 91 U/L (baseline 28 U/L). ALK and Tbili remained within normal limits. As follow-up to these abnormal transaminases, additional laboratory studies were obtained on Day 28 (following treatment with levofloxacin and Flumadine) and showed a further increase in transaminase levels, with an ALT of 402 U/L and an AST of 147 U/L. Additional laboratory at this time showed a relative and absolute eosinophilia, with a differential showing 24% eosinophils (normal: 0.0-6.8), and an absolute eosinophil count of 2.85 GG/L (normal range: 0.0-0.57). Laboratories drawn 32 days later (study day 60) showed resolution of the leukocytosis and eosinophilia, and improvement in transaminase levels, although these did not return to normal baseline, with an ALT of 97 U/L and an AST of 52 U/L.

CEC Adjudication Summary: Probable drug-related HAESI. Hepatic adjudication form comments: normal baseline, ALT rose to 402 and fell to 97. Bilirubin normal. Had fatigue and fever. Hepatitis serologies normal.

FDA medical reviewer assessment: Agreed with the CEC summary. The initial transaminase elevations at Study Day 19 were possibly related to telithromycin, although further elevation and eosinophilia noted at Day 28 could also have been caused by the administration of additional medications (Levaquin). However, this case was excluded from the possible drug-related clinically significant hepatic injury reports noted although the rationale for this is not clear. The clinical

symptomatology noted, including fever and nausea may have been attributed to an upper respiratory problem rather than hepatic symptomatology.

d) HAESIs with liver biopsy data

Three subjects (two in the telithromycin group and one in the amoxicillin/clavulanate group) had liver biopsies performed, presumably due to abnormalities in hepatic laboratory values noted during the course of this study. One of the telithromycin patients undergoing biopsy (#2004 002, described above under section c) was adjudicated by the CEC as having a positive CEC endpoint. However, the timing of these biopsies, which were generally performed more than 30 days into the study, greatly limited the amount of information they could provide in evaluating the relationship between study drug administration and occurrence of a HAESI. This was especially true given the presence of potentially confounding conditions such as cholecystitis or chronic hepatitis C infection. Narratives for the two patients who had biopsies but were not assessed as having a drug-related event are presented in Appendix E.

e) Other HAESIs of note

One subject in the telithromycin treatment group (Patient #0187 026), who did not meet the criteria for the CEC-adjudicated possible drug-related clinically significant hepatic injury endpoint was diagnosed with possible autoimmune hepatitis by the investigator and treated with prednisone. A narrative of this event is presented below.

Patient #0187 026, a 60-year-old female with a history of asthma and recurrent cystitis was randomized to treatment with telithromycin for 7-10 days for AECB. Concomitant medications included Premarin, microzide Toprol XL, Allegra, Ativan, and Bactrim DS. The patient took 10 days of drug and was seen in follow-up at Visit 2 (Study Day 17), at which time hepatic laboratory values were similar to her normal baseline levels as shown below. On Day 25, the patient was noted to have asymptomatic elevation of hepatic transaminases. Because of these elevations, the patient had a repeat ALT level drawn four days later which measured 245 U/L. Follow-up studies on study day 36 included a repeat hepatic profile, CBC with differential, hepatitis A, B, and C serologies, and autoimmune serologies, including ANA, AMA, and ASMA. Hepatic laboratory studies are shown below. CBC and differential results showed an absolute lymphocytosis of 3.67 GG/L, absolute eosinophilia of 0.75 GG/L, with 8.7% eosinophils. ANA was positive at 1:160 with a homogeneous pattern, with a negative anti-DNA, negative AMA, and positive ASMA. Hepatitis A IgM antibody, hepatitis B surface antigen, and hepatitis C antibody serologies were negative. On Day 33, an abdominal ultrasound was unremarkable, with no evidence of cholelithiasis, biliary duct dilatation, or focal liver lesions. Although the patient was asymptomatic, she was treated by the investigator for possible autoimmune hepatitis with prednisone at that time prior to an upcoming vacation out of her local area. Long-term follow-up (6 month) for this patient through her primary care physician indicates that she has been clinically well and has had no recurrence of abnormal hepatic laboratory tests.

Analyte	Normal range	Analyte value/flag				
		Baseline	Day 17	Day 25	Day 36	Day 71
ALT (U/L)	6 – 34	21	30	113 H	347 H	30
AST (U/L)	9 - 34	22	21	85 H	183 H	21
Alk phos (U/L)	35 – 123	97	105	101	120	105
Total bili (μmol/L)		5.0 ULN 20.8*	8.5[#] 0.5 mg/dL	5.0 ULN 20.8*	7.0 ULN 21.2*	10.26 ULN 22.3*
Direct bili (μmol/L)						
* Reference values not provided. Value extrapolated from ratio of patient value to reference value. [#] Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL = 17 μmol/L						

CEC Adjudication Summary: Possibly related to drug (Adjudication form comments: Normal baseline. ALT rose to 347 and AST to183. Last data ALT 281 and AST 138. Hepatitis serologies negative. ANA and SMA positive. Eosinophilia developed.)

FDA Assessment: Agreed with CEC assessment.

f) Hepatic Laboratory Analyte Elevations from Baseline to Post-Therapy

Table S17 shows ALT values obtained during the course of Study 3014 (post-therapy at Day 17-22 and late post-therapy as indicated in the table footnote below) in subjects with normal baseline hepatic function. These tests were collected in a usual care setting at various time-points in an unstructured fashion.

Table S17. Study 3014: ALT changes at the Post-Therapy and Late Post-Therapy Visits

Changes in ALT	n/N (%) Subjects			
	Post-Therapy		Late Post-Therapy	
	TEL (N=7708)	AMC (N=7516)	TEL (N=664)	AMC (N=659)
≤1 x ULN	7158 (92.9)	7044 (93.8)	585 (88.1)	607 (92.1)
>1 to ≤2 x ULN	488 (6.3)	433 (5.8)	57 (8.6)	42 (6.4)
>2 to ≤3 x ULN	35 (0.5)	22 (0.3)	6 (0.9)	4 (0.6)
>3 to ≤5 x ULN	12 (0.2)	8 (0.1)	4 (0.6)	3 (0.5)
>5 to ≤ 8 x ULN	8 (0.1)	7 (0.1)	4 (0.6)	0 (0.0)
>8 x ULN	7 (0.1)	2 (0.0)	8 (1.2)	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 *Some subjects had laboratory tests conducted at visit 3 (late post-therapy, from Day 30 to approximately 6 months post-treatment) due to missing protocol-defined laboratory or as part of abnormal value follow-up.				

There was no difference between treatment groups with regard to low level elevation of ALT levels. However, ALT elevations of ≥3 x ULN occurred more commonly in the telithromycin treatment group, although it is important to note the degree of transaminase elevation is not predictive of the degree of hepatocellular damage. Also, there was a higher rate of subjects with persistent elevations of ALT at the late post-therapy visit in the telithromycin treatment group.

Table S18 shows the AST values at post-therapy in subjects with normal baseline hepatic function.

Table S18. Study 3014: AST changes at the Post-Therapy Visits

	n/N (%) Subjects	
	Post-Therapy	
Changes in AST	**TEL (N=7570)**	**AMC (N=7390)**
≤1 x ULN	7264 (96.0)	7129 (96.5)
>1 to ≤2 x ULN	267 (3.5)	227 (3.1)
>2 to ≤ 3 x ULN	19 (0.3)	20 (0.3)
>3 to ≤5 x ULN	10 (0.1)	12 (0.2)
>5 to ≤ 8 x ULN	5 (0.1)	1 (0.0)
>8 x ULN	5 (0.1)	1 (0.0)
Tel = telithromycin, AMC = amoxicillin/clavulanic acid, ULN = upper limit of normal Note: Denominator based on number of subjects with a valid assay		

The AST changes mirror those for ALT, with a higher incidence of AST >5 x ULN in the telithromycin treatment group.

Table S19 shows the frequency of elevations of ALT post-treatment in telithromycin treated subjects with normal baseline LFTs according to the duration of exposure to the drug.

Table S19. Study 3014: ALT changes in Telithromycin treated patients at the Post-Therapy Visits, by duration of herapy

	n/N (%) Subjects	
	Post-Therapy	
Changes in ALT	**TEL 7-10 Days (N=3024)**	**TEL 5 days (N=4684)**
≤ 1 x ULN	2779 (91.9)	4379 (93.5)
>1 to ≤ 2 x ULN	210 (6.9)	278 (5.9)
>2 to ≤ 3 x ULN	19 (0.6)	16 (0.3)
>3 to ≤ 5 x ULN	7 (0.2)	5 (0.1)
>5 to ≤ 8 x ULN	4 (0.1)	4 (0.1)
>8 x ULN	5 (0.2)	2 (0.0)
Tel = telithromycin, AMC = amoxicillin/clavulanic acid, ULN = upper limit of normal Note: Denominator based on number of subjects with a valid assay		

There was a trend toward a higher level of ALT elevation (ALT >3 X ULN) with increasing duration of telithromycin exposure.

Table S20 shows the frequency of elevations in hepatic analytes at post-therapy and late post-therapy, irrespective of baseline hepatic analyte values.

Table S20. Study 3014: Hepatic analyte changes at the Post-Therapy and Late Post-Therapy Visits

	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 (0.0)	2/9784 (0.0)	1/1027 (0.1)	0/1033 (0.0)
ALT ≥3 x ULN and total bilirubin ≥1.5 x ULN	3/9991 (0.0)	5/9723 (0.0)	0/1026 (0.0)	2/1027 (0.2)
Alkaline phos. ≥3 x ULN	4/10809 (0.0)	1/10535 (0.0)	0/1094 (0.0)	1/1126 (0.1)
Tel = telithromycin, AMC = amoxicillin/clavulanic acid, ULN = upper limit of normal Note: Denominator based on number of subjects with a valid assay				

As noted in the CDER-PHRMA-AASLD Conference 2000 Clinical White Paper,[12] the combination of pure hepatocellular injury and jaundice is of concern, since hepatocellular injury severe enough to interfere with bilirubin excretion must involve a large fraction of the liver cell mass. This combination may be predictive of post-marketing serious liver injury (fatal or requiring transplant). Therefore, subjects were analyzed for simultaneous abnormalities in transaminase and total bilirubin levels.

Three subjects in the telithromycin treatment group were noted to have ALT ≥3 x ULN and total bilirubin ≥1.5 ULN versus five subjects in the amoxicillin/clavulanate treatment group at post-therapy. The three subjects in the telithromycin group had concomitant elevations in alkaline phosphatase; an elevation of alkaline phosphatase in this setting decreases the probability that an event represents pure hepatocellular injury. Of note, however, one subject (#2004 002) had been adjudicated as having a positive hepatic endpoint. Of the patients in the amoxicillin/clavulanic group having an elevated bilirubin and ALT, 3/5 had concomitant elevations in alkaline phosphatase with all subjects recovering near to pretherapy/entry values (within 2 x ULN). The other two amoxicillin/clavulanate treated subjects did not have associated elevations in alkaline phosphatase; however, one had a history of hepatitis C and the other had a history of substantial alcohol use and daily consumption of ibuprofen. Additionally, at late post-therapy two amoxicillin/clavulanate subjects had elevation of transaminases and bilirubin and with no subjects noted in the telithromycin group. Both of these subjects, however, had simultaneous elevations in alkaline phosphatase levels and had resolution of abnormalities at extended follow-up within the six month study period.

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[12] www.fda.gov/cder/livertox/clinical.pdf

6. Post-marketing hepatic safety

Table S21 summarizes all post-marketing hepatic adverse events occurring in countries where telithromycin has been approved and which have been submitted to FDA through the MedWatch system since submission of the amended NDA. All events were considered to be possibly related to telithromycin exposure.

Table S21. Post-Marketing Telithromycin-associated Hepatic Adverse Events*

Adverse Event	Total #	Serious	Not Serious	No Determination **
Liver Function Test NOS abnormal	11	6	3	2
Transaminases Increased	6	2	1	3
Jaundice NOS	5	0	0	5
Hepatitis NOS	5	5	0	0
Bilirubin Increased	4	0	0	4
AST increased	4	0	0	4
ALT increased	4	0	0	4
Prothrombin time prolonged	2	0	2	0
International normalised ratio increased	2	0	2	0
Hepatocellular damage	2	2	0	0
Gamma-glutamyltransferase increased	2	0	0	2
Blood lactate dehydrogenase increased	2	0	0	2
Hepatitis cholestatic	1	1	0	0
Hepatic function abnormal NOS	1	1	0	0
Hepatic disorder NOS	1	1	0	0
Cholestasis	1	1	0	0
Blood alkaline phosphatase NOS increased	1	0	0	1

* Patients may have had more than one adverse event

**No determination was made by the reporter as to whether the adverse event was serious.

Detailed FDA review of individual patients with post-marketing hepatic adverse events is currently ongoing.

C. Cardiovascular safety

1. Overview of cardiovascular safety

The cardiovascular risk profile of telithromycin is notable for the following:

- *In vitro*, telithromycin blocks myocyte repolarization and prolongs action potential duration, a characteristic of drugs associated with torsades de pointes.

- In dog studies, telithromycin prolongs the corrected QT interval, to a greater extent than does clarithromycin

- In Phase 1 studies, telithromycin shows concentration-dependent prolongation of the corrected QT interval; although small, this effect is reproducible.

- Although the Applicant studied the effect of co-administration of ketoconazole and telithromycin in patients with renal impairment in order to examine the electrophysiologic effects of multiple impairments of telithromycin clearance mechanisms, only two patients with a creatinine clearance <30 mL/min were studies. One of these patients had an increase in QTc of 35 msec.

- In controlled Phase 3 studies, telithromycin-treated patients consistently showed an increase in QTc of approximately 2 msec.

- As of the date of this briefing document, post-marketing safety reports received by the FDA regarding telithromycin-treated patients in countries where telithromycin has been approved have included 26 cardiac adverse events; 18 of these were considered serious. One case was reported as a fatal episode of torsades de pointes.

2. Preclinical studies

FDA analyses of preclinical studies in the original NDA relevant to cardiac safety are presented in Section VB of the FDA briefing document (presented as Appendix A of this briefing document) for the April 2001 AIDAC meeting. A brief synopsis is presented here.

In vitro, telithromycin blocks repolarization of myocardial cells, in part by inhibiting the rapid component of the delayed rectifying current (IK_r), with an inhibition constant similar to that of a number of quinolones and macrolides. Consistent with its ability to induce IK_r blockade, telithromycin also increases action potential duration in isolated rabbit Purkinje fibers.

Of note, telithromycin markedly potentiates sotalol-induced prolongation of action potential duration. Although the telithromycin concentration at which this effect occurs (8 mg/L) is significantly greater than the mean telithromycin C_{max} (~2 mg/L), it should be kept in mind that there is substantial variability in telithromycin pharmacokinetics, with a maximal C_{max} in Phase 1 studies of 9.9 mg/L. In addition, rat studies have demonstrated myocardial telithromycin concentrations up to 7.7 times those in plasma. Because tissue concentrations may be physiologically more relevant to drug

effects on cardiac repolarization, conclusions about apparent clinical safety margins extrapolated from *in vitro* free drug concentrations may be misleading.

In dog studies, intravenous infusion of a single dose of telithromycin caused a rapid increase in QT_c (QT interval corrected by Bazett's formula[13]) by 30 msec, within 1 minute after administration, as well as an increase in heart rate. Although Bazett's formula overcorrects the QT interval at higher heart rates, analysis of QT_f (QT interval corrected by Fridericia's formula[14]) also showed prolongation of the QT interval by of telithromycin, by 16 – 31 msec. Clarithromycin increased the QT_c interval by a lesser amount (17 msec) and did not affect heart rate. A multiple oral dose study of telithromycin in dogs showed significant QT prolongation (27-30 msec) at high doses (100 mg/kg/d).

3. Phase 1 studies

FDA analyses of Phase 1 studies in the original NDA relevant to cardiac safety are presented in Section vb of the FDA briefing document (presented as Appendix A of this briefing document) for the April 2001 AIDAC meeting. These studies showed that telithromycin causes QTc prolongation in a dose- and concentration-dependent fashion; the magnitude of the effect was comparable to that of cisapride. The effect was enhanced by co-administration of a CYP3A4 inhibitor. Telithromycin appeared to show considerable pharmacokinetic variability, particularly in populations such as the elderly. This concentration dependence of telithromycin-associated QTc prolongation in combination with potential drug interactions and pharmacokinetic variability suggested that significant QTc prolongation could occur in at-risk patients receiving concomitant interacting medications, increasing the risk of malignant ventricular arrhythmias such as torsades de pointes.

To address these issues, the Applicant conducted additional Phase 1 studies, examining the pharmacokinetics of multiple doses of telithromycin in patients with hepatic or renal impairment, as well as in patients with renal impairment receiving a potent inhibitor of CYP 3A4.

FDA analyses of the pharmacokinetic results of these studies are presented in Section IIC. This section will present the FDA analysis of electrocardiographic data from the study of renally impaired patients receiving a potent inhibitor of CYP 3A4 (Study 1063).

Teithromycin is metabolized by CYP 3A4; thus, drug exposure and potential toxicities (including effects on cardiac repolarization) may be increased if this metabolic pathway in blocked. The Applicant had submitted data in the original NDA showing that co-administration of telithromycin and ketoconazole, a potent 3A4 inhibitor, increases telithromycin C_{max} and AUC by 52% and 95%, respectively, in healthy subjects. Significantly, co-administration of ketoconazole and telithromycin prolongs the corrected QT interval to a greater extent than does telithromycin alone.

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[13] $QT_c = QT/(RR\ interval)^{1/2}$

[14] $QT_f = QT/(RR\ interval)^{1/3}$

Given that telithromycin is cleared both metabolic and renally, impairment of both of these clearance mechanisms (e.g., by administration of a medication inhibiting 3A4 to a renally impaired patient) could lead to a significant increase in drug exposure; given the concentration-dependent effects of telithromycin on cardiac repolarization, this could, in turn, increase the risk of torsades de pointes.

To address this issue, the Applicant conducted Study 1063; from a cardiovascular safety perspective, one objective was essentially to study the impact of multiple impairments of telithromycin clearance on the effect of telithromycin on the QT interval. This was a multicenter, multinational, open-label, 3-treatment parallel group, multiple oral dose study.

The three treatments were:

Ketoconazole 400 mg once daily for 5 days

Telithromycin 800 mg once daily plus ketoconazole 400 mg once daily for 5 days

Clarithromycin 500 mg twice daily plus ketoconazole 400 mg once daily for 5 days

A total of 36 elderly subjects >60 years of age) were to be recruited (12 in each treatment group). Subjects were to have diminished renal function (planned creatinine clearance [CLcr] range 30 to 80 mL/min), and were to be hemodynamically and medically stable with no major diseases other than renal impairment, hypertension, or diabetes. Subjects were to be excluded if they had a family or congenital history of long QT syndrome or known acquired QT interval prolongation.

12-Lead ECGs were measured at serial timepoints over the 24 hours after time zero on Day -1 and Day 5 (at timepoints: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours, which coincided with the timepoints for pharmacokinetic blood sampling on Day 5). at 2 and 4 hours after time zero on Days 1 to 4.

In addition, 3 ECGs were measured at time zero on Days -1 and 1, and the respective means of the 3 measurements were used as the baseline for Day -1 and Day 5. ECGs were over-read by a central expert cardiologist who was blinded to subject number, treatment, and time of measurement. QT intervals were corrected for heart rate using Bazett's formula (QTcB), Fridericia's formula (QTcF), and a population-specific formula (QTcN). The Day −1 values were evaluated for any significant, consistent circadian variation during the day.

Table S22 presents changes in mean QTc values for the different treatment groups (using different heart rate correction formulae) between screening and end of dosing. When co-administered with ketoconazole in renally impaired patients, both telithromycin and clarithromycin showed increases in QTc (using Bazett's correction, generally considered the most conservative approach); however, only the change in the telithromycin group was statistically significant. However, this finding should be interpreted very cautiously, given normal variability in the QT interval and issues with the accuracy of correction for heart rate with Bazett's formula. There were no QTc intervals >450 ms for men or >470 ms for women in the telithromycin plus ketoconazole group.

Table S22. Difference in maximum observed QTc between Day –1 and Day 5: within treatment-group analysis

	N	A Mean (SD)	N	B Mean (SD)	N	C Mean (SD) *a*
QTcB (ms)						
Day -1	11	426.5 (18.1)	12	410.4 (22.5)	6	421.2 (26.0)
Day 5	11	419.7 (17.5)	12	424.4 (19.0)	6	436.2 (26.8)
p-Value		0.0881		0.0142		0.0847
QTcF (ms)						
Day -1	11	410.9 (21.2)	12	414.3 (15.8)	6	410.2 (18.1)
Day 5	11	406.6 (19.7)	12	420.4 (11.8)	6	421.7 (19.4)
p-Value		0.1636		0.1194		0.0681
QTcN (ms)						
Day -1	11	411.5 (21.0)	12	414.0 (16.2)	6	410.5 (18.5)
Day 5	11	407.0 (19.5)	12	420.5 (11.9)	6	422.2 (19.6)
p-Value		0.1283		0.1198		0.0736

Treatment A: ketoconazole 400 mg once daily; Treatment B: telithromycin 800 mg once
daily plus ketoconazole 400 mg once daily; Treatment C: clarithromycin 500 mg twice

daily plus ketoconazole 400 mg once daily.

Table S23 shows numbers of patients in each treatment groups with increases in corrected QT intervals greater than a predefined amount between screening and end of dosing. An increase in QTc (using Bazett's formula) of 30 to 60 msec may be considered a signal of possible effect on cardiac repolarization, while an increase of >60 msec generally represents a stronger indication of an effect on cardiac repolarization. Using Bazett's formula, there were five patients in the telithromycin group with an increase of 30-60 msec, and none in the clarithromycin group. There were no telithromycin-dosed patients with an increase >60 msec; there were two clarithromycin-dosed patients with an increase >60 msec.

Table S23.

Study day	No. predefined increases for QTcB/F/N		
	Treatment A N=10	**Treatment B N=9**	**Treatment C N=8**
ΔQTc increase 30–60 ms			
Day -1	1/0/1	0/0/0	0/0/0
Day 5	0/0/0	5/2/2	0/2/2
ΔQTc increase >60 ms			
Day -1	0/0/0	0/0/0	0/0/0
Day 5	0/0/0	0/0/0	2/0/0

Treatment A: ketoconazole 400 mg once daily; Treatment B: telithromycin 800 mg once
daily plus ketoconazole 400 mg once daily; Treatment C: clarithromycin 500 mg twice
daily plus ketoconazole 400 mg once daily.

Only two telithromycin-treated patients had severe renal impairment (creatinine clearance of less than 30 mL/min). As noted in section IIC, these patients had increased exposure to telithromycin, with an increase in AUC by 4 to 5-fold. One of these patients

had an increase in QTc of 35 msec; the other had an increase of 6 msec. A renal impairment study (Study 1062) that a significant increase in telithromycin concentration was found only in severly renaly impaired subjects but not patients with mild and moderate renal impaired subjects. Thus, this study results represent mostly ketoconazole effect on telithromycin concentration but provides little information on the additive effect of ketoconazole and severe renal impairment.

As in previous Phase 1 studies, a positive correlation was found between telithromycin plasma concentration and changes in QTc, with an increase of 2.1 msec for each mg/L increase in telithromycin plasma concentration ($r^2 = 0.037$, $p = 0.03$).

4. Phase 3 studies

a) Electrocardiographic data

FDA analyses of ECG data from the original NDA are presented in Section VB of the original briefing document for the April 2001 AIDAC meeting (Appendix A of this document). In the amended NDA, ECG data from Study 3013 was added to the existing integrated Phase 3 ECG data in the original NDA. ECG data from studies 4003 and 3012 were not integrated because ECGs were only recorded in selected subjects in these studies.

QT interval data are shown in the following tables for telithromycin-treated subjects and for studies where clarithromycin was the comparator. Bazett's correction formula is used unless otherwise stated.

Table S24 shows a summary of the integrated ECG data obtained for telithromycin-treated subjects in 12 Phase 3 studies.

Table S24. QT interval data for telithromycin-treated subjects in Phase 3 studies (controlled and uncontrolled)*

Variable	Pre-therapy (N=3098)	On-therapy (N=2411)[a]	Post-therapy (N=1867)[b]
QTc (ms)	408.0 ± 23.6	409.7 ± 23.4	405.7 ± 22.8
ΔQTc (ms)	–	1.5 ± 22.3 [c]	–2.0 ± 23.3 [d]
QTc increase (n/N (%) subjects)			
>30 and <60 ms	–	212/2411 (8.8)	124/1867 (6.6)
≥60 ms	–	22/2411 (0.9)	9/1867 (0.5)
QTc outlier (n/N (%) subjects)			
≥450 ms (men)	62/1571 (3.9)	51/1236 (4.1)	17/929 (1.8)
≥470 ms (women)	14/1527 (0.9)	17/1215 (1.4)	7/938 (0.7)
≥500 ms (men or women)	8/3098 (0.3)	4/2451 (0.2)	2/1867 (0.1)
QT dispersion (ms)	24.2 ± 16.9	23.3 ± 15.6	22.9 ± 11.9

Data are mean ± SD
[a] Represents number of subjects with both a pre-therapy and on-therapy ECG
[b] Represents number of subjects from the on-therapy group who also had a post-therapy ECG
[c] QTc interval on-therapy minus QTc interval pre-therapy
[d] QTc represents QTc interval post-therapy minus QTc interval pre-therapy
* Excludes Studies 3010, 3011, 3012 and 4003 where ECGs were performed only in selected subjects

Data from new new AECB Study 3013 were integrated with data from controlled CAP study 3006 and tonsillitis/pharyngitis study 3008 to compare QT interval data between telithromycin and clarithromycin. The QTc findings are summarized in table S25.

Table S25. QT interval data for telithromycin vs. clarithromycin (controlled studies 3006, 3008, and 3013)

Variable	Pretherapy		On-therapy		Post-therapy	
	TEL	CLA	TEL	CLA	TEL	CLA
	(N=700)	(N=705)	(N=622)[a]	(N=672)[a]	(N=546)[b]	(N=541)[b]
QTc (ms)	407.6 ± 20.4	410.2 ± 20.3	411.6 ± 19.6	413.3 ± 19.6	409.2 ± 19.8	411.5 ± 19.7
			c	c	d	d
ΔQTc (ms)	–	–	3.8 ± 19.3[c]	3.3 ± 19.6[c]	1.5 ± 22.7[d]	1.3 ± 22.0[d]
QTc increase (n/N (%) subjects)						
>30 and <60 ms	–	–	52/622 (8.4)	60/672 (8.9)	49/546 (9.0)	40/541 (7.4)
>60 ms	–	–	2/622 (0.3)	1/672 (0.1)	5/546 (0.9)	4/541 (0.7)
QTc outlier (n/N (%) subjects)						
>450 ms (men)	10/326 (3.1)	13/339 (3.8)	10/300 (3.3)	14/332 (4.2)	3/259 (1.2)	6/266 (2.3)
>470 ms (women)	0/374 (0.0)	2/366 (0.5)	1/326 (0.3)	2/355 (0.6)	1/287 (0.3)	1/275 (0.4)
>500 ms (men or women)	0/700 (0.0)	1/705 (0.1)	0/626 (0.0)	0/687 (0.0)	0/546 (0.0)	0/541 (0.0)
QT dispersion (ms)	25.5 ± 17.4	24.7 ± 13.4	25.3 ± 17.2	25.9 ± 14.4	25.2 ± 13.0	25.8 ± 18.0

Data are mean ± SD TEL = telithromycin; CLA = clarithromycin

[a] Represents number of subjects with both a pretherapy and on-therapy ECG

[b] Represents number of subjects from the on-therapy group who also had a post-therapy ECG

[c] ΔQTc interval on-therapy minus QTc interval pretherapy

[d] ΔQTc represents QTc interval post-therapy minus QTc interval pretherapy

In the three new Phase 3 studies, 3 telithromycin-treated subjects (all in uncontrolled Study 3012) and 1 comparator-treated subject (in Study 3013) had a QTc ≥500 ms. All four of these subjects had this prolongation at the baseline (pretherapy) visit. None of the subjects had an on-therapy QTc value ≥500 ms.

b) Cardiac Serious and Non-Serious Adverse Events

The incidence of serious TEAEs of the cardiac disorders system organ class was similar in telithromycin- (8/4472, 0.2%) and comparator-treated subjects (8/2139, 0.4%). None of the serious cardiac events were considered possibly related to study medication. The MedDRA preferred terms for those patients with serious TEAE's of the cardiac system organ class includes the following: left ventricular failure (2), acute myocardial infarction (1), angina pectoris (1), cardiac arrest (1), cardiac failure aggravated (1), cardiac failure NOS (1), and cardiomyopathy NOS (1).

Table S26 summarizes all and possibly related TEAE's of the cardiac system organ class. The most frequent cardiac TEAE was palpitations. None of the cases of palpitations was characterized as serious and ECG data for these patients was not collected.

Table S26. All and possibly related TEAEs* of cardiac disorders system organ class by decreasing frequency in All Integrated Phase 3 studies

	Number (%) of subjects			
	Possibly related cardiac disorders TEAEs		All cardiac disorders TEAEs	
	Telithromycin	Comparator	Telithromycin	Comparator
Preferred term	**(N=4472)**	**(N=2139)**	**(N=4472)**	**(N=2139)**
All TEAEs of cardiac disorders SOC	8 (0.2)	7 (0.3)	42 (0.9)	32 (1.5)
Palpitations	2 (0.0)	2 (0.1)	6 (0.1)	9 (0.4)
Sinus arrhythmia	2 (0.0)	1 (0.0)	4 (0.1)	2 (0.1)
Cardiac failure NOS	0 (0.0)	0 (0.0)	3 (0.1)	2 (0.1)
Tachycardia NOS	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)
Angina pectoris	0 (0.0)	0 (0.0)	2 (0.0)	3 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

* Based on all TEAE frequency of 0.1% in telithromycin or comparator treatment group.
NOS = not otherwise specified

Additional cardiac TEAEs of interest were reported at very low rates (<0.1%) in the All Integrated Phase 3 safety database, as follows:

Atrial fibrillation
2/4472 (0.05%) telithromycin-treated subjects

1/2139 (0.05%) comparator-treated subject had a TEAE of atrial fibrillation

Cardiac Arrest
1/4472 (0.02%) telithromycin-treated subjects

No comparator treated subjects had a TEAE of cardiac arrest.

Syncope
1/4472 (0.02%) telithromycin-treated subject

2/2139 (0.09%) comparator-treated subject s

None of these events were considered possibly related to study medication.

5. Study 3014

The results of the preclinical, clinical pharmacology, and controlled Phase 3 studies in the original NDA raised concerns about the potential for telithromycin to increase the risk for malignant ventricular arrhythmias in at-risk patients. This concern was exacerbated by the exclusion criteria used in the original Phase 3 trials, which

generally excluded patients at increased risk for torsades de pointes (e.g., patients with hypokalemia), limiting the available safety information for this population.

Study 3014 was conducted by the Applicant to address these issues. For a description of the general objectives and design of study 3014, see Section IVA3. In interpreting the results of this study, two important limitations of the study design should be noted.

1.) There was no pre-specified algorithm for how patients with cardiac adverse events were to be evaluated.

2.) Most AESI reports were sent to CEC in batch, instead of at the time of each individual AE. This prevented members of the CEC from requesting additional information or tests for individual patients.

There were a total of 73 patients with a cardiac adverse event of special interest (CAESI). All of these cases were reviewed by the Clinical Expert Committee (CEC) which made a blinded adjudication to determine if any cases fulfilled the cardiac safety endpoints. Cardiac safety endpoints were defined as those likely to represent malignant ventricular arrhythmias, 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. In addition, deaths up to study Day 35 were to be documented as CAESIs.

The protocol for study 3014 pre-specified that all deaths be sent to the Cardiac CEC for adjudication. However, there were eight patients who died but whose cases were not sent to the Cardiac CEC (three telithromycin, five amoxicillin/clavulanic acid). Review of the telithromycin patients who were not evaluated by the Cardiac CEC revealed that death occurred on study days 41, 44, and 66 and were unlikely to have been the result of telithromycin toxicity.

Table S27 compares the number of each type of cardiac events of special interest for telithromycin versus the control drug, as well as information about patient age.

Table S27. Study 3014: Cardiac Adverse Events of Special Interest

Adverse Event	Telithromycin			Amoxicillin/Clavulanate		
	n	**Mean Age**	**Age Range**	**n**	**Mean Age**	**Age Range**
Syncope/Pre-syncope	8	60.8	38-80	6†	40	19-73
Arrhythmia	9**	72.2	60-83	7	60.7	20-82
Palpitations	5	50.6	35-75	2	77	76-78
Cardiac Ischemic Events/ Congestive Heart Failure	4	66.3	57-77	6	72.2	51-90
Fatal Cardiac Arrest	7	58.3	43-82	3	65.7	62-73
Non-Cardiac Events*	7	64.5	48-82	11	72.1	46-83
Total	40	62.9	35-83	35	64.6	19-83

*Includes atypical chest pain
** One of these patients did not take any study medication.
†Patient 3014.0923.0923009 had both syncope and CHF

There were greater numbers of patients from the telithromycin arm with several of the cardiac adverse event categories. However, a detailed review of the case report forms for all patients with cardiac events of special interest did not definitively demonstrate telithromycin toxicity as the cause of this difference.

Syncopal episodes occurred more slightly more frequently in the telithromycin arm; however, because of the small number of such events, a definite conclusion cannot be drawn. Many of the telithromycin-treated patients who experienced a syncopal or pre-syncopal episode had reasonable alternative etiologies such as high blood alcohol level, post-tussive event, or prior long-term history of frequent syncopal episodes. One patient with a brief syncopal episode on day five of therapy had an ECG performed within 24 hours of the event. The ECG revealed a prolonged QTc interval of 0.472, however, this was felt by the CEC to be irrelevant because the patient's prior ECG from 5/26/99 also revealed a prolonged QTc of 0.461. It is possible however, that this patient has a prolonged QT syndrome which may have resulted in increased risk for an arrhythmogenic event contributed to by telithromycin exposure. This patient stopped taking the telithromycin after the event.

Although there were more instances of cardiac arrest in the telithromycin-treated population, based on the available information, it is not possible to conclusively attribute any of these deaths to telithromycin. Most of these cases did not have a plausible temporal relationship to telithromycin administration (none occurred while on therapy) and all of the patients had extensive confounding pre-existing co-morbidities (i.e., coronary artery disease, diabetes, hyperlipidemia, etc.).

There were also slightly more arrhythmias in the telithromycin arm. The temporal relationship to telithromycin exposure, as shown in Table S28, is similar to that of amoxicillin/clavulanic acid. All but one patient (who had frequent PVC's) in this group had arrhythmias of atrial origin and all of these patients had multiple confounding factors which could have caused these arrhythmias. These potential confounders include one or more of the following factors: older age, pre-existing cardiovascular disease (ischemic and/or structural), hypertension, stress of an acute infection, prior history of atrial fibrillation, thyroid disease, and chronic obstructive pulmonary disease. It is not possible to attribute these arrhythmias to telithromycin exposure based on the available information.

Table S28 summarizes the temporal relationship of the cardiac events of special interest in relation to drug exposure.

Table S28. Relationship between exposure to telithromycin and onset of cardiac AESI.

	Arrhythmia	Cardiac Arrest	Syncope/ Pre-syncope	Palpitations	Cardiac ishemic event	Non-cardiac
Telithromycin						
On therapy	4	0	1	4	1	4
0-14 days after last dose	3	1	5	1	3	1
>14 days after last dose	1	6	2	0	0	2
Amox/Clav						
On therapy	3	0	1	0	2	0
0-14 days after last dose	2	2	3	0	3	2
>14 days after last dose	1	1	1	2	1	9

There does not appear to be a temporal relationship between cardiac arrest and telithromycin exposure. Arrhythmias also occurred temporally in a similar way in the telithromycin arm as in the amoxicillin/clavulanic arm.

There were more palpitations in the telithromycin arm than the Augmentin arm and these occurred more commonly during exposure to drug. However, an accurate assessment of these events is not possible. This is because the study design did not include a pre-specified protocol on how patients with cardiac adverse events of special interest should be evaluated. As a result, definitive data (i.e., ECG's at the time of the palpitations) is not available and in most of the cases of palpitations, ECG data was collected too long after the event to be of diagnostic use. None of the cases of palpitations resulted in a serious complications.

6. Post-marketing cardiovascular safety

Table S29 summarizes all post-marketing cardiac adverse events occurring in countries where telithromycin has been approved and which have been submitted to FDA through the MedWatch system since submission of the amended NDA.

Table S29. Post-marketing telithromycin cardiac adverse events

Adverse Event	Total #	Serious	Not Serious	No Determination*
Tachycardia NOS	8	2	4	2
Palpitations	6	1	3	2
Cardiovascular disorder NOS	4	2	1	0
Arrhythmia NOS	2	1	0	1
Atrial fibrillation	2	2	0	0
Atrial flutter	1	1	0	0
Atrial tachycardia	1	0	1	0
Cardiac failure acute	1	1	0	0
Cardiac failure congestive	1	1	0	0
Cardiopulmonary failure	1	1	0	0
Coronary artery emoblism	1	1	0	0
Cyanosis NOS	1	1	0	0
Sinoatrial block	1	1	0	0
Supraventricular arrhthmia NOS	1	1	0	0
Torsade de pointes/ ventricular fibrillation	1	1	0	0

*No determination was made by the reporter as to whether the adverse event was serious.

There was one case of reported torsades de pointes. The FDA medical reviewer's summary of the MedWatch narrative for this patient is presented below below. In addition, all ECG data was requested and is provided as well (only a brief rhythm strip was available).

Mfr report#200214256DE

AE: Syncope equivalent, depressed level of consciousness, torsade de pointes – Fatal, ventricular fibrillation.

Source: spontaneous report by general practitioner via company representative.

Patient: 59 years, male.

Medical History: coronary heart disease, state after percutaneous transluminal angioplasty with stent implantation after angina pectoris attack in 2001, hypertension, transverse lesion of the cord with paraplegia TH 5/6 (car accident in 1990), spastic vesical paralysis, adiposity, hypertriglyceridemia, hypercholesterolemia, manic depressive disease.

Family History: two brothers died in the age of 48/49 from MI; his mother was found dead in bed at the age of 59 years.

Concomitant medications: methionin, triamterene, baclofen, isosorbide mononitrate, diazepam, atorvastatin, mirtazapin, metoprolol, amlodipine.

Course: The patient started treatment on 5/23/02 with Ketek for sinusitis and tracheobronchitis and on 5/28/02 he experienced an episode of confusion, retrospectively considered an equivalent of syncope. ECG at that time was normal as was blood pressure. Ketek was discontinued. On 5/30/02, the patient lost control while driving his car and he quickly regained his orientation. He was hospitalized and ECG showed no abnormalities. According to patient's wife, Ketek was re-administered. The patient was without symptoms until the next afternoon when the patient's long term ECG monitor revealed "classic torsade, persisting, finally changing to ventricular fibrillation that results in a zero line." ECG rhythm strip is shown in Figure 5.

The FDA medical reviewer noted that although the second syncopal episode occurred while off therapy with telithromycin, the patient had received 5 days of Telithromycin ending only two days prior. And, given the long half life of telithromycin, it can be expected that the patient was still being exposed to telithromycin during this syncopal episode.

Figure 5
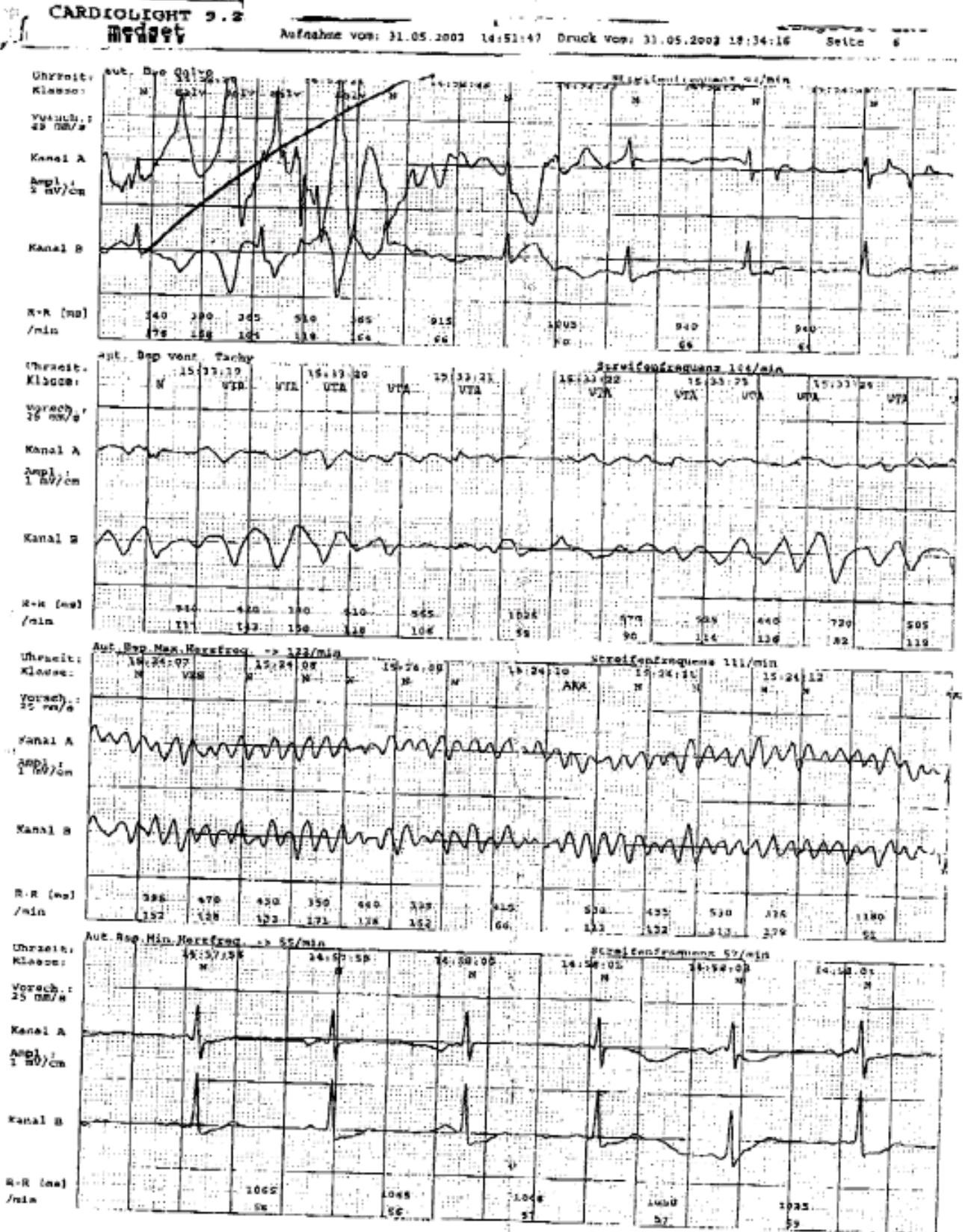
D. Visual safety

1. Overview of visual safety

The visual risk profile of telithromycin is notable for the following:

- In placebo-controlled Phase 1 studies, in younger patients receiving a single 2400 mg dose of telithromycin, the incidence of blurred vision ranged from 26.7% to 83.3%. In older patients receiving this dose, the incidence of blurred vision ranged from 0% to 33%. Blurry vision developed 1 to 3 hours after dosing. In subjects developing blurry vision, the adverse event lasted up to 20 hours. One placebo-treated subject developed blurry vision. The effect was described as a difficulty to focus at far distance without any change in intraocular pressure or anterior chamber angle, without modification of the visual field or color vision or fundus. Blurred vision was associated in one case with a reduced near visual acuity and in 2 cases with a reduced amplitude of accommodation but not associated with alteration of far visual acuity, refraction or tear film. Detailed ophthalmologic examinations during the occurrence of blurry vision did not reveal any significant change from baseline.

- The concentration of telithromycin in tears was higher in younger subjects than in older subjects. At the 2400 mg dose at which the adverse event of blurred vision was elicited, the concentration of telithromycin in tear fluid was 341 ng/Schirmer strip in subjects aged 18-40 years, versus 201 ng/strip in subjects aged 50 to 65 years.

- In Phase 3 studies, the incidence of blurred vision in telithromycin-treated patients in the integrated database was 20/4472 (0.4%) and was 2/2139 (0.09%) among comparator-treated patients. Women were more likely to have blurred vision during telithromycin treatment than were men. Of telithromycin-treated patients developing blurry vision, 16/20 (80%) were 40 or younger. The mean duration of blurry vision in these studies was 3.3 days (range, 1 – 10 days).

- In telithromycin-treated patients receiving a concomitant CYP 3A4 inhbitor in Phase 3 trials, the incidence of blurry vision was almost 5 times that in patients not receiving a 3A4 inhibitor (1.9% vs. 0.4%)

- In Study 3014, 74 (0.6%) of telithromycin-treated patients had a confirmed visual endpoint, versus 0.04% of comparator-treated patients. 33% of telithromycin-treated patients developing blurry vision reported a significant impact on activities; of the 17 subjects where a specific comment was included, 7 had difficulty reading, 5 were unable to work and one of these was also unable to drive, a further 4 were also unable to drive, and one was unable to baby-sit a grandson.

- As of the date of this briefing document, post-marketing safety reports received by the FDA regarding telithromycin-treated patients in countries where telithromycin has been approved have included 167 visual adverse events; 42 of these were considered serious.

2. Phase 1 studies

Two Phase 1 studies (Studies 1059 and 1064) are descibed of the visual effects of telithromycin were submitted by the Applicant. Pharmacokinetic aspects of these studies are described in Section IIC. Safety aspects of these studies are described in this section.

a) Study 1059: "Mechanism of blurred vision induced by HMR 3647 [telithromycin] at single supraclinical doses (2400 mg) versus therapeutic single dose (800 mg) in a younger and older population of healthy subjects"

Methods

This study was a single-center, randomized, placebo-controlled, double-blind, single-dose, three-way crossover study with a one-week washout period between treatments. Two groups of healthy adult subjects were studied:

Group I: 15 subjects 18 to 40 years of age with normal uncorrected vision

Group II: 15 subjects 50 to 64 years of age with presbyopia

Approximately equal numbers of males and females were to be enrolled in each group. Each subject received three treatments: telithromycin 800 mg, telithromycin 2400 mg, and placebo. The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period.

Plasma concentrations and amounts of drug in tears were determined at baseline and at 1, 2, 3, 4, 6, 8, and 24 hours after study drug administration. Eye examinations were performed at the following times:

At baseline and at 1, 2, 3, 4, 6, 8, and 24 hours after study drug administration:

- Far and near visual acuity for each eye
- Accommodation (near point and amplitude) using a Clark rule
- Pupil diameter
- Refraction
- Clinical evaluation of visual signs and symptoms (pain, discomfort, foreign body sensation, photophobia, blurred vision, stinging, burning, tearing)

At baseline and between 4 and 8 hours after study drug administration:

- Visual field with Amsler's grid
- Color vision
- Slit lamp examination (lids, cornea, lens, iris, fundus)
- Intraocular pressure using air puff tonometry method

Results

Thirty subjects were enrolled, 15 in each group. Group I had 7 male and 8 female subjects; mean age was 26 years (range 18 to 37 years). Group II had 6 male and 9 female subjects; mean age was 56 years (range 49 to 63 years). All subjects completed the study.

Plasma pharmacokinetic parameters were similar between groups. Measured amounts of telithromycin in tears were somewhat higher in Group I.

Four of 15 subjects (3 females, 1 male) in Group I and no subjects in Group II reported blurred vision. These reports are summarized in Table S30.

Table S30. Subjects with blurred vision in Study 1059

Subject	Age/ gender	Dose (mg)	Time post dose	Duration	Intensity	Description/symptoms	Eye exam	Other AE
2	18/F	2400	4 h	2 h	mild	blurred vision/far vision	No change	None
6	21/F	2400	6 h	1 h	mild	blurred vision/instability of far vision both eyes	No change	Nausea
9	25/F	2400	3 h	1 h	mild	blurred vision/difficulty focusing eyes, short latent period needed to focus for far vision	No change	Nausea
11	25/M	2400	3 h	30 min	mild	blurred vision/short latent period to focus for near and far vision	No change	Nausea, diarrhea

All cases occurred at the 2400 mg dose of telithromycin. Blurring developed 3 to 6 hours following drug administration, lasted 30 minutes to 2 hours, and was described as mild in intensity. Far vision was affected in all four subjects and near vision as well in one. The investigator reported that two subjects had a short latent period to focus, either for far vision alone or for both far and near vision. Three subjects had concurrent nausea, and one also had diarrhea. There was no concurrent eye pain, discomfort, foreign body sensation, photophobia, stinging, burning, or tearing. During the episodes of blurred vision, there were no changes in visual acuity, refraction, pupillary diameter, color vision, visual fields, and slit lamp examinations. There were no decreases in amplitude of accommodation and no increases in intraocular pressure. These subjects reported no blurred vision and there were no changes observed in their eye examinations after they received either the 800 mg dose of telithromycin or placebo. No changes from baseline eye examinations were observed in any of the subjects in Groups I or II following receipt of study medication.

b) Study 1064: "Assessment of ophthalmological safety of telithromycin at supraclinical dose (2400 mg) in healthy subjects"

<u>Methods</u>

This was a single-center, randomized, placebo-controlled, double-blind, single-dose, two-way crossover study with a one-week washout period between treatments. Twenty-four healthy adult subjects were studied. At least 35% were to be between 50 and 64 years of age. All subjects were required to have normal uncorrected far vision; a correction for near vision was acceptable for the older subjects. Each subject received two treatments: telithromycin 2400 mg and placebo. The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period.

Plasma concentrations were determined at baseline and at 1, 2, 3, 4, and 6 hours after study drug administration. Eye examinations were performed at the following times:

At screening: uncorrected and corrected visual acuity, fixation disparity test, refraction, intraocular pressure, color vision, slit lamp examination, fundus photography

At baseline, 3 hours, and 7 days after study drug administration:
- Far and near visual acuity for each eye
- Contrast sensitivity function for each eye
- Refraction
- Continuous recording of accommodation and pupil size using an autorefractor
- Slit lamp examination (lids, cornea, lens, iris, anterior chamber angle, fundus)
- Color vision
- Visual field threshold automated testing
- Tear film stability using a tearscope
- Intraocular pressure using air puff tonometry method
- Clinical evaluation of visual signs and symptoms (pain, discomfort, foreign body sensation, photophobia, blurred vision, stinging, burning, tearing)

At end of study: fundus photography

Results

Twenty-four subjects were enrolled; 18 were 18 to 49 years of age, and 6 were 50 to 64 years of age. Thirteen males and 11 females were enrolled. All subjects completed the study.

Telithromycin mean C_{max} was 5.11 mg/L (range 2.84-7.81 mg/L) and median t_{max} was 3 hours (range 1-4 hours). These values are consistent with those obtained with this dose in previous studies.

Twelve (50%) of the 24 subjects (7 females, 5 males) reported blurred vision, 10 of 12 (83%) in the 18 to 49 year age group and 2 of 6 (33%) in the 50 to 64 year age group. These reports are summarized in Table S31.

Table S31. Subjects with blurred vision in Study 1064

Subject	Age/gender	Treatment	Time post dose	Duration	Intensity
1	55/M	Telithromycin	1h 10m	2h 50m	Moderate
2	20/F	Telithromycin	3h 20m	18h 29m	Moderate
5	21/M	Telithromycin	1h 18m	4h 27m	Mild
6	19/M	Telithromycin	5h	0h 53m	Mild
10	30/F	Placebo	3h	18h 55m	Mild
10	30/F	Telithromycin	2h 50m	3h 15m	Moderate
13	34/M	Telithromycin	3h 6m	1h 14m	Mild
15	40/F	Telithromycin	3h 7m	2h 43m	Mild
17	54/F	Telithromycin	3h 5m	2h 25m	Mild
18	22/M	Telithromycin	1h 25m	20h 20m	Mild
21	47/F	Telithromycin	2h	5h 30m	Moderate
23	27/F	Telithromycin	2h 55m	3h 55m	Mild
24	41/F	Telithromycin	2h 35m	2h 40m	Mild

Adapted from study report, p.56

All 12 subjects reported blurred vision following administration of telithromycin; one subject also reported blurred vision following administration of placebo. Blurring developed 1 to 5 hours after dosing (median 3 hours) and lasted for a median of 2h 50 min (range, 53 m to 20 h 20 m). Three subjects (two telithromycin, one placebo) had a duration of blurring of 18 to 20 hours; the exact duration is uncertain because these subjects reported blurring at bedtime and were questioned the following morning. Narrative detail about the episodes of blurred vision is limited. The blurring was most commonly described as difficulty focusing, particularly on distant objects. The intensity was described as mild for eight subjects and moderate for four. Several subjects had concurrent dizziness, nausea, and diarrhea. One subject reported photophobia, one reported ocular discomfort, and one had diplopia; there were otherwise no concurrent eye complaints.

Eye examinations following drug administration demonstrated no consistent findings attributable to telithromycin, either in those reporting blurred vision or in those exposed but without blurring. There were no changes from baseline in visual fields, color vision, intraocular pressure, anterior chamber angle, or pupil diameter. One subject with blurring had impairment of near visual acuity, decrease in amplitude of accommodation, and impaired near-to-far reaction and response times. Continuous recording of accommodation in all subjects revealed no consistent changes in reaction or response times following drug administration. Tear film stability was reduced in three subjects with blurring and in three without blurring (one following telithromycin, two following placebo). Slit lamp examination was abnormal in one subject with blurring who had a corneal defect believed possibly due to eye rubbing; all remaining slit lamp examinations were normal.

3. Phase 3 studies

In the original submission, the incidence of blurred vision in the telithromycin treated patients (15/3265 or 0.5%) was higher than in controls (0/1672). Review of the three new studies revealed an additional 5 patients with blurred vision and 1 with "visual acuity reduced." In the comparator group, there were two patients with complaints of blurred vision. The incidence of blurred vision in telithromycin-treated patients in the integrated database was 20/4472 (0.4%) and was 2/2139 (0.09%). Table S32 summarizes details of all patients with blurred vision in telithromycin studies. This adverse event occurred on all telithromycin-treatment regimens (5 days: 11; 7 days: 3 ; 7-10 days: 3 ; 10 days: 3) .

Table S32. Subjects with adverse event of blurred vision in <u>all Phase 3 clinical trials</u> with age, sex, duration of blurred vision, intensity of blurred vision, and whether blurred vision occurred while on therapy.

Indication	Treatment (d=days)	Age	Sex	Duration (days)	Intensity	AE On therapy
Acute Sinusitis	Telithromycin 5 d [1]	22	M	1	Moderate	Yes
	Telithromycin 5 d	25	F	1	?	Yes
	Telithromycin 10 d	29	F	6	Severe	Yes
	Telithromycin 10 d	45	F	2	Mild	Yes
Tonsillitis/ Pharyngitis	Telithromycin 5 d	30	F	4	Mild	Yes*
	Telithromycin 5 d	31	F	2	Mild	Yes
	Telithromycin 5 d	22	F	1	Mild	Yes
	Telithromycin 5 d	26	F	2	Mild	Yes
	Telithromycin 5 d	19	F	2	Mild	Yes
	Telithromycin 5 d	36	F	10	Mild	Yes
	Telithromycin 5 d	34	M	1	Mild	Yes
Community Acquired Pneumonia	Telithromycin 5 d	40	M	1	moderate	Yes
	Telithromycin 7 d	43	F	10	Mild	Yes
	Telithromycin 7 d	25	F	2	Mild	Yes
	Telithromycin 7 d	29	M	2	Mild	Yes
	Telithromycin 7-10 d	42	M	8	Moderate	Yes
	Telithromycin 7-10 d	33	F	2	Mild	Yes
	Telithromycin 7-10 d	36	F	5	Mild	Yes
	Telithromycin 10 d	28	M	Unk.	Mild	Yes
	Clarithromycin[3]	69	F	1	mild	Yes
Acute Exacerbation of Chronic Bronchitis	Telithromycin 5 d	54	F	1	Moderate	Yes
	Amoxicillin/clavulanate [2]	47	F	Ongoing	Mild	No**
	Clarithromycin[3]	69	F	3	mild	No

[1]telithromycin 800 mg; [2]amoxicillin 500 mg/clavulanate 125 mg; [3]clarithromycin 500mg
*Study medication discontinued
** Visual problem pre-dated entry into study

Telithromycin-treated females were more likely to experience this adverse event than males with 15 females vs. 6 males experiencing blurred vision. Table S33 shows the incidence of blurred vision for females vs. males for <u>controlled studies</u> only.

Table S33. Incidence of Blurred Vision by sex in controlled Phase 3 studies.

	Women		Men	
Preferred Term	**Telithromycin (n=1385)**	**Comparators (n=1108)**	**Telithromycin (n=1317)**	**Comparators (n=1031)**
Vision Blurred	12 (0.9%)	3 (0.3%)	5 (0.4%)	0 (0.0%)

Telithromycin is metabolized by cytochrome CYP3A4; Phase 1 data shows that the C_{max} and AUC for telithromycin are markedly increased with it is co-administered with a CYP3A4 inhibitor. As an exploratory analysis, certain adverse events were examined to determine if concomitant use of a CYP3A4 inhibitor resulted in an increase

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in the adverse event rates. Table S34 shows the incidence of blurred vision in <u>controlled trials</u> both with and without the presence of a CYP3A4 inhibitor.

NOTE: Since patients were not randomized on the basis of CYP3A4 inhibitor intake, the results of this analysis should be interpreted cautiously.

Table S34. Frequency of Blurred Vision in All <u>Controlled Studies</u> by the presence of a CYP3A4 inhibitor

MedDRA Preferred Term	Received CYP 3A4 Inhibitor		Did not Receive CYP 3A4 Inhibitor	
	Telithromycin N=484	Comparators N=424	Telithromycin N=2218	Comparators N=1715
Eye Disorders (SOC)	**12 (2.5%)**	**2 (0.5%)**	**29 (1.3%)**	**13 (0.8%)**
Vision Blurred	**9 (1.9%)**	**0 (0.0%)**	**8 (0.4%)**	**3 (0.2%)**
95% CI*	**(0.47% , 3.1%)**			

* Exact 95% CI for the difference in rates of blurred vision between patients who received CYP3A4 inhibitors and those who did not.

This analysis is consistent with blurred vision being related to telithromycin exposure. Increased drug exposure may have occurred in the presence of a CYP3A4 inhibitor resulting in an increase of the incidence of blurred vision.

4. Study 3014

The visual adverse event of special interest (AESI) was "blurred vision," which was not otherwise defined in the study protocol. As with the other AESIs, there was no defined algorithm for investigators to follow in evaluating visual complaints in patients in study 3014. The clinical expert committee (CEC) for visual AESIs had a single member, a university-affiliated ophthalmologist. The confirmed safety endpoint definition used by the CEC for blurred vision was "all drug-related episodes of blurred vision that occurred after first ingestion of study drug through 48 hours after study drug intake." As with the other AESIs, the CEC adjudication form required that any alternative explanation be excluded before an event could be considered a positive endpoint, rather than considering any possibly drug-related AESI to be a positive endpoint.

The applicant reported CEC-confirmed visual endpoints in 74 of 12,096 (0.612%; 95% CI 0.481-0.767%) telithromycin-treated patients and in 5 of 11,883 (0.042%; 95% CI 0.014-0.098%) amoxicillin-clavulanate-treated patients. Table S35 describes the characteristics of the confirmed visual endpoints.

Table S35. Characteristics of confirmed visual endpoints in Study 3014

	Number of patients	
	Telithromycin (N=74)	Amoxicillin-clavulanate (N=5)
Symptoms		
Blurred vision	69	5
Distance only	10	-
Near only	13	-
Distance and near	46	4
Color abnormalities: color appears lighter	3	-
Light perception: increased brightness	7	-
Median onset after drug administration (h)	1 (1 – 48)	37 (2 – 456)
Median duration (h)	2 (0 – 48)	16 (2 – 72)
Intensity (mild/moderate/severe)	61/17/6	4/1/0
Significant impact on activities	33	2
Discontinuation due to adverse event	25	1
Serious adverse event	3	-

In the telithromycin group, the most commonly described abnormality was blurred vision affecting both distance and near vision. The blurring was not generally reported to occur with each dose. The median reported time of onset was one hour after taking the drug, and the event lasted a median of two hours. The blurring was mild to moderate in most cases; six patients reported severe blurring. In 45% of cases (33/74), the blurring had a significant impact on the patients' activities; the most frequently reported specific problems were difficulty reading (7 patients), inability to work (5 patients), and inability to drive (5 patients). In 34% of cases (25/74), telithromycin was discontinued because of blurring. All patients recovered without sequelae.

Three reports were considered by investigators to represent serious adverse events. One patient had severe blurring that was incapacitating, causing him to miss work and be confined to bed for two days; this patient completed his five day course of therapy for acute sinusitis. Another patient had diarrhea, dehydration, hypotension, chest pain, shortness of breath, and mild blurring of vision that were considered to be medically important and that resulted in discontinuation of telithromycin. The third patient had mild blurring that was considered to be medically important; she completed her 10-day course of therapy for community-acquired pneumonia, missed no time from work, and reported that the blurring had no significant effect on her activities.

The most common adverse events reported concurrently with blurred vision in telithromycin recipients were dizziness (14 patients), nausea (11 patients), and headache (10 patients). Several patients reported concurrent vomiting, dry mouth, abdominal pain, taste disturbance, fatigue, or diarrhea.

The telithromycin patients with confirmed endpoints were disproportionately female (62/74; 82.8%, compared with 60.9% of all telithromycin patients). There was no significant age predominance; the median age of patients with CEC-confirmed blurring was 48 years, the same as that of the safety evaluable population.

In contrast to the controlled Phase 3 studies, the incidence of blurred vision was not increased in patients taking both telithromycin and a CYP3A4 inhibitor (2/353; 0.6%). One patient taking a strong CYP3A4 inhibitor and one taking a mild CYP3A4 inhibitor had blurred vision.

5. Post-marketing visual safety

Two Periodic Safety Update Reports covering the periods 7/9/01 to 1/9/02 and 1/10/02 to 7/9/02 were reviewed. The applicant reported 159 events in the MedDRA System Organ Class "Eye Disorders." The most commonly reported events were blurred vision (67 cases), visual disturbance NOS (47 cases), accommodation disorder (10 cases), diplopia (10 cases), and vision abnormal NOS (7 cases). The remaining 18 reports were for events that occurred in one or two patients each. Most of the reports of visual disturbance were consistent with the reports of blurred vision from the clinical studies. The reported cases of diplopia were not confirmed by ophthalmologists and were often associated with blurred vision.

In addition to these periodic reports, post-marketing reports of visual events have also been received by the FDA. Table S36 summarizes all post-marketing hepatic adverse events occurring in countries where telithromycin has been approved and which have been submitted to FDA through the MedWatch system since submission of the amended NDA.

Table S36. All reported post-marketing visual adverse events.

Adverse Event	Total #	Serious	Not Serious	No Determination*
Vision Blurred	84	14	58	12
Visual Disturbance	42	17	20	5
Accommodation disorder	12	2	7	3
Diplopia	9	2	6	1
Visual acuity reduced	3	1	0	2
Eyelid Edema	3	1	0	2
Photophobia	2	2	0	0
Myosis	2	1	0	1
Mydriasis	2	0	1	1
Strabismus	2	0	1	1
Uveitis	1	1	0	0
Blindness/Visual Loss	1	0	0	1
Photopsia (flashes)	1	0	0	1
Lacrimation increased	1	0	0	1
Eyelid ptosis	1	1	0	0
Vitreous floater	1	0	0	1

*No determination was made by the reporter as to whether the adverse event was serious.

Examples of some of the patients with the adverse event of "Visual Disturbance" include the following verbatim reporter terms: two patients with "Could not see anything" (Reports 200210800DE, 200212138DE); one patient with "Severe dimming of sight" (Report 200211111EU); one patient with "black before eyes" (Report

200121084DE); one patient with "Temporary total loss of vision repeated for five times" (Report 200218526GDDC) ; one patient with "Extreme visual disturbance" (Report 200212375DE); one patient with "Seeing abnormal color (orange/red)" (Report 200211185DE).

Narratives

The following are verbatim transcriptions of MedWatch reports for five patients who reported visual disorders while taking telithromycin.

Mfr. Report# 200220212GDDC

>   AE: "Visual Lost"

>   Narrative: Initial Report: This spontaneous report from Brazil involves a 39 yo female patient who received therapy with Ketek 800mg daily from 10/25/02-10/26/02 for the treatment of sinusitis. There was no mention of relevant history or concommittant drugs. On 10/25/02 the patient experienced vision loss and cephalgia. She had partial recovery of vision on 10/29/02. The events are ongoing at the time of this report. The reporter assessed the events as highly probable and medically important.

>   Serious: Yes.

Mfr report# 200215827DE

>   AE: "Severe Visual Disturbance"

>   Source: spontaneous report by physician (internal medicine).

>   Patient: female, 36 years. No information on medical history and concomitant medication.

>   The patient was treated with Ketek orally (indication unknown), first intake on 10/1/02. One hour later the patient developed severe visual disturbance so that she had to rely on her husband's help. The event resolved after 9 hours. The physician assessed the causal relationship between event and treatment with Ketek as "highly probable."

>   Serious: Yes.

Mfr report #200210800DE

AE: "Massive visual disturbance (could not see anything)

Source: spontaneous report.

Patient: male, years.

The patient was treated with Ketek 1 x 400mg/day orally from 1/13/02 till 1/15/02 for sinusitis and tracheitis; no information on further medication. The patient had no medical history of visual disorders. On 1/15/02 the patient developed visual disturbance (blurred vision, affecting near and far sight); he was considerably impaired in his activities. The symptoms started increasingly within hours after intake of Ketek and resolved hours after stop of treatment with Ketek (end of

event: 1/16/02). The patient was not seen by a specialist. According to physician there was no alternative explanation for the event. He assessed the causal relationship between event and treatment with Ketek as "highly probable."

Serious: Yes.

Mfr report#200214345 DE

AE: Accomodation disturbance.

Source: spontaneous report by gynecologist (patient herself) via Drug Commission of the German Physicians Drug Association (Doc No. 133595) and via the German Health Authority (BfArM nl. 02005997).

Patient: Female, 44 years.

Medical History: allergy to penicillin. Concomitant medication: acetylsalicylic acid, zylometazoline HCl, contraceptives.

The reporting physician was the patient herself and took Ketek at a dose of 800mg/day orally from 4/11/02 to 4/15/02 because of sinusitis and imminent bronchitis and otitis media. No medical history was reported. Approximately one hour after intake of each dosage she experienced accommodation disturbance (e.g., unable to read) which slightly increased after 6-8 hours and completely resolved between 11-12 hours. She continued on telithromycin. However, the reporter states that she would have been incapable to work if she had taken the dose in the morning since she could not read.

Serious: not mentioned.

Mfr report #200215449GDDC

AE: Visual Disorder, Visual Loss"

This spontaneous report from a physician involves a 27 year old female patient who received therapy with telithromycin 800mg daily from 5/31/02 until 6/2/02 for the treatment of probably mycoplasm cough and expectoration. Relevant medical history includes hypothyroidism and dysrhythmia. Concomitant drugs include salbutamol, betamethasone and thyroxine sodium. On 6/2/02 the patient experienced visual disorder with visual loss. She discontinued the treatment with telithromycin. She underwent CAT scan and visual field studies, both were reported to be normal. The patient experienced a complete recovery upon discontinuing drug. The physician assessed the event as highly probable (for causality).

Serious: Yes.

(Reviewer's note: it is not clear from this report at what time the CAT scan and visual field testing was performed, as these may have been performed after symptoms had resolved or begun to resolve.)

E. Vasculitis-related aspects of safety

1. Phase 3 studies

In Phase 3 studies, one telithromycin-treated subject had a possibly related TEAE of skin vasculitis; this subject was a 65 year old white male treated with telithromycin for nine days for CAP. Two days after the end of treatment, the patient developed a nonpruritic rash on his upper and lower extremities. A skin biopsy showed leukocytoclastic vasculitis. The investigator and the FDA reviewer assessed this event as possibly related to study drug. A second telithromycin-treated patient developed "painful lower legs" during telithromycin therapy for CAP; this event was recorded as 'lower leg vasculitis'. However, the investigator felt that this event was not related to study drug. The FDA medical reviewer's assessment was that the presence or absence of vasculitis could not be established in this patient in the absence of more definitive data. No comparator-treated subject had a TEAE of vasculitis.

2. Study 3014

Vasculitic AESIs were identified in three telithromycin-treated subjects and one AMC-treated subject. For the three telithromycin subjects, one had biopsy-confirmed leukocytoclastic vasculitis, one had vasculitis NOS prior to study drug treatment, and one had urticaria acute, which the CEC reviewer considered a delayed (serum sickness type) reaction. The one AMC subject with a vasculitic AESI had a nonserious livedo reticularis after using a heating pad in the area. None of these were considered to be a drug-related vasculitis by the CEC reviewer.

The FDA medical reviewer agreed with the CEC reviewer's assessments, with the exception of the telithromycin-treated patient with biopsy-proven leukocytoclastic vasculitis. The Applicant's narrative for this patient is as follows:

Subject 0566/004 (telithromycin), a 40-year-old white female was enrolled in the study on 28 November 2001, with AS. She had no history of collagen vascular disease. The last dose of study medication was taken on 02 December 2001. On 05 December 2001, the subject experienced leukocytoclastic vasculitis (verbatim term: leukocytoclastic vasculitis). Associated symptoms included joint pain and headache and physical examination showed palpable purpura and pain at the rash site. Skin biopsy of the right ankle showed perivascular and interstitial neutrophils with prominent hemorrhage in the dermis. Fibrin was present, which was interpreted as most likely an early lesion of leukocytoclastic vasculitis. The investigator assessed the event to be nonserious, of severe intensity, and possibly related to study medication. The event resolved without sequelae on 12 December 2001. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC.

CEC Adjudication Summary: The skin biopsy results from the right ankle were equivocal, with findings suspicious, but not diagnostic for, leukocytoclastic vasculitis. Study drug was continued and the event not treated, but the event had resolved by follow-up 7 days later‐ a course not consistent with systemic vasculitis. A possible transient early

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leukocytoclastic vasculitis of unknown etiology may be present, but this case is not compatible with systemic vasculitis.

FDA reviewer assessment: The protocol-specified endpoint did not limit events to systemic vasculitis; the event described is compatible with a drug-induced cutaneous vasculitis, given the findings of palpable purpura, the biopsy results, and resolution of the event at follow-up without treatment. The onset of the event after drug discontinuation does not exclude the possibility of a relation to study drug, given the long half-life of telithromycin. Thus, this event should be considered a positive vasculitic endpoint.

3. Post-marketing vascular safety

There have been no reported cases of post-marketing telithromycin-associated vasculitis.

F. Other Post-marketing Adverse Events of Interest

Review of post-marketing adverse events has revealed several adverse events of potential concern.

Neurological Adverse Events

There have been a total of 48 reported cases of dizziness. Seven of these did not specify as to seriousness or severity. Eight were reported as serious and one was reported as severe but not serious. All of these events were suspected by the reporter as have been related to exposure to telithromycin.

There have been four reports of myasthenic crisis/myasthenia gravis aggravated with telithromycin exposure. One of these (Mfr report# 200121593) required an overnight hospitalization with no sequelae. The reporter assumed a causal relationship between telithromycin exposure and the event. The second (Mfr report# 200216097) resulted in life threatening ventilatory failure on the first day of treatment with telithromycin. This event requiring prolonged hospitalization. It is not clear how soon after the first dose that his event occurred. The reporter of this event considered telithromycin to be "highly probable" as the cause. The third case (Mfr report #200212530DE) had an adverse event reported as "myasthenia" however, further details are not available at this time. The fourth patient (Mfr report # 200211064EU) was a 69-year-old male with a past medical history of myasthenia gravis, diabetes, and respiratory insufficiency. Two to three hours after administration of the first dose of telithromycin, the patient experienced cardio-respiratory failure. The physician reporter considered the death as probably related to a myasthenic crisis, and he considered the death as a coincidence with telithromycin administration.

Other Gastrointestinal Adverse Events

There were two young patients who were reported as having had severe esophagitis after telithromycin exposure. Although there are two separate reports, it appears as though they may represent the same patient. Confirmation of this is pending. Summaries of MedWatch reports are as follows:

Mfr #20021217EU

AE: Hemorrhagic esophagitis

This spontaneous case reported by a physician from Spain involves a 18 year old male patient who was given Ketek (1600mg/day) starting on June 6, 2002 for sinusitis. The patient had a relevant medical history of depression since 1 year, for which he was receiving paroxetine. No allergy, no toxic habits. On June 7,2002, he developed severe esophagitis and was hospitalized on June 19, 2002, requiring parenteral nutrition. He was diagnosed as having severe hemorrhagic esophagitis. Telithromycin and paroxetine were stopped on June 19 and the patient was treated with IV omeprazole. On June 21, 2002, the patient recovered. The physician reporting this case felt that the causality of telithromycin was "highly probable" and considered it to be a serious adverse event.

Mfr #200212268EU

AE: Acute and severe esophagitis

This spontaneous case reported by Spanish Health Authorities (CAN ; C20020223) involves an 18 year-old patient who was given Ketek (400mg po BID) starting on June 6, 2002. On June 9, 2002, the patient experienced "acute and severe esophagitis directly related with telithromycin due to chemical aggression." Telithromycin was stopped and despite intensive therapy with antisecretor drugs, the event did not improve. The patient had absolute oral intolerance, pain, pyrosis that required parenteral nutrition. Endoscopy showled lower and medium area with diffuse erythema, petechiae and spontaneous bloody points (cardia). Stomach and duodenum were normal. The patient was discharged with anorexia but without dysphasia. On June 21, 2002 the patient completely recovered from the event.