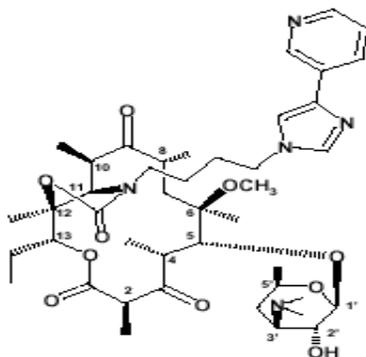


# **Appendix A**

# FDA Briefing Package

## Anti-Infective Drugs Advisory Committee

April 26<sup>th</sup>, 2001



**New Drug Application (NDA) 21-144**  
**Ketek<sup>TM</sup> (telithromycin)**

## 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<sub>B</sub>) family. The FDA has reviewed the primary data provided to support the safety and efficacy of telithromycin. Concerns regarding telithromycin will focus on the following specific areas:

- cardiac repolarization effect (QT interval prolongation);
- hepatotoxicity;
- pharmacokinetic variability and drug-drug interactions;
- resistance claims for *S. pneumoniae* (penicillin and macrolides).

### Safety:

Recently, approvals of non-cardiac drugs with a documented effect on QT interval have come under considerable scrutiny within the FDA. Assessment of risk/benefit must be considered in the decision to approve such drugs.

Telithromycin elicited delayed repolarization in *in vitro* models of cardiac repolarization, and *in vivo* in animals. In phase I studies, telithromycin caused concentration-dependent increases in the QT<sub>c</sub> interval. In phase III studies, telithromycin caused a consistent effect on mean QT<sub>c</sub> duration in humans, with evidence that interactions with drugs metabolized by CYP 3A4 may further prolong QT<sub>c</sub> duration.

Telithromycin's effect on QT<sub>c</sub> is concentration-dependent; thus, understanding sources of pharmacokinetic variability is important. Telithromycin concentrations in human plasma are highly variable (1.99 mg/L after a single dose in phase I, up to 9.9 mg/L after multiple doses in phase III), with a significant increase in C<sub>max</sub> in elderly subjects. Telithromycin is a CYP 3A4 substrate, and is primarily metabolized and eliminated by the liver. Co-administration of a 3A4 inhibitor significantly increases telithromycin concentrations. In hepatically impaired subjects, the t<sub>1/2</sub> of telithromycin was significantly increased.

Telithromycin has significant toxicologic effects on liver and heart in mice, rats, dogs and monkeys. These include increased liver-associated enzymes, increased total bilirubin, hepatic necrosis and associated inflammation, and phospholipidosis. Toxicologic comparisons between telithromycin and clarithromycin are discussed in the briefing package.

### Efficacy:

The applicant has requested approval for telithromycin in adults for the following indications:

- tonsillitis/pharyngitis (T/P);
- 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. This is the first time the Anti-Infectives Advisory Committee is to discuss a possible erythromycin resistance claim. 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. Summary of Selected Microbiologic Information

### Chemistry

- Semisynthetic
- Belongs to the ketolide family of antimicrobials within the macrolide-lincosamide streptogramin (MLS<sub>B</sub>) class.

### Mechanism of Action

- Inhibition of bacterial protein synthesis by action at the 23S ribosomal RNA.

### Spectrum of Activity

- *In vitro* activity against Gram-positive bacteria, fastidious Gram-negative bacteria, some anaerobes, and atypical pathogens (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydiae pneumoniae*).
- MIC<sub>90</sub> (µg/ml) range for target pathogens:
  - *S. pneumoniae* (including penicillin- and erythromycin-resistant strains): 0.25
  - *H. influenzae*: β-lactamase-negative – 2 ; β-lactamase-positive – 4
  - *M. catarrhalis* (including β-lactamase-positive strains) – 0.5
  - *S. pyogenes*: erythromycin-susceptible – 0.06; erythromycin-resistant – 8
  - Bacteriostatic against *S. pyogenes*, *S. aureus*
  - Bactericidal against penicillin- or erythromycin-susceptible and resistant *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.
  - None to minimal activity against methicillin-resistant *S. aureus* or methicillin-resistant coagulase-negative staphylococci.

### Resistance

- *In vitro* activity against some strains of *S. pneumoniae* that carry the *mefE* and *ermB* genes.
- *In vitro* activity against *S. pyogenes* that do not carry *ermB* gene. Increased MIC<sub>90s</sub> in *S. pyogenes* that carry *ermB*.

### Other microbiologic characteristics of telithromycin

- Synergism: no data available
- Antagonism: no data available
- Post-Antibiotic effect: Telithromycin has been shown to have a PAE ranging from approximately 1 h to 8 h at 10x MIC against the pathogens of interest.
- pH effect: A decrease in pH from 7 to 5.5 increases the telithromycin MIC for *S. pneumoniae* by approximately 15-fold.
- Inoculum effect: Increasing inoculum size from 10<sup>4</sup> to 10<sup>6</sup> cfu/mL does not affect the MIC. If the inoculum size is 10<sup>7</sup> or greater, the telithromycin MIC for *S. pneumoniae* goes up approximately 2 to 4-fold.

## II. 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. (See Appendix D of this briefing document for the complete report.) 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 toxicity are included in the Safety section (section V) of this briefing package.

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- $\beta$ -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.

### **III. Clinical Pharmacology**

Standard pharmacokinetic parameters for oral telithromycin are given in **Table 1**. Clinical pharmacology concerns of particular importance include:

- Pharmacokinetic variability: drug exposure may be significantly increased in the elderly and hepatically impaired patients.
- Drug-drug interactions: telithromycin exposure may be significantly increased by co-administration of a CYP 3A4 inhibitor such as ketoconazole.
- Cardiac repolarization effects: telithromycin prolongs the QT interval in a concentration-dependent fashion.
- The potential for these factors to act in an additive or synergistic fashion, leading to an increased risk of torsades de pointes.

Specific details are discussed in the Safety section (section V) of this document.

**Table 1. Summary of oral telithromycin pharmacokinetics**

<b>PK Assessments in Healthy Subjects</b>	<b>PK Parameters After 800 mg QD (Unless Noted) Expressed as Mean (CV)</b>
Absorption and Systemic Bioavailability (Study 1044)	Absolute Bioavailability: Young: 57.3% (31); Elderly 56.6% (20) $T_{max}$ : 2.5–3 hours
Food Effects (Study 1003)	None
Distribution	Protein Binding: 60% – 70% Bound $V_{ss}$ (L): Young subjects:210 (27); elderly subjects: 226 (21) Penetration into tissues: Blister fluid/tonsil secretion/pulmonary tissue/saliva
Metabolism (Study 1009)	Mainly metabolized (22% and 12% unchanged in feces and urine) CYP3A substrate Four metabolites have been identified.
Excretion (Study 1009)	Urine: 12% Unchanged telithromycin Feces: 22% Unchanged telithromycin
	Single dose: $C_{max}$ (mg/L)= 1.90 (42); range:0.964-3.252 $AUC_{0-\infty}$ (mg·h/L)= 8.25 (31) $t_{1/2}$ (h): 7.16 (19) CL/F (L/h): 102.3 (31) range: 53.5-184.8 CLr/F <sub>0-24</sub> : (L/h): 12.32 (17) Multiple doses: $C_{max}$ (mg/L)= 2.27(31); range:1.40-3.77 mg/L $AUC_{0-\infty}$ (mg·h/L)= 12.5 (43); range: 7.08-31.53 $t_{1/2}$ (h): 9.81 (20) CL/F (L/h): 71.1 (29) range: 25.4-85.2 CLr/F: (L/h): 12.5 (34)
Disposition Kinetics	Nonlinear pharmacokinetics Slightly more than dose proportional Increases in AUC and $C_{max}$ after 400 mg, 800 mg and 1600 mg. Accumulation factor was about 1.5 after multiple doses.
Significant Interactions	CYP3A4 inhibitor: ↑ telithromycin by ketoconazole/itraconazole ↔ telithromycin by grapefruit juice CYP3A4 substrate: ↑ cisapride /↑ simvastatin CYP2D6 substrate: ↔paroxetine CYP1A2 substrate: ↑ theophylline CYP2C9 substrate: ↔ warfarin Others: ↑ digoxin / ↔ oral contraceptive (ethinylestradiol) Gastric pH: telithromycin not changed by ranitidine and Maalox
Renal impairment	AUC and $C_{max}$ not significantly changed after single dose. No dose adjustment recommended by sponsor.
Hepatic Impairment	AUC and $C_{max}$ are comparable but $t_{1/2}$ ↑ significantly. No dose adjustment recommended by sponsor.
Effects of Age on PK	AUC and $C_{max}$ increased by 100% in elderly after multiple doses but no dose adjustment recommended by sponsor.
Effects of Gender on PK	None

#### IV. Clinical/Statistical Efficacy Analysis of Phase III trials

This section summarizes the FDA analyses of pivotal and supportive phase III trials contained in the NDA. 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 and erythromycin, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *C. pneumoniae*, *L. pneumophila*, and/or *M. pneumoniae*.
- **Acute bacterial exacerbation of chronic bronchitis** due to *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, and/or *M. pneumoniae*.
- **Acute sinusitis** due to *S. pneumoniae*, including strains resistant to penicillin and erythromycin, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, and/or *S. aureus*.
- **Tonsillitis/pharyngitis** due to *S. pyogenes* in patients 13 years old and above.

The NDA for telithromycin presents efficacy and safety data from 9 phase III pivotal trials and 4 phase III supportive trials. While some studies included patients from the US, there were no studies that enrolled US patients only. Phase III studies were conducted between 1997 and 2000. There were a total of 6113 patients enrolled, 5193 randomized and 5169 actually treated. There were 3390 subjects exposed to telithromycin and 1779 to comparators as shown by study protocol and indication in **Table 2**.

**Table 2. Subject disposition by indication for all phase III studies**

Indication/ Protocol #	Enrolled	Randomized			Treated		
		Ketek	Comparator <sup>b</sup>	Total	Ketek	Comparator <sup>b</sup>	Total
<b>CAP<sup>a</sup></b>							
3006	493	224	225	449	224	224	448
3009	312	124	124	248	124	124	248
3001	405	199	205	405	199	205	404
3000*	240	240	-	240	240	-	240
3009OL*	221	221	-	221	221	-	221
3010*	442	432	-	432	432	-	432
<b>Total CAP</b>	<b>2133</b>	<b>1440</b>	<b>554</b>	<b>1994</b>	<b>1440</b>	<b>553</b>	<b>1993</b>
<b>AECB<sup>a</sup></b>							
3007	571	244	254	498	243	253	496
3003	325	163	161	324	161	160	321
<b>Total AECB</b>	<b>896</b>	<b>407</b>	<b>415</b>	<b>822</b>	<b>404</b>	<b>413</b>	<b>817</b>
<b>Sinusitis</b>							
3005	1244	528	263	791	528	262	790
3002 <sup>c</sup>	343	341	-	341	336	-	336
3011	593	260	125	385	252	122	374
<b>Total</b>	<b>2180</b>	<b>1129</b>	<b>388</b>	<b>1517</b>	<b>1116</b>	<b>384</b>	<b>1500</b>
<b>SINUSITIS</b>							
<b>Tonsillitis/ Pharyngitis</b>							
3008	526	232	231	463	232	231	463
3004	398	198	199	397	198	198	396
<b>Total</b>	<b>924</b>	<b>430</b>	<b>430</b>	<b>860</b>	<b>430</b>	<b>429</b>	<b>859</b>
<b>TONS/PHAR<sup>a</sup></b>							
<b>GRAND TOTAL</b>	<b>6113</b>	<b>3406</b>	<b>1787</b>	<b>5193</b>	<b>3390</b>	<b>1779</b>	<b>5169</b>

\* Open label studies

<sup>a</sup> CAP = Community acquired pneumonia, AECB = Acute exacerbation of chronic bronchitis, TONS/PHAR = Tonsillitis/pharyngitis

<sup>b</sup> Comparators included: CAP [clarithromycin (3006), trovafloxacin (3009), amoxicillin (3001)], AECB [cefuroxime axetil (3007), amoxicillin/clavulanic acid (3003)], SINUSITIS [amoxicillin/clavulanic acid (3005), cefuroxime axetil (3011)], TONS/PHAR [penicillin VK (3004), clarithromycin (3008)]

<sup>c</sup> A double-blind, trial comparing two telithromycin regimens (5-Days vs. 10-Days)

### Study populations

**Table 3** shows the definitions of the various study populations used in the analysis of efficacy; **Table 4** shows the sizes of the populations for the various indications. The definition of the mITT is different from the classic definition of intent-to-treat (ITT, i.e., all randomized patients). The purpose behind analyzing mITT rather

than ITT populations was to exclude subjects with a clear misdiagnosis and to provide a more conservative approach to establish statistical and clinical equivalence between telithromycin and the comparators under study. The difference between the ITT and mITT populations was largely explained by subjects who did not meet the predefined radiologic criteria as specified for the various infections.

**Table 3. Definitions of the various populations used in the FDA efficacy analysis**

<b>Population</b>	<b>Definition</b>
<b>mITT</b>	All randomized subjects, as treated, with a confirmed diagnosis of the infection, as defined in the respective study protocol, who received at least one dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms and radiologic findings supportive of the diagnosis, as defined in the protocols. This definition was intended to exclude subjects with a clear misdiagnosis, in whom study medication was not expected to demonstrate the desired therapeutic effect.
<b>PPc</b>	All mITT subjects except those with major protocol violations and/or indeterminate responses.
<b>bmITT</b>	All mITT subjects with a pathogen at pretherapy/entry considered by the investigator to be responsible for infection.
<b>PPb</b>	All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.

**Table 4. Populations used for efficacy analysis by indication, excluding subjects from censored sites**

<b>Indication</b>	<b>Efficacy Populations</b>					
	<b>Randomized</b>	<b>Treated</b>	<b>mITT</b>	<b>PPc/PP</b>	<b>bmITT</b>	<b>PPb</b>
<b>CAP<sup>a</sup></b>						
Telithromycin	1440	1427	1373	1132	562	344
Comparator	554	553	521	394	142	90
<b>AECB<sup>a</sup></b>						
Telithromycin	407	404	343	255	82	64
Comparator	413	413	353	254	79	58
<b>Sinusitis</b>						
Telithromycin	1129	1116	980	731	345	253
Comparator	388	384	318	226	71	57
<b>Tonsillitis/pharyngitis</b>						
Telithromycin	430	430	430	302	325	265
Comparator	430	429	428	254	323	424

<sup>a</sup> CAP = Community acquired pneumonia, AECB = Acute exacerbation of chronic bronchitis

Nine clinical trial sites were inspected at random by the FDA's Division of Scientific Investigation. Six of these sites (representing 4 investigators) failed to meet good clinical practice guidelines and were therefore censored by the Agency due to data integrity issues. A total of 186 subjects from these sites were excluded from all analyses for efficacy and safety. **Table 5** summarizes the number of subjects censored by the FDA.

**Table 5. Number of subjects censored by the agency from applicant's original submission**

Indication	Study Protocol	Number of subjects		
		Telithromycin	Comparator	Total
CAP	3009	13	12	25
AECB	3007	62	62	124
Sinusitis <sup>1</sup>	3005	26	11	37
Total				186

<sup>1</sup> 11 additional subjects were censored prior to submission of the major amendment because two sites were associated with investigators who were previously censored by the agency.

The following outcome definitions were applied in all studies:

- **Clinical Cure:** all infection-related signs and symptoms had disappeared or had returned to the pre-infection state and (for CAP) Chest X-ray findings showed improvement or lack of progression; OR  
 Infection-related signs and symptoms had improved, (for CAP) chest X-ray findings showed improvement or lack of progression and NO subsequent antibiotic therapy was started for the treatment of the disease under investigation.
- **Bacteriologic Eradication** was defined as either of the following:
  - 1.) proven eradication (the causative pathogen was absent in a culture obtained during the post therapy/TOC time window and no subsequent antibiotic therapy was started prior to the culture being obtained, AND
  - 2.) presumed eradication (the subject had improved clinically to such an extent that a proper follow-up culture could not be obtained and no subsequent antibiotic therapy had been started up to the end of the post therapy/TOC time window.

### A. Community Acquired Pneumonia

The applicant submitted five clinical studies in support of community-acquired pneumonia indication for Ketek™ (telithromycin) tablets in the original NDA submission on February 28, 2000. Three of the clinical studies were pivotal (3001, 3006, 3009OL) and two studies were supportive (3000 and 3009OL). The applicant submitted an additional clinical study (3010) on March 1, 2001, primarily to supplement the efficacy data on resistance claims. **Table 6** summarizes all submitted studies of CAP.

**Table 6. Community-Acquired Pneumonia: Pivotal and Supportive Studies**

STUDY	DESIGN	TREATMENT	DAYS	N	GEOGRAPHIC REGION
<b>Pivotal Comparative Studies</b>					
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 Trovaflaxacin 200 mg po qd	7 - 10 d 7 - 10 d	204	USA, Canada, South Africa
<b>Supportive Non-Comparative Studies</b>					
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	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, trovaflaxacin.

The primary efficacy variable was clinical response (cure, failure or indeterminate) assessed by the investigator at the posttherapy/TOC visit, 7 to 10 days after the end of therapy. The primary analysis study population was the per protocol population (PPc). The PPc population was defined as all protocol-compliant subjects who received study medication and remained in the study. Clinical outcome was also analyzed for the modified-intent-to treat population (mITT) who were all subjects treated with a confirmed diagnosis of CAP (as defined in the protocol) and received at least one dose of

study drug. Clinical cures include patients who had complete resolution of symptoms and those who had improved.

**Tables 7A-7C** summarize the clinical and bacteriologic efficacy data for all studies of CAP at the TOC visit in both per-protocol and mITT populations.

**Table 7A. Clinical cure rates for telithromycin versus comparators at the test-of-cure visit – CAP**

	Telithromycin			Comparators <sup>1</sup>			2-sided 95% Confidence Interval		
	N	n	%	N	n	%			
<b>PPc Population</b>									
Study 3001	TEL 10 d	149	141	94.6	AMX 10 d	152	137	90.1	(-2.1%, 11.1%) <sup>2</sup>
Study 3006	TEL 10 d	150	129	88.3	CLA 10 d	143	121	88.5	(-7.9%, 7.5%) <sup>2</sup>
Study 3009	TEL 7-10 d	80	72	90.0	TVA 7-10d	86	81	94.2	(-13.6%, 5.2%) <sup>2</sup>
Study 3000*	TEL 7-10 d	197	183	92.9	-	-	-	-	[88.1% , 95.9%] <sup>3</sup>
Study 3009OL*	TEL 10-d	187	175	93.6	-	-	-	-	[88.8%, 96.5%] <sup>3</sup>
Study 3010*	TEL 7 d	357	332	93.0	-	-	-	-	[89.7% , 95.3%] <sup>3</sup>
<b>mITT Population</b>									
Study 3001	TEL 10 d	199	171	85.9	AMX 10 d	205	161	78.5	(- 0.5% , 15.3%) <sup>2</sup>
Study 3006	TEL 10 d	204	156	76.5	CLA 10 d	212	171	80.7	(- 9.9% , 6.5%) <sup>2</sup>
Study 3009	TEL 7-10 d	100	82	82.0	TVA 7-10d	104	89	85.6	(-14.7%, 7.5%) <sup>2</sup>
Study 3000*	TEL 7-10 d	240	191	79.6	-	-	-	-	[73.8%, 84.4%] <sup>3</sup>
Study 3009OL*	TEL 10-d	212	182	85.8	-	-	-	-	[80.3%, 90.1%] <sup>3</sup>
Study 3010*	TEL 7 d	418	357	85.4	-	-	-	-	[81.6%, 88.6%] <sup>3</sup>

\* Studies which did not include an *active control* arm

<sup>1</sup> TEL 10-d = telithromycin 10-Days, AMX = amoxicillin, CLA= clarithromycin, TVA = trovafloxacin,

<sup>2</sup> Confidence interval for the difference of the two cure rates.

<sup>3</sup> Confidence interval for the cure rate observed in the open label trial.

**Table 7B. Bacteriologic response by subject for telithromycin versus comparators at the test-of-cure visit - CAP**

	Telithromycin			Comparators <sup>1</sup>			2-sided 95% Confidence Interval <sup>2</sup>		
	N	n	%	N	n	%			
<b>PPb</b>									
<b>Population</b>									
Study 3001	TEL 10 d	40	36	90.0	AMX 10 d	40	35	87.5	(- 13.8%, 18.9%) <sup>2</sup>
Study 3006	TEL 10 d	28	25	89.3	CLA 10 d	28	27	96.4	(- 3.3%, 10.4%) <sup>2</sup>
Study 3009	TEL 7-10 d	14	13	92.9	TVA 7-10 d	22	22	100	(- 26.5%, 12.2%) <sup>2</sup>
Study 3000*	TEL 7-10 d	45	40	88.9	-	-	-	-	[ 75.2%, 95.8%] <sup>3</sup>
Study 3009OL*	TEL 10-d	68	61	89.7	-	-	-	-	[ 79.3%, 95.4%] <sup>3</sup>
Study 3010*	TEL 7 d	149	137	91.9	-	-	-	-	[ 86.0%, 95.6%] <sup>3</sup>
<b>bmITT</b>									
<b>Population</b>									
Study 3001	TEL 10 d	56	49	87.5	AMX 10 d	54	46	85.2	(- 12.3%, 17.0%) <sup>2</sup>
Study 3006	TEL 10 d	40	36	90.0	CLA 10 d	39	37	94.9	(- 14.4%, 22.7%) <sup>2</sup>
Study 3009	TEL 7-10 d	29	27	93.1	TVA 7-10 d	32	30	93.8	(- 19.0%, 9.3%) <sup>2</sup>
Study 3000*	TEL 7-10 d	54	49	90.7	-	-	-	-	[ 78.9%, 96.5%] <sup>3</sup>
Study 3099OL*	TEL 10-d	88	80	90.9	-	-	-	-	[ 82.3%, 95.7%] <sup>3</sup>
Study 3010*	TEL 7 d	255	215	84.3	-	-	-	-	[ 79.1%, 88.4%] <sup>3</sup>

\* Studies which did not include an active control comparator arm

<sup>1</sup> TEL 10-D = telithromycin 10-Days, AMX = amoxicillin, CLA= clarithromycin, TVA = trovafloxacin,

<sup>2</sup> Confidence interval for the difference of the two cure rates.

<sup>3</sup> Confidence interval for the cure rate observed in the open label trial.

**Table 7C. Overall eradication rates of Baseline Pathogens Pooled from all CAP Studies at posttherapy/TOC- PPb population**

All Combined Studies	Telithromycin			Comparator		
	N	n	%	N	n	%
<b>Pathogen</b>						
<i>S. pneumoniae</i>	174	166	95.4	50	44	88.0
<i>H. influenzae</i>	105	94	89.5	28	26	92.8
<i>M. catarrhalis</i>	30	27	90.0	6	6	100.0
<i>H. parainfluenzae</i>	60	53	88.3	10	9	90.0
<i>S. aureus</i>	19	15	79.0	3	3	100.0
<b>Other</b>	46	37	80.4	16	13	81.2

**Penicillin-resistant *S. pneumoniae* (PRSP)/Erythromycin-resistant *S. pneumoniae* (ERSP)**

The applicant is requesting the indication of community-acquired pneumonia due to *S. pneumoniae*, including penicillin- and erythromycin-resistant strains. **Table 8** summarizes the efficacy of telithromycin across the five CAP studies in the PPb population that contained resistant organism. The definition of the breakpoints for *S. pneumoniae* is as follows:

<b><u>Penicillin</u></b>		<b><u>Erythromycin</u></b>	
Sensitive	< 0.6 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

It should be noted that the majority of subjects were treated as outpatients with oral therapy, and were classified as having mild to moderate pneumonia upon entry into the studies.

**Table 8. Summary of Outcomes by Resistance patterns for *Streptococcus pneumoniae* (single and mixed cultures) – Telithromycin (PPb population, 5 studies combined\*)**

	<b>Outcome- Cured</b>				
	<b>Pen-S</b>	<b>PRSP</b>	<b>Ery-S</b>	<b>Ery-R</b>	<b>PRSP+EryR</b>
<b>TOTAL</b>	125/128 (97.6%)	14/17 (82%)	135/137 (99%)	14/17 (82%)	6/9 (66.6%)
<b>Blood</b>	27/29 (93%)	4/6 (66.7%)	32/34 (94%)	4/6 (66.7%)	1/3 (33.3%)
<b>Sputum</b>	98/99 (98.9%)	10/11 (91%)	103/103 (100%)	10/11 (91%)	5/6 (83.3%)
<b>Mixed**</b>	33/34 (97.1%)	5/7 (71.4%)	33/34 (97.1%)	5/7 (71.4%)	3/5 (60%)

\* Studies 3000, 3001, 3006, 3009OL, 3010

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

Overall, the cure rate in telithromycin-treated patients was 97.6% for those with *S. pneumoniae* penicillin-sensitive isolates compared to 82% for those with PRSP isolates. PRSP was isolated from 17 telithromycin-treated patients; six of these had documented *S. pneumoniae* bacteremia. Of the six patients with PRSP bacteremia, the cure rate was 66.7%. There was only one PRSP isolated from the sputum in a comparator-treated patient, who was reported as cured.

Erythromycin resistance was seen in 17 telithromycin-treated patients. The cure rate for telithromycin-treated patients with erythromycin-sensitive isolates was 99%, compared to 82% for patients with erythromycin-resistant isolates. Only 6 telithromycin-treated patients had ERSP isolated from the blood. The cure rate in patients with ERSP bacteremia was 66.7%.

ERSP was isolated from 3 patients among the comparator-treated patients, all of whom were cured. Of note, 5 of these patients had telithromycin MICs greater than the suggested FDA resistance breakpoint for telithromycin (0.25 µg/mL).

Outcomes in patients with erythromycin-resistant isolates of different genotypes were examined. There were 9 *ermB* isolates with MICs ranging from 4.0 to 32.0 ug/mL. The cure rate was 77.8% (7/9). The two patients who failed had severe pneumonia, were hospitalized and had penicillin-resistant *S. pneumoniae*. Ten patients had *S. pneumoniae* isolates with the *mefE* genotype (two of the 17 patients had both genes). Only one patient, who was bacteremic, was a clinical failure. The telithromycin MICs of these isolates ranged from 0.3 to 1.0 µg/mL. Using the FDA breakpoint for telithromycin, 5 of these patients' isolates were resistant to telithromycin.

Of PRSP isolates, 52.9% (9/17) were also resistant to erythromycin. Although these are small numbers, patients with a PRSP+EryR isolate were more likely to have poorer clinical outcomes than those with either a PSRP or Ery-R phenotype alone. All of these isolates were sensitive to telithromycin with a MIC or  $\leq 0.5$  µg/ml. All of the MICs reported for the isolates classified as PRSP were  $\leq 2.0$  µg/ml (final MICs are pending).

**Tables 9A and 9B** display details regarding the individual patients with PRSP isolates. It should be noted that the bmITT patients were listed in order to give the reader an understanding of the types of outcomes that were recorded. It is particularly interesting to note that of the 5 patients who were in the bmITT group and were not included in the PPb subgroup, 3 were classified as having Indeterminate outcomes. One patient died due to aspiration pneumonia on day 5 after showing improvement on a chest X-ray on day 4.

**Table 9A. Subjects with *S. pneumoniae* penicillin resistant (PRSP)[ MIC ≥2 μg/mL]–bmITT+PPb Populations: ALL CAP Studies – Telithromycin group**

Study Number/ Investigator No./ Subject Number/ Location	Fine Score/ Severity	Pathogen/ (Single or Mixed)/ Genotype	Source	MIC to Pen G (ug/ml)	MIC to Ery A (ug/ml)	MIC to Ketek (ug/ml)	Clinical Outcome	Bacteriological Outcome
<b><i>bmITT</i></b>								
3000/101/1365 Argentina	I	<i>S. pneumoniae</i> / (Single)/ NA	BLOOD	<u>2.000</u>	0.030	0.015	Indeterminate	Indeterminate
3001/0111/010 Argentina/	III	<i>S. pneumoniae</i> / (Single)/ NA	BLOOD	<u>2.000</u>	0.060	0.015	Indeterminate	Indeterminate
3001/0902/002 New Zealand	III	<i>S. pneumoniae</i> / (Single)/ NA	SPUTUM	<u>2.000</u>	0.060	0.015	Failure	Eradication
3010/0473/009 USA	V	<i>S. pneumoniae</i> / (Mixed)/mefE	SPUTUM	<u>2.000</u>	8.000	2.000	Indeterminate <sup>d</sup>	Indeterminate
3010/0526/002 South America	II	<i>S. pneumoniae</i> / (Single)	SPUTUM	<u>2.000</u>	0.250	0.030	Cure	Presumed eradication
<b>Total = 5</b>								
<b><i>PPb</i></b>								
3000/603/1081 France	II	<i>S. pneumoniae</i> / (Single)/ NA	BLOOD	<u>2.000</u>	0.030	0.015	Cure	Eradication
3000/605/1091 France	III	<i>S. pneumoniae</i> / (Mixed)/ermB	BLOOD	<u>2.000</u>	32.000	0.030	Failure	Pres.persistence
3000/610/1110 France	I	<i>S. pneumoniae</i> / (Single)/NA	SPUTUM	<u>2.000</u>	0.030	0.015	Cure	Pres. eradication
3001/1002/027 South Africa	IV	<i>S. pneumoniae</i> / (Mixed)/ermB	SPUTUM	<u>2.000</u>	32.000	0.030	Failure	Pres.persistence
3001/1401/002 Australia	Moderate	<i>S. pneumoniae</i> / (Single)/ NA	SPUTUM	ND*	ND	ND	Cure	Pres. eradication
3006/0008/031 USA	I	<i>S. pneumoniae</i> / (Single)/NA	BLOOD	<u>2.000</u>	0.060	0.008	Cure	Eradication
3006/0008/039 USA	I	<i>S. pneumoniae</i> / (Single)/mefE	SPUTUM	<u>2.000</u>	4.000	0.030	Cure	Pres. eradication
3006/0012/019 USA	I	<i>S. pneumoniae</i> / (Mixed)/ NA	SPUTUM	<u>2.000</u>	0.060	0.008	Cure	Pres. eradication
3009OL/0355/104 South Africa	II	<i>S. pneumoniae</i> / (Single)/mefE	BLOOD	<u>2.000</u>	4.000	0.060	Cure	Pres. eradication
3009OL/0368/105 South Africa	I	<i>S. pneumoniae</i> / (Single)/ NA	BLOOD	<u>2.000</u>	0.060	0.030	Cure	Pres. eradication
3009OL/0369/105 South Africa	II	<i>S. pneumoniae</i> / (Single)/mefE	BLOOD	<u>2.000</u>	4.000	0.120	Failure	Pres. persistence
3010/0483/008 USA	I	<i>S. pneumoniae</i> / (Mixed)/mefE	SPUTUM	<u>2.000</u>	4.000	0.060	Cure	Pres. eradication
3010/0494/036 USA	III	<i>S. pneumoniae</i> / (Mixed)/ermB	SPUTUM	<u>2.000</u>	8.000	0.250	Cure	Pres. eradication
3010/0503/001 USA	II	<i>S. pneumoniae</i> / (Mixed)/ NA	SPUTUM	<u>2.000</u>	0.060	0.030	Cure	Pres. eradication
3010/0526/001 South America	III	<i>S. pneumoniae</i> / (Single)/ NA	SPUTUM	<u>2.000</u>	0.250	0.030	Cure	Pres. eradication
3010/0533/007 South Africa	I	<i>S. pneumoniae</i> / (Single)/ermB/ mefE	SPUTUM	<u>2.000</u>	8.000	0.500	Cure	Pres. eradication
3010/0534/059 South Africa	I	<i>S. pneumoniae</i> / (Single)/ermB/ mefE	SPUTUM	<u>2.000</u>	8.000	0.500	Cure	Pres. eradication
<b>Total = 17</b>								

*d* - death due to aspiration pneumonia.

\* ND – not done

**Table 9B. Subjects with *S. pneumoniae* erythromycin-resistant (ERSP) [MIC ≥1 µg/mL], alone and combination with PRSP–bmITT+PPb Populations: All CAP Studies –Telithromycin Group**

Study Number/ Investigator No./Subject Number/Location	Fine Score/ Severity	Pathogen/ (Single or Mixed)/ Genotype	Source	MIC to Pen G (µg/mL)	MIC to Ery A (ug/ml)	MIC to Ketek (ug/ml)	Clinical Outcome	Bacteriologic Outcome
<b><i>BmITT</i></b>								
3000/605/1090/France	III	<i>S. pneumoniae</i> / (Single)/ermB	SPUTUM	0.120	0.030	0.030	Cure	Pres. eradication
3010/0473/009/USA	V	<i>S. pneumoniae</i> / (Mixed)/mefE	SPUTUM	<u>2.000</u>	<u>8.000</u>	2.000	Indeterminate	Indeterminate
3010/0494/026/USA	I	<i>S. pneumoniae</i> / (Mixed)/ermB	SPUTUM	0.500	<u>8.000</u>	0.030	Cure	Pres. eradication
<b>Total = 3</b>								
<b><i>PPb</i></b>								
3000/605/1091/ France	III	<i>S. pneumoniae</i> / (Mixed)/ermB	BLOOD	<u>2.000</u>	<u>32.000</u>	0.030	Failure	Pres.persistence
3001/1002/027 South Africa	IV	<i>S. pneumoniae</i> / (Mixed)/ermB	SPUTUM	<u>2.000</u>	<u>32.000</u>	0.030	Failure	Pres.persistence
3001/1401/002/* Australia	Moderate	<i>S. pneumoniae</i> / (Mixed)/ermB	SPUTUM	ND**	ND**	ND	Cure	Pres. eradication
3001/1101/005/ Sweden	IV	<i>S. pneumoniae</i> / (Single)/ ermB	BLOOD	0.008	<u>32.000</u>	0.030	Cure	Pres.eradication
3006/0008/039 USA	I	<i>S. pneumoniae</i> / (Single) /mefE	SPUTUM	<u>2.000</u>	<u>4.000</u>	0.030	Cure	Pres. eradication
3006/0425/008 Argentina	I	<i>S. pneumoniae</i> / (Single)/mefE	SPUTUM	0.500	<u>8.000</u>	0.030	Cure	Eradication
3009OL/0355/104 South Africa	II	<i>S. pneumoniae</i> / (Single)/mefE	BLOOD	<u>2.000</u>	<u>4.000</u>	0.060	Cure	Pres. eradication
3009OL/055/154 South Africa	II	<i>S. pneumoniae</i> / (Single)/ermB	SPUTUM	0.250	<u>32.000</u>	0.030	Cure	Pres. eradication
3009OL/055/157 South Africa	I	<i>S. pneumoniae</i> / (Single) /mefE	SPUTUM	0.030	<u>32.000</u>	1.000	Cure	Pres. eradication
3009OL/0369/105 South Africa	II	<i>S. pneumoniae</i> / (Single)/mefE	BLOOD	<u>2.000</u>	<u>4.000</u>	0.120	Failure	Pres. persistence
3010/0483/008/ USA	I	<i>S. pneumoniae</i> / (Mixed)/mefE	SPUTUM	<u>2.000</u>	<u>4.000</u>	0.060	Cure	Pres. eradication
3010/0494/036/ USA	III	<i>S. pneumoniae</i> / (Mixed)/ermB	SPUTUM	<u>2.000</u>	<u>8.000</u>	0.060	Cure	Pres. eradication
3010/0523/001/ South America	I	<i>S. pneumoniae</i> / (Single)/ ermB	SPUTUM	<u>2.000</u>	<u>4.000</u>	0.250	Cure	Pres. eradication
3010/0533/007/ South Africa	I	<i>S. pneumoniae</i> / (Single)/ermB/mefE	SPUTUM	0.030	<u>8.000</u>	0.030	Cure	Pres. eradication
3010/0523//059 South Africa	I	<i>S. pneumoniae</i> / (Mixed)/ermB/mefE	SPUTUM	<u>2.000</u>	<u>8.000</u>	0.500	Cure	Pres. eradication
3010/0536/014/ South Africa	I	<i>S. pneumoniae</i> / (Mixed)/mefE	BLOOD	0.250	<u>8.000</u>	1.000	Cure	Pres. eradication
3010/0536/031/ South Africa	I	<i>S. pneumoniae</i> / (Mixed)/mefE	BLOOD	0.500	<u>8.000</u>	1.000	Cure	Pres. eradication
<b>Total = 17</b>								

\* Subject#1401/002 in Study 3001 had an ERSP isolate resistant by oxacillin disk in the regional lab, however the subculture was not viable in CMI. therefore no MIC was performed.

\*\* ND – not done

Narratives of the three telithromycin-treated patients who were clinical failures can be found in Appendix B.

**Atypical Pneumonia Results**

Table 10 summarizes outcomes in patients with pneumonia due to *C. pneumoniae*, *M. pneumoniae* or *L. pneumophila*. All cases were diagnosed serologically rather than by culture.

**Table 10. Clinical outcome of subjects with infection due to atypical pathogens at posttherapy/TOC-PPc population: All CAP Studies\***

Pathogen	Telithromycin 7-10 Days			Comparators 7-10 Days		
	N	Cure	%	N	Cure	%
<i>Chlamydia pneumoniae</i>	34	32	(94.1%)	18	17	(94.4%)
<i>Mycoplasma pneumoniae</i>	31	30	(96.8%)	19	18	(94.7%)
<i>Legionella pneumophila</i> **	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.

**CAP Efficacy Summary**

- The clinical efficacy data from two adequate and well controlled studies demonstrate equivalence in the treatment of mild to moderate CAP between oral telithromycin and its comparators (amoxicillin, clarithromycin). This includes cases due to the major pathogens causing CAP (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*)
- Across all CAP studies, 14/17 (82%) telithromycin-treated patients with PRSP were considered cured. All three failures in patients with PRSP isolates occurred in patients with severe infection who were treated in the hospital setting.
- Patients with CAP and documented PRSP bacteremia had a cure rate of only 4/6 (66.7%).
- The efficacy of telithromycin in this indication must be weighed against its safety profile (see Safety section (section V))

## B. Acute Bacterial Exacerbation of Chronic Bronchitis

The applicant submitted two pivotal controlled studies of telithromycin for the treatment of patients with acute bacterial exacerbation of chronic bronchitis (AECB). The comparators were different for each study. **Table 11** summarizes the two clinical studies (3003 and 3007).

**Table 11. Acute Bacterial Exacerbation of Chronic Bronchitis: Pivotal Studies**

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	5 days	163	Argentina , Australia, Belgium, France, Germany, Ireland,  South Africa, United Kingdom
		Amoxicillin 500mg/ clavulanate 125mg 3x day	10 days	161	
3007**	Multicenter, double-blind, randomized, active-controlled, comparative, 2-arm parallel group	Telithromycin 800 mg qd	5 days	183	United States, Canada
		Cefuroxime axetil 500 mg 2x day	10 days	193	

\* 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.

### Clinical Efficacy

The primary efficacy variable was clinical cure, as assessed by the investigator at the post-therapy/TOC visit 5 to 10 days after the end of therapy. The protocol definition of AECB was as follows:

- Subjects with a documented history of chronic bronchitis, characterized by cough and excessive sputum production for >2 consecutive years and most days in a consecutive 3-month period.
- Subjects with FEV<sub>1</sub>/FVC <70% (lung function tests made in the previous 12 months)
- Subjects with a clinical diagnosis of AECB presumably due to bacterial infection based on the following clinical signs and symptoms of AECB: increased sputum volume and increased sputum purulence and increased cough, and/or dyspnea.

Clinical cure was defined as resolution of all infection-related signs and symptoms AND improved signs and symptoms without subsequent antibiotic therapy. **Table 12** summarizes the clinical efficacy data for Studies 3003 and 3007.

**Table 12. Clinical response rates for telithromycin versus comparators for the treatment of acute exacerbation of chronic bronchitis at the test-of-cure visit**

	Telithromycin 5-Days			Comparators 10-Days			2-sided 95% Confidence Interval
	N	n	%	N	n	%	
<b>PPc Population</b>							
Study 3003	115	99	86.1	AMC <sup>1</sup>	112	92	82.1 (-6.4%, 14.3%)
Study 3007	140	121	86.4	CXM <sup>1</sup>	142	118	(-5.7%, 12.4%)
<b>PPb Population</b>							
Study 3003	39	30	76.9	AMC	30	25	83.3 (-12.4%, 25.2%)
Study 3007	25	20	80.0	CXM	28	22	(-12.2%, 28.2%)
<b>mITT Population</b>							
Study 3003	160	130	81.3	AMC	160	125	(-6.3%, 12.6%)
Study 3007	182	142	78.0	CXM	191	138	(-9.5%, 10.1%)

<sup>1</sup>AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil

These studies demonstrate that telithromycin is equivalent to the comparators in the treatment of acute exacerbation of chronic bronchitis.

### Bacteriological Efficacy in AECB

Bacteriological efficacy was the secondary efficacy variable in this indication at posttherapy/TOC visit in the per protocol-bacteriologic population (PPb).

The success rate in study 3003 was 69.2% (27/39) for telithromycin, compared to 70.0% (21/30) for amoxicillin/clavulanate. The bacteriologic success rate in study 3007 was 80% (20/25) for telithromycin and 78.6% (22/28) for cefuroxime axetil. The bacteriologic efficacy of telithromycin varied between trials.

Bacteriologic eradication rates (eradicated and presumed eradication) for pretherapy/entry causative pathogens from the two AECB studies at posttherapy/TOC visit in PPb population are summarized in **Table 13**.

**Table 13. Pretherapy/entry Causative Pathogens (Mixed) Eradicated at Posttherapy/TOC in the PPb Population: Combined AECB Studies #3003 and #3007**

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

The bacteriologic efficacy rate for telithromycin is lower than that for comparator against *H. influenzae*. The bacteriological efficacy of telithromycin for the treatment of *S. pneumoniae* appears adequate. No conclusions regarding efficacy for the other pathogens listed can be made due to the small numbers reported.

**Acute Bacterial Exacerbation of Chronic Bronchitis Summary**

- The clinical efficacy data demonstrated equivalence between telithromycin 800 mg qd orally given for 5 days and its comparators given for 10 days in the treatment of acute bacterial exacerbation of chronic bronchitis.
- The bacteriologic efficacy of telithromycin against *H. influenzae* appears to be lower than that of the comparators.
- Patients in these studies had mild to moderate disease; thus, the potential benefit of telithromycin for this indication must be weighed against its risks. (See Safety section (section V)).

**C. Acute Sinusitis**

The applicant submitted three clinical studies, summarized in **Table 14**, in support of efficacy for telithromycin in the indication of acute bacterial sinusitis.

**Table 14. Acute Bacterial Sinusitis: Pivotal Studies**

Protocol	Study Type	Dose/Frequency/Duration	Patients Randomized	
Study 3002 <sup>1</sup>	Multicenter, randomized, double-blind, uncontrolled trial	Telithromycin 800 mg qd for 5 d	170	Austria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Sweden
		Telithromycin 800 mg qd for 10 d	171	
Study 3005	Multicenter, randomized, controlled, three-arm trial	Telithromycin 800 mg qd for 5 d	258	Argentina, Canada, Chile, S. Africa, US (US patients 64.3%)
		Telithromycin 800 mg qd for 10 d	270	
		Augmentin®500/125 mg tid for 10 d	262	
Study 3011 <sup>1,2</sup>	Multicenter, randomized, double-blind, controlled trial	Telithromycin 800 mg qd for 5 days	252	France, S. America, S. Africa, US (US patients 56.4%)
		Cefuroxime axetil 250 mg bid for 10 d	122	

<sup>1</sup>Studies were primarily intended to capture patients who had maxillary sinus punctures for bacteriologic studies.

<sup>2</sup> Submitted to the NDA as part of a major amendment on February 20, 2001. Additional case-report forms were submitted on March 05, 2001.

The clinical efficacy rates are displayed in **Table 15** for the mITT and PPc analysis. The Division of Scientific Investigations (FDA) inspected two sites to validate the data collected by the applicant. Due to data integrity issues, 37 patients were excluded from the data analyses in study 3005.

**Table 15. Cure rates for telithromycin versus comparators for the treatment of acute maxillary sinusitis at the test-of-cure visit**

	Telithromycin 5-Days			Comparators 10-Days			2-sided 95% Confidence Interval
	N	n	%	N	n	%	
<b>PPc Population</b>							
Study 3002 <sup>1</sup>	123	112	91.1	TEL 10-D <sup>2</sup>	133	121	91.0 (-7.7%, 7.9%)
Study 3005	146	110	75.3	AMC <sup>2</sup>	137	102	74.6 (-9.9%, 11.7%)
Study 3011	189	161	85.2	CXM <sup>2</sup>	89	73	82.0 (-7.1%, 13.4%)
<b>PPb Population</b>							
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%)
<b>mITT Population</b>							
Study 3002	167	138	82.6	TEL 10-D	168	147	87.5 (-13.1%, 3.3%)
Study 3005	201	132	65.7	AMC	202	132	65.3 (-9.5%, 10.1%)
Study 3011	240	193	80.4	CXM	116	84	72.4 (-2.2%, 18.2%)

<sup>1</sup>Study 3002 was a randomized, double blind study which compared two dosing regimens of KETEK (5 days vs. 10 days).

<sup>2</sup>TEL 10-D = telithromycin 10-Days, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil

The PPc analysis supports the efficacy of telithromycin for treatment of sinusitis. Studies 3002 and 3011 were intended to collect information regarding baseline isolates by performing maxillary sinus taps. Both studies had similar cure rates. Study 3005 was more difficult to analyze since it was mainly a clinical study and about 15% of patients enrolled had a history of allergic rhinitis. Therefore, the efficacy of telithromycin for the treatment of true bacterial sinusitis may not have been studied. However, this clinical study did demonstrate equivalence to the comparator.

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.

Bacteriologic efficacy rates are displayed in **Table 16**. This table includes selected pathogens of clinical importance in acute bacterial sinusitis. It includes patients who had single and mixed isolates. The number of specific isolates is small among the control groups when compared with telithromycin; however, the cure rates are similar to the overall cure rates observed in the clinical trails.

**Table 16. Bacteriologic Outcome (Cure) in subjects with pathogens of importance in AS – PPb population at posttherapy/TOC (single and mixed isolates)**

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

The applicant is requesting the indication of acute sinusitis due to *S. pneumoniae*, including penicillin- and erythromycin-resistant strains. The following table reviews the efficacy of telithromycin across the three studies in the PPb population.

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

**Penicillin**

Sensitive < 0.06 µg/ml  
Intermediate 0.12 ≤ MIC ≤ 1 µg/ml  
Resistant ≥ 2 µg/ml

**Erythromycin**

Sensitive ≤ 0.25 µg/ml  
Intermediate 0.25 < MIC < 1 µg/mL  
Resistant ≥ 1 µg/ml

**Table 17. Summary of Outcomes in AS 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
<b>3002</b>	<b>32/37 (86.5%)</b>	3/3 (100%)	<b>30/34 (88%)</b>	7/8 (87.5%)	<b>30/34 (88%)</b>	3/3 (100%)
<b>3005</b>	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
<b>3011</b>	10/12 (83%)	7/9 (77.8%)	9/11 (82%)	10/12 (83.3%)	9/11 (82%)	5/7 (71.4%)
<b>TOTAL</b>	44/51 (86.3%) <i>12 mixed*</i> (10/12, 83%)	11/13 (84.6%) <i>2 mixed</i> (2/2, 100%)	41/47 (87%) <i>12 mixed</i> 9/12 (75%)	18/21 (85.7%) <i>5 mixed</i> (5/5, 100%)	41/47 (87%) <i>11 mixed</i> (10/11, 91%)	9/11 (82%) <i>2 mixed</i> (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 3001, and all were considered cures.

**Acute Sinusitis Summary**

- The clinical efficacy of telithromycin across 3 pivotal studies ranged from 73% to 91%. Telithromycin was equivalent to comparator in the treatment of acute sinusitis.
- The number of telithromycin-treated patients with PRSP and macrolide-resistant infections was small.
- The patient population in these studies had mild to moderate sinus infection; thus, the benefit of telithromycin must be weighed against its risks (see Safety section (section V)).

#### D. Tonsillitis / Pharyngitis

Two clinical trials were conducted to demonstrate the bacteriological and clinical efficacy and assess the safety of 5 days of telithromycin in the treatment of group A  $\beta$ -hemolytic streptococcal (GABHS) pharyngitis/tonsillitis; these are summarized in **Table 18**. Study 3004 was a multicenter, double-blind study conducted at 62 foreign centers. Three hundred and ninety-eight subjects, aged 15 to 65 years, were enrolled and randomized to receive either telithromycin 800 mg orally once daily for 5 days, or penicillin VK, 500 mg orally three times daily for 10 days. Study 3008 was a multicenter, double-blind, comparative study conducted at 56 centers in the United States and Canada. Four hundred and sixty-three subjects, 13 years and older, were randomized to receive either telithromycin 800 mg orally once daily for 5 days or clarithromycin, 250 mg orally two times daily for 10 days. In general, the study design for the two trials was similar.

FDA regulatory guidance suggests:

- one statistically adequate and well-controlled multicenter trial to establish safety and effectiveness (i.e. similar or superior effectiveness to an approved product).
- any product with an absolute eradication rate at test of cure of < 85% should not be approved as a first-line therapy
- the primary effectiveness parameter should be microbiologic eradication; however, studies should establish the general correlation between clinical cure and bacterial eradication
- applications for treatment with dosing regimen durations less than generally approved for that infection should ordinarily contain 2 statistically adequate and well controlled clinical trials

**Table 18. Tonsillitis/Pharyngitis (T/P): Pivotal Studies**

Protocol	Study Design	Dose/Frequency/duration	Number of Patients randomized	Study Location
3008	Multicenter, double-blind, active-controlled, randomized (1:1) study	Telithromycin 800mg qd x 5 days	232	US and Canada
		Clarithromycin 250mg bid x 10 days	231	
3004*	Multicenter, double-blind, active-controlled, randomized (1:1) study	Telithromycin 800 mg qd x 5 days	198	Europe, South Africa, and New Zealand
		Pen VK 500 mg tid x 10 days	199	

\*Not conducted under a US IND.

Study evaluations were planned for 3 to 5 days after the initiation of therapy, at end of therapy (days 11 to 13), at the test of cure (TOC) (days 16 to 20), and late post-therapy (days 38 to 45).

The **primary efficacy endpoint** was defined as the bacteriological outcome at the TOC visit in the per protocol population. For the efficacy analysis, an extended window of days 16 to 23 for the test of cure visit was used; the results are summarized in the following table. The secondary endpoints were the clinical outcome at test of cure and the bacteriologic outcome at the late post therapy visit.

**Table 19. Bacteriologic outcome by subject at the test-of-cure visit – T/P**

	Telithromycin			Comparators			2-sided 95% Confidence Interval
	N	n	%	N	n	%	
<b>PP Population</b>							
Study 3004	115	97	84.3	PCN <sup>1</sup>	119	106	89.1 (-14.3%, 4.8%)
Study 3008	150	137	91.3	CLA <sup>1</sup>	135	119	(-4.6%, 11.0%)
<b>bmITT Population</b>							
Study 3004	138	110	79.7	PCN	150	119	(-9.0%, 9.7%)
Study 3008	187	152	81.3	CLA	173	134	(-5.1%, 12.8%)

<sup>1</sup> PCN = penicillin VK, CLA = clarithromycin

In study 3004, bacteriologic response in the telithromycin group was lower than in the penicillin group in the per protocol population; however, the results in the bmITT population were more consistent across treatment groups. Bacteriologic responses were similar between telithromycin and clarithromycin in study 3008.

The results of secondary sensitivity analyses are displayed in **Tables 20 and 21**.

**Table 20. Clinical outcome at the TOC visit – T/P**

	Telithromycin			Comparators			2-sided 95% Confidence Interval
	N	n	%	N	n	%	
<b>PP Population</b>							
Study 3004	115	109	94.8	PCN <sup>1</sup>	119	112	(-5.2%, 6.5%)
Study 3008	150	139	92.7	CLA <sup>1</sup>	135	123	(-5.5%, 8.6%)
<b>mITT Population</b>							
Study 3004	198	170	85.9	PCN	197	169	(-6.8%, 6.9%)
Study 3008	232	193	83.2	CLA	231	192	(-6.7%, 6.9%)

<sup>1</sup> PCN = penicillin VK, CLA = clarithromycin

**Table 21. Bacteriologic outcome by subject at the late post-therapy visit – T/P**

	Telithromycin			Comparators			2-sided 95% Confidence Interval
	N	n	%	N	n	%	
<b>PP Population</b>							
Study 3004	108	89	82.4	PCN <sup>1</sup>	111	94	(-13.0%, 8.5%)
Study 3008	136	112	82.4	CLA <sup>1</sup>	120	98	(-8.7%, 10.1%)
<b>bmITT Population</b>							
Study 3004	138	103	74.6	PCN	150	109	(-8.9%, 12.8%)
Study 3008	187	133	71.1	CLA	173	116	(-6.0%, 14.2%)

<sup>1</sup> PCN = penicillin VK, CLA = clarithromycin

Bacteriologic and clinical efficacy was assessed in patients with erythromycin-resistant strains of *S. pyogenes*.

**Table 22. Eradication rates at the test of cure visit in subjects with erythromycin-resistant strains of *S. pyogenes***

	Telithromycin			Comparators			
	N	n	%	N	n	%	
<b>PP Population</b>							
Study 3004	6	1	16.7	PCN	9	8	88.9
Study 3008	5	2	40	CLA	4	0	0

**Tonsillitis/Pharyngitis Summary**

- Equivalence was demonstrated between telithromycin 800 mg q day for 5 days and clarithromycin 250 mg q 12 hours for 10 days.
- Equivalence was demonstrated between telithromycin 800 mg once a day for 5 days and penicillin 500 mg tid for 10 days. However, the lower bound of the confidence interval in the per protocol population was -14.3%.
- When compared with clarithromycin, telithromycin had a lower bacteriologic eradication rate in patients with erythromycin-resistant *S. pyogenes*. This was also true for the comparison between penicillin and telithromycin. However, the numbers are small.
- Several patients, all in the telithromycin group, reported blurred vision of duration ranging from 1 to 10 days (see Safety section (section V) for further details).
- The potential benefit of telithromycin in this indication must be weighed against its risks (see Safety section (section V)).

**E. *Streptococcus pneumoniae*: resistance claims and FDA regulatory history**

The Anti-Infective Drug Products Advisory Committee has previously discussed several agents for which applicants have requested a marketing claim for treatment of community-acquired pneumonia (CAP) due to penicillin-resistant *S. pneumoniae* (PRSP). **Table 23** provides a brief summary of some of the data about these agents presented to the Committee for review. In these discussions and in prior Advisory Committee meetings on antimicrobial resistance in general, the Advisory Committee and the FDA have considered the following elements in discussions related to requests for an indication for PRSP in CAP:

- Strength of the evidence (human clinical studies, in vitro, and animal model data) in support of the proposed resistant pathogen claim
- Public health need and the impact of awarding such a resistant pathogen claim

- The clinical implications of such a claim
- Seriousness of disease for which the resistant pathogen indication is being sought
- The relationship of the mechanism of resistance for the resistant pathogen to the mechanism of action of the agent being considered (out-of-class vs. in-class)

In assessing the data in support of a specific claim for PRSP, the Committee’s discussions have considered:

- data supporting efficacy in the treatment of CAP:
  - due to *S. pneumoniae* in general
  - due to PRSP
- data supporting efficacy in the treatment of CAP with concurrent bacteremia:
  - due to sensitive strains of *S. pneumoniae*
  - due to PRSP
- Severity of illness in the cases presented

**Table 23. Penicillin-Resistant *S. pneumoniae* CAP Claims Requested for Selected Antimicrobials**

Drug	Requested	Approved Label	Highlights of Evidence
<b>Avelox</b>	due to <i>S. pneumoniae</i> (including PSSP, PISP, and PRSP)	mild to moderate CAP due to <i>S. pneumoniae</i>	Clinical success rates for patients with CAP due to : <ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i> 80/89 (90%).</li> <li>• <i>S. pneumoniae</i> with bacteremia treated with Avelox 7/10 (70%) vs. 11/11 (100%) for amoxicillin (1000 mg tid)</li> <li>• PRSP - Avelox-treated 4/6 (67%) vs. 3/3 (100%) for amoxicillin-treated patients (Study 0140)</li> <li>• PRSP for Avelox-treated patients from all studies combined 6/8 (75%)</li> </ul>
<b>Levaquin</b>	due to <i>S. pneumoniae</i> (including PISP, PRSP,	CAP due to <i>S. pneumoniae</i> (including PRSP)	Clinical success rates for patients with CAP due to: <ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i> across studies were 245/250 (98%)</li> <li>• PRSP 15/15 (100%) achieved clinical success.</li> <li>• 6 of these 15 patients were bacteremic and 5 had disease classified as severe.</li> </ul>
<b>Zyvox</b>	due to <i>S. pneumoniae</i> (PRSP and PSSP)	CAP due to <i>S. pneumoniae</i> (PSSP only)	Clinical success rates for patients with CAP due to: <ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i> 63/73 (86%),</li> <li>• <i>S. pneumoniae</i> bacteremia 27/30 (90%)</li> <li>• PRSP = 3/5</li> </ul>
<b>Ketek</b>	due to <i>S. pneumoniae</i> (including PRSP and, ERSP)	-----	Clinical success rates for patients with CAP due to: <ul style="list-style-type: none"> <li>• <i>S. pneumoniae</i> 166/174 (95.4%) :</li> <li>• <i>S. pneumoniae</i>: PSSP 125/128 (97.6) vs. PRSP 14/17 (82%)</li> <li>• <i>S. pneumoniae</i> bacteremia: PSSP 27/29 (93%) vs. PRSP 4/6 (66.7%)</li> </ul>

The Committee also discussed the implication of an out-of-class resistance claim. Data on the epidemiology of drug-resistant *Streptococcus pneumoniae* (DRSP) was also presented for the Advisory Committee's consideration.

The applicant is also requesting an indication for erythromycin-resistant *Streptococcus pneumoniae*. This is an indication that has not been previously awarded, or formally discussed in relation to a specific product before the Committee. We seek the Advisory Committee's comments with regards to this proposed second category of resistant pathogen claim within the realm of drug-resistant *Streptococcus pneumoniae* (DRSP). Is there a clinical need for such a claim at the present time? Would such a claim assist the practitioner in the treatment of patients? What is the likelihood of clinical success of telithromycin, given the presence of *in vitro* erythromycin resistance? If it is the opinion of the Committee that such a claim merits consideration as a second claim within the realm of DRSP, then the Committee's impression regarding the amount and type of clinical data needed to support the clinical efficacy in the face of *in vitro* resistance would be helpful.

## V. Safety Analysis

### A. Overview of FDA Integrated Summary of Safety Review

#### 1. Extent of Exposure

The safety database for NDA 21-144 comprises data from 4937 patients (3265 telithromycin and 1672 comparator) who received at least one dose of study drug and who had post-baseline safety information; an additional 48 patients (25 telithromycin, 23 comparator) were excluded from the database because of lack of follow-up information. In the telithromycin group, 1429 patients received 5 days of treatment and 1836 received 7-10 days of drug. For the controlled trials within the database, there were 2045 telithromycin-treated patients and 1672 comparator-treated patients. Demographics for patients in controlled and uncontrolled may be found in the applicant's briefing package.

#### 2. Deaths

There were 11 deaths in phase 3 trials (7 telithromycin and 4 comparator). Ten deaths occurred in studies of community-acquired pneumonia (CAP); one (in a patient with acute lymphoid leukemia receiving penicillin) occurred in a study of tonsillopharyngitis. The adverse event leading to death occurred on treatment for 5/7 telithromycin patients and 3/4 comparator-treated patients. First-listed causes of death in the telithromycin group included multi-organ failure, heart failure, leptospirosis, Gram-negative septicemia, aspiration, acute myocardial infarction, and pneumonia. First-listed causes of death in the comparator group included asthma, lung carcinoma, pneumonia, and acute lymphoid leukemia. None of the deaths were assessed as being related to study drug.

Patients may have had multiple causes of death listed in addition to the first-listed cause. For telithromycin-treated patients, 6/7 deaths had a primary or secondary cardiovascular cause listed. None of the deaths in comparator-treated patients had a cardiovascular cause listed. Details of deaths related to cardiovascular causes may be found in the Cardiovascular section of this briefing document.

#### 3. Nonfatal serious adverse events

In controlled phase 3 trials, 40/2045 (2.0%) of telithromycin-treated patients had nonfatal serious adverse events (SAEs), while 41/1672 (2.5%) of comparator-treated patients had nonfatal SAEs. Eight telithromycin-treated patients and 4 comparator-treated patients had nonfatal SAEs possibly related to study drug. **Table 24** shows possibly related nonfatal SAEs in phase 3 trials.

**Table 24 .** Nonfatal SAEs possibly related to study drug in phase 3 controlled trials.

	<b>Telithromycin</b>	<b>Comparators</b>
Any SAE	8 (0.4%)	4 (0.2%)
Allergic reaction	2 (0.1%)	1 (0.1%)
Liver damage	2 (0.1%)	0 (0.0%)
Gastroenteritis	1 (<0.1%)	0 (0.0%)
Pseudomembranous colitis	1 (<0.1%)	1 (0.1%)
Erythema multiforme	1 (<0.1%)	0 (0.0%)
Vomiting	1 (<0.1%)	0 (0.0%)
Dyspnea	0 (0.0%)	1 (0.1%)
Gastrointestinal disorder	0 (0.0%)	1 (0.1%)

In uncontrolled trials, 40/1220 (3.3%) of telithromycin-treated patients had a nonfatal SAE. Four (0.3%) of these were possibly related to telithromycin: gastroenteritis, vasculitis, hepatitis, and leukopenia.

A discussion of serious cardiovascular and hepatic SAEs may be found in the Cardiovascular and Hepatic safety sections of this briefing document.

**Adverse events**

**Table 25** shows the most common treatment-emergent adverse events (TEAEs) in phase 3 controlled trials.

**Table 25.** Incidence of TEAEs by decreasing frequency in phase 3 controlled trials

	<b>Telithromycin (n=2045)</b>	<b>Comparators (n=1672)</b>
Diarrhea	295 (14.4%)	167 (10.0%)
Nausea	184 (9.0%)	73 (4.4%)
Headache	118 (5.8%)	118 (7.1%)
Dizziness	91 (4.4%)	48 (2.9%)
Vomiting	67 (3.3%)	40 (2.4%)
Abnormal LFTs	32 (1.6%)	25 (1.5%)
Dyspepsia	50 (2.4%)	30 (1.8%)
Abdominal pain	40 (2.0%)	26 (1.6%)

Other TEAEs of note in controlled trials included taste perversion (telithromycin 1.8%, comparators 2.2%), gastrointestinal pain (telithromycin 1.5%, comparators 0.8%), flatulence (telithromycin 1.7%, comparators 0.8%) and blurred vision (telithromycin 0.7%, comparators 0.1%).

Because of the difference in incidence of blurred vision between telithromycin- and comparator-treated patients, visual-related adverse events were examined in more detail. In controlled and uncontrolled phase 3 trials, visual-related adverse events occurred in 29 subjects (telithromycin: 26 (0.7%), comparators: 3 (0.2%)). The numbers and incidences of adverse events were: blurred vision (telithromycin: 15 (0.5%), comparators: 1 (0.1%)); abnormal vision (telithromycin: 10 (0.3%), comparators: 2 (0.1%)); and abnormal accommodation (telithromycin: 1 (<0.1%), comparators: 0). Blurred vision possibly related to study drug occurred in 11 (0.3%) telithromycin-treated patients and 0 comparator-treated patients.

As shown in **Table 26**, blurred vision occurred in telithromycin-treated subjects on all dose regimens for telithromycin (5 days: 9; 7-10 days: 3; and 10 days: 3). Cases were reported for three indications (community-acquired pneumonia (4), sinusitis (4), and tonsillitis/pharyngitis (7)). These events predominantly in females (females: 11, males 4). Subjects treated with telithromycin who experienced blurred vision had a mean age of 30 years (range: 19-45 years). There were no blurred vision adverse events among patients treated with clarithromycin.

**Table 26. Subjects with adverse event of blurred vision in phase III clinical trials.**

Indication	Treatment	Age	Sex
<b>Acute Sinusitis</b>	Telithromycin 10 d	29	F
	Telithromycin 10 d	45	F
	Telithromycin 5 d	22	M
	Telithromycin 5 d	25	F
<b>Tonsillitis/Pharyngitis</b>	Telithromycin 5 d	30	F
	Telithromycin 5 d	31	F
	Telithromycin 5 d	22	F
	Telithromycin 5 d	26	F
	Telithromycin 5 d	19	F
	Telithromycin 5 d	36	F
	Telithromycin 5 d	34	M
<b>Community Acquired Pneumonia</b>	Telithromycin 7-10 d	42	M
	Telithromycin 10 d	28	M
	Telithromycin 7-10 d	33	F
	Telithromycin 7-10 d	36	F
<b>Acute Bacterial Exacerbation of Chronic Bronchitis</b>	Amoxicillin/clavulanic <sup>2</sup>	47	F

<sup>1</sup>telithromycin 800 mg, <sup>2</sup>amoxicillin 500mg/clavulanate 125 mg

Telithromycin is metabolized by cytochrome CYP3A4; phase I data shows that the C<sub>max</sub> and AUC for telithromycin are markedly increased when it is co-administered with a CYP3A4 inhibitor (see the Cardiovascular safety section (section V.B), p. 39). It was therefore of interest whether intake of 3A4 inhibitors affected the incidence of adverse events in telithromycin-treated patients. **Table 27** shows the most common TEAEs in controlled trials according to whether or not patients received a concomitant medication that inhibited CYP3A4. For a number of these TEAEs, the absolute incidence was increased in telithromycin-treated patients who received a concomitant 3A4 inhibitor, compared to telithromycin-treated patients who did not receive an inhibitor. In addition, the incidence of these TEAEs was increased in telithromycin-treated patients who received an inhibitor relative to comparator-treated patients who received an inhibitor.

The analysis in Table 27 should be regarded as exploratory and interpreted cautiously, since patients were not randomized on the basis of CYP3A4 inhibitor intake.

**Table 27. Incidence of TEAEs in controlled trials by intake of 3A4 inhibitors**

	Received 3A4 inhibitor		Did not receive 3A4 inhibitor	
	Telithromycin (n=207)	Comparators (n=164)	Telithromycin (n=1838)	Comparators (n=1508)
Diarrhea	34 (16.4%)	9 (5.5%)	261 (14.2%)	158 (10.5%)
Nausea	21 (10.1%)	5 (3.0%)	163 (8.9%)	68 (4.5%)
Headache	12 (5.8%)	12 (7.3%)	106 (5.8%)	106 (7.0%)
Dizziness	13 (6.3%)	6 (3.7%)	78 (4.2%)	42 (2.8%)
Vomiting	14 (6.8%)	6 (3.7%)	53 (2.9%)	34 (2.3%)
Abnormal LFTs	3 (1.4%)	0 (0.0%)	29 (1.6%)	25 (1.7%)
Abdominal pain	6 (2.9%)	5 (3.0%)	34 (1.8%)	21 (1.4%)
Dyspepsia	10 (4.8%)	2 (1.2%)	40 (2.2%)	28 (1.9%)

Discussions of cardiovascular and hepatic AEs may be found in the Safety section (section V) of this briefing document.

#### 4. Discontinuations

In phase 3 controlled trials, discontinuations due to adverse events occurred in 98/2045 (4.8%) of telithromycin-treated patients and 73/1672 (4.4%) of comparator-treated patients. **Table 28** shows the most common reasons for discontinuation in controlled trials.

**Table 28. Incidence of study drug discontinuation for specific AEs in phase 3 controlled trials**

	Telithromycin (n=2045)	Comparators (n=1672)
Any	98 (4.8%)	73 (4.4%)
Diarrhea	20 (1.0%)	13 (0.8%)
Vomiting	19 (0.9%)	9 (0.5%)
Nausea	18 (0.9%)	10 (0.6%)
Abnormal LFTs	5 (0.2%)	5 (0.3%)
Gastroenteritis	3 (0.1%)	2 (0.1%)
Gastrointestinal pain	2 (0.1%)	2 (0.1%)
Dyspepsia	2 (0.1%)	1 (0.1%)
Allergic reaction	5 (0.2%)	2 (0.1%)
Abdominal pain	5 (0.2%)	3 (0.2%)
Dizziness	5 (0.2%)	1 (0.1%)
Abnormal vision	2 (0.1%)	0 (0.0%)
Blurred vision	1 (<0.1%)	0 (0.0%)
Prolonged QT interval	1 (<0.1%)	1 (0.1%)

In uncontrolled trials, discontinuations due to adverse events occurred in 31/1220 (2.5%) of telithromycin-treated patients. **Table 29** shows the most common reasons for discontinuation in uncontrolled trials.

**Table 29. Incidence of study drug discontinuation for specific AEs in phase 3 uncontrolled trials**

	<b>Telithromycin (n=1220)</b>
Any	31 (2.5%)
Diarrhea	3 (0.2%)
Vomiting	3 (0.2%)
Abnormal LFTs	2 (0.2%)
Gastrointestinal pain	2 (0.2%)
Infection	2 (0.2%)
Pleural effusion	2 (0.2%)
Allergic reaction	1 (0.1%)
Nausea	1 (0.1%)
Dyspepsia	1 (0.1%)

## B. Cardiovascular Safety

### 1. *In vitro* and preclinical data

*In vitro*, telithromycin blocks repolarization of myocardial cells, in part by inhibiting the rapid component of the delayed rectifying current (IK<sub>r</sub>), with an inhibition constant similar to that of a number of quinolones and macrolides. Consistent with its ability to induce IK<sub>r</sub> blockade, telithromycin also increases action potential duration in isolated rabbit Purkinje fibers (**Table 30**).

**Table 30. Percentage increase in action potential duration of rabbit Purkinje fibers, stimulated at 60 pulses per minute, induced by telithromycin and comparator macrolides**

Test agent		% increase in APD at (μM)						
		0.1	0.3	1	3	10	30	100
Telithromycin	APD <sub>50</sub>	-3.1	2.3	11.4	21.3	33.7	73.7	164.0
	APD <sub>90</sub>	0.1	3.2	7.0	13.9	24.5	60.3	148.7
Clarithromycin	APC <sub>50</sub>	-	-	-	13.4	30.4	49.5	72.6
	APD <sub>90</sub>	-	-	-	6.1	15.7	31.8	58.4
Erythromycin	APD <sub>50</sub>	-	-	-	3.5	9.8	24.2	58.5
	APD <sub>90</sub>	-	-	-	3.1	9.0	21.9	57.5
Roxithromycin	APD <sub>50</sub>	-	-	-	3.8	10.0	16.2	30.8
	APD <sub>90</sub>	-	-	-	3.0	9.1	22.4	39.5

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<sub>max</sub> (~2 mg/L), it should be kept in mind that there is substantial variability in telithromycin pharmacokinetics, with a maximal C<sub>max</sub> in phase I studies of 9.9 mg/L (see below under Pharmacokinetic Variability in Special Populations, section V.B.5). In addition, rat studies have demonstrated myocardial telithromycin concentrations up to 7.7 times those in plasma. Because tissue concentrations are 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<sub>c</sub> (QT interval corrected by Bazett's formula<sup>1</sup>) by 30 msec, within 1 minute after administration, as well as an increase in heart rate. Normally, heart rate and QT interval are inversely related; thus, the observed changes cannot be explained by tachycardia. Clarithromycin increased QT 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).

## 2. Phase I data QT<sub>c</sub> prolongation and pharmacokinetics in normal subjects

### a) Dose-response relationship

Two studies (1030 and 1046) demonstrated that telithromycin and placebo treatments are associated with significantly different maximal changes in QT<sub>c</sub>. These studies also demonstrated that the time at which the maximal change in QT<sub>c</sub> occurred in telithromycin-treated patients may have been after maximal serum concentrations were reached.

#### **Study 1030:**

This phase I study was designed to study changes in QT<sub>c</sub> intervals in telithromycin-treated subjects. Four treatment groups were included in this study:

**Group A:** A four-period, double-blind, randomized, placebo-controlled treatment group. 8 healthy young subjects received a single oral dose of telithromycin. Each subject received 3 incremental single doses of telithromycin (1600, 2000, 2400 mg) and 1 placebo dose. During each period, 6 subjects received active treatment (at one or more dose strengths) and 2 subjects received placebo.

**Group B:** A double-blind, parallel, randomized, placebo-controlled treatment group. 8 healthy young subjects received telithromycin (1600 mg) once a day for 5 days. Each subject was randomly allocated to 1 of 2 treatments (telithromycin: 6 subjects or placebo: 2 subjects).

**Group C:** Identical design to group A, except that 8 elderly (aged 60 years to 85 years) male and postmenopausal female subjects were enrolled. Each subject received 3 incremental single doses of telithromycin (1200, 1600, 2000 mg).

**Group D:** Identical design to group B, except that 8 elderly (aged 60 years to 85 years) male and postmenopausal female subjects were enrolled. Subjects received placebo or 1200 mg telithromycin once a day for 5 days.

Resting EKGs and blood samples for pharmacokinetic measurements were obtained at various timepoints after telithromycin or placebo dosing. For groups A and C, mean  $\Delta$ QT<sub>c</sub> and  $\Delta$ QT<sub>f</sub> (QT interval by corrected Fridericia's formula<sup>2</sup>) values were calculated at each sample collection time. The maximal means are shown in **Table 31**. The maximum mean  $\Delta$ QT<sub>c</sub> occurred at 1.5 hours in young subjects after single telithromycin doses of 1600 mg, 2000 mg and 2400 mg, with values of 20 ms, 18 ms and

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<sup>1</sup>  $QT_c = QT / (RR \text{ interval})^{1/2}$

<sup>2</sup>  $QT_f = QT / (RR \text{ interval})^{1/3}$

28 ms, respectively. The corresponding  $\Delta QT_c$  after placebo was 4 ms. The differences between treatments and placebo were statistically significant. In elderly subjects, the mean maximum  $\Delta QT_c$  occurred at 4 hours after single doses of 1200 mg, 1600 mg and 2000 mg, with values of 12 ms, 18 ms and 19 ms, respectively. The corresponding  $\Delta QT_c$  after placebo was -3 ms. The differences between treatments and placebo were statistically significant.

In the multiple dose groups (B and D), when telithromycin was compared with placebo, no statistically significant difference in  $\Delta QT_c$  between telithromycin and placebo was found after repeated doses of 1600 mg in young subjects or 1200 mg in elderly subjects. However, it should be noted that in these groups, the placebo and treatment arms were parallel instead of crossed over. Because of normal inter-individual variability in  $QT_c$ , a design using control subjects different than those exposed to test drug may have decreased power to detect a difference in  $QT_c$  intervals.

**Table 31. Mean ( $\pm$ SD) maximum changes in  $QT_c$ ,  $QT_f$  and heart rate after telithromycin treatment.**

	Treatment A				Treatment B	
	Placebo	1600 mg	2000 mg	2400 mg	Placebo	1600 mg
Number of subjects	8	8	8	7	2	6
Mean maximum $\Delta QT_c^a$	4 (18)	20 (14)	18 (10)	28 (19)	0 (1)	17 (17)
Mean maximum $\Delta QT_f^a$	3 (14)	10 (11)	7 (8)	15 (11)	-1 (2)	5 (12)
Mean heart rate increase	0 (7)	9 (5)	10 (7)	13 (7)	1 (4)	11 (5)
Parameters	Treatment C				Treatment D	
	Placebo	1200 mg	1600 mg	2000 mg	Placebo	1200 mg
Number of subjects	8	8	8	8	2	6
Mean maximum $\Delta QT_c^b$	-3 (8)	12 (15)	18 (17)	19 (11)	-6 (9)	4 (14)
Mean maximum $\Delta QT_f^b$	3 (5)	13 (11)	12 (15)	12 (7)	-6 (7)	-5 (13)
Mean heart rate increase	-5 (4)	-2 (6)	5 (4)	7 (4)	1 (1)	9 (6)

<sup>a</sup> The mean average  $QT_c$ ,  $QT_f$ , and heart rate (HR) were calculated for each time point at which observations were obtained. The maximum  $QT_c$  and  $QT_f$  were observed at 1.5 hours after a single dose in treatment A. The maximum  $QT_c$  and  $QT_f$  were observed at 1.5 hours after the last dose on day 5 for treatment B.

<sup>b</sup> The maximum  $QT_c$  and  $QT_f$  were observed at 4 hours after a single dose in treatment C. The maximum  $QT_c$  and  $QT_f$  were observed at 1.5 hours after the last dose on day 5 for treatment D.

Of note, in treatment group C, the maximum serum telithromycin concentration was observed at 2 hours after dosing for all doses, while the maximum  $QT_c$  was observed at 4 hours after dosing.

### **Study 1046**

This was a double-blind, randomized, placebo-controlled, 3-period cross-over study, with 2 escalating single oral doses of telithromycin (2400 mg and 3200 mg) and an interspersed single placebo dose. Twenty-four healthy young subjects (12 men and 12 women, mean age  $29 \pm 7$  years) were studied. Resting EKGs and blood samples for pharmacokinetic measurements were obtained at various timepoints after telithromycin or placebo dosing.

Changes in  $\Delta QT_c$  and  $\Delta QT_f$  were calculated at each sample collection time. The maximal mean telithromycin concentration was observed at 4 hours (range, 1-6 h) after dosing with 2400 mg telithromycin and at 3 h (range 1.5-6 h) after dosing with 3200 mg telithromycin.

The maximal mean  $\Delta QT_c$  occurred at 4 hours with the values of 17 ms and 17 ms, respectively, after telithromycin 2400 mg and 3200 mg. The corresponding  $\Delta QT_c$  for placebo was -7 ms. There was a statistically significant difference between both of the telithromycin doses (2400 mg and 3200 mg) and placebo. However, no statistically significant difference was found in  $\Delta QT_f$  between placebo and treatment groups (2400 mg telithromycin and 3200 mg telithromycin), possibly because of the small sample size. It should be noted that the mean telithromycin  $C_{max}$  was about 3.72 mg/L after oral administration of 2400 mg telithromycin, which was lower than the mean telithromycin  $C_{max}$  of 5.98 mg/L obtained in Study 1030. The mean telithromycin  $C_{max}$  was only 4.41 mg/L after a 3200 mg oral dose. Therefore, although a higher dose (3200 mg) was studied, the observed  $C_{max}$  values were not as high as expected.

### **b) Population concentration response**

Data from 7 phase 1 studies (Study 1030, 1031, 1032, 1037, 1041, 1045, 1046) were pooled to explore the potential relationship between  $\Delta QT_c$ ,  $\Delta QT_f$ , and telithromycin concentration. Both  $\Delta QT_c$  and  $\Delta QT_f$  showed statistically significant correlations with telithromycin concentration (**Figures 1 and 2**). Similar results were obtained using a naïve pooled method and a linear mixed effects method.

### **3. $QT_c$ prolongation and pharmacokinetics in patients with cardiac disease**

#### **Study 1049**

This dose-escalation study was conducted in 24 subjects with underlying cardiac disease to assess the effects of telithromycin on  $QT_c$  in high-risk patients. It was a double-blind, randomized, placebo-controlled, 4-way crossover study. During 4 different study periods, subjects received telithromycin 800 mg or telithromycin 1600 mg as single oral doses, clarithromycin 500 mg twice daily for one day, or placebo as a single dose treatment.

The mean  $\Delta QT_c$  was calculated at each time point when EKGs were recorded. The mean maximal serum telithromycin concentration was observed at 1.5 hours after dosing with 800 mg telithromycin and 2 hours after dosing with 1600 mg telithromycin. The maximal mean  $\Delta QT_c$  occurred at 4 hours, with values of 2, 5, 7, and 12 ms after placebo, 800 mg telithromycin, 500mg clarithromycin and 1600 mg telithromycin, respectively. No statistically significant difference in  $\Delta QT_c$  was found between placebo and 800 mg HMR or 500 mg clarithromycin, but a statistically significant difference was found in  $\Delta QT_c$  between placebo and 1600 mg telithromycin. However, significant time and time by treatment interaction were found for  $\Delta QT_c$ , indicating comparisons should be made between treatments at each time.  $\Delta QT_c$  at 2 hours after dosing with 800 mg telithromycin and 1600 mg was statistically significantly different from placebo; respective changes from baseline for these doses were 8.91 and 17.15 msec greater than changes for placebo. For 1600 mg, there were also statistically significant differences at

timepoints ranging from 1.5 to 8 hours after dosing. There were no statistically significant differences for 800 mg at other time points. The applicant did not conduct regression analyses of  $QT_f$  and telithromycin concentrations. The correlations between  $\Delta QT_c$  and telithromycin or clarithromycin concentrations are shown in **Figures 3 and 4**.  $\Delta QT_c$  was correlated with telithromycin and clarithromycin concentrations.

It is important to note that this was a single-dose study employing a relatively small sample, using subjects without active infection. Multiple doses may lead to a greater effect on  $QT_c$  because of accumulation (see below under Pharmacokinetic Variability in Special Populations).

#### 4. $QT_c$ prolongation in drug-interaction studies (Study 1041 - cisapride)

Because of the well-described association of cisapride with QT prolongation, the applicant conducted Study 1041 to explore the potential for pharmacokinetic drug-drug interactions between cisapride and telithromycin. This study was a single blind with respect to telithromycin only, randomized, complete two-period crossover design. The study consisted of two parts and four treatments.

Part I: Treatment A: once daily oral doses of placebo for 7 days followed by a single 20 mg (2 x 10 mg) dose of cisapride on day 7.

Treatment B: placebo on day 1, once daily oral doses of 800 mg telithromycin (2 x 400 mg) on days 2 through 7, and cisapride 20 mg (2 x 10 mg) on day 7.

Part II: Treatment C: once daily oral doses of placebo on days 1 through 6 and cisapride 10 mg (1x10 mg) three times daily (total of 13 doses) on days 2 through 6.

Treatment D: placebo on day 1, then 800 mg telithromycin (2 x 400 mg) once daily on days 2 through 6 concurrently with 10 mg (1 x 10 mg) cisapride three times daily on days 2 through 6 (total of 13 doses).

In addition to pharmacokinetic assessment, this study design also allowed for comparison of  $QT_c$  prolongation between placebo, 20 mg cisapride, 800 mg telithromycin and 20 mg cisapride coadministered with 800 mg telithromycin. The results showed that telithromycin increased cisapride AUC and  $C_{max}$  by 150% and 95.2%, respectively. Further, it appears that the QT prolongation effect of telithromycin is similar to the effect of cisapride (**Figures 5 and 6**).

#### 5. Pharmacokinetic variability in special populations

Since the regression analyses shown below demonstrate that  $\Delta QT_c$  and  $\Delta QT_f$  are associated with plasma telithromycin concentration, it is important to understand the variability of telithromycin pharmacokinetics and factors affecting telithromycin concentrations.

1. The mean  $C_{max}$  was 1.99 mg/L after a single oral dose of 800 mg telithromycin (n=232 from 11 phase 1 studies (Study 1003, 1006, 1004, 1044, 1008, 1009, 1005, 1015, 1016, 1031, 1014)). The largest  $C_{max}$  was 5.13 mg/L. The accumulation factor after multiple doses was about 1.5.

2. In Phase 3 studies, telithromycin concentrations as high as 7.6 mg/L (Study 1051) and 9.9 mg/L (Study 1052) were observed.
3. The results from study 1005 showed that  $C_{max}$  and AUC increased approximately 2-fold in elderly patients when compared to young subjects after multiple doses of 800 mg telithromycin.
4. It was shown in study 1015 that  $C_{max}$  and AUC were similar between healthy subjects and hepatic impaired patients after a single oral dose of 800 mg telithromycin. However,  $t_{1/2}$  was significantly increased from about 10 hours to 14 hours in hepatic impaired patients, indicating potential accumulation after multiple doses. This study also showed that renal function was increased and appeared to compensate for impaired hepatic function so observed  $C_{max}$  and AUC values were similar to the values in healthy subjects. Potential accumulation of telithromycin could be problematic for hepatic impaired patients with decreased renal function.

### 6. Potential for drug interactions with 3A4 inhibitors

Telithromycin is a CYP 3A substrate. The potential for drug-drug interactions with a CYP3A inhibitor, ketoconazole, was studied by the applicant in study 1045. The results showed that ketoconazole increased the mean  $C_{max}$  and AUC of telithromycin after multiple doses by 52% and 95%, respectively. Ketoconazole increased telithromycin concentrations and telithromycin-associated  $QT_c$  prolongation (Table 32).

**Table 32. Maximum  $QT_c$  after once daily oral dosing with 800 mg telithromycin alone, 400 mg ketoconazole alone, 800 mg telithromycin concomitantly with 400 mg ketoconazole, or placebo**

Parameter	Treatment	Mean	N	Comparison	Estimated Difference	(90% CI) around the difference	P-value
Maximum $QT_c$ (msec)	A	410.4	11	A-D	3.344	(-2.3, 9.00)	0.322
	B	413.4	14	B-D	6.388	(0.92, 11.9)	0.057
	C	417.5	11	C-D	10.493	(4.80, 16.2)	0.004
				C-A	7.149	(1.42, 12.9)	0.043
				C-B	4.105	(-1.5, 9.67)	0.220
	D	407.0	12				

A = Telithromycin 800 mg once daily for 5 days

B = Ketoconazole 400 mg once daily for 7 days

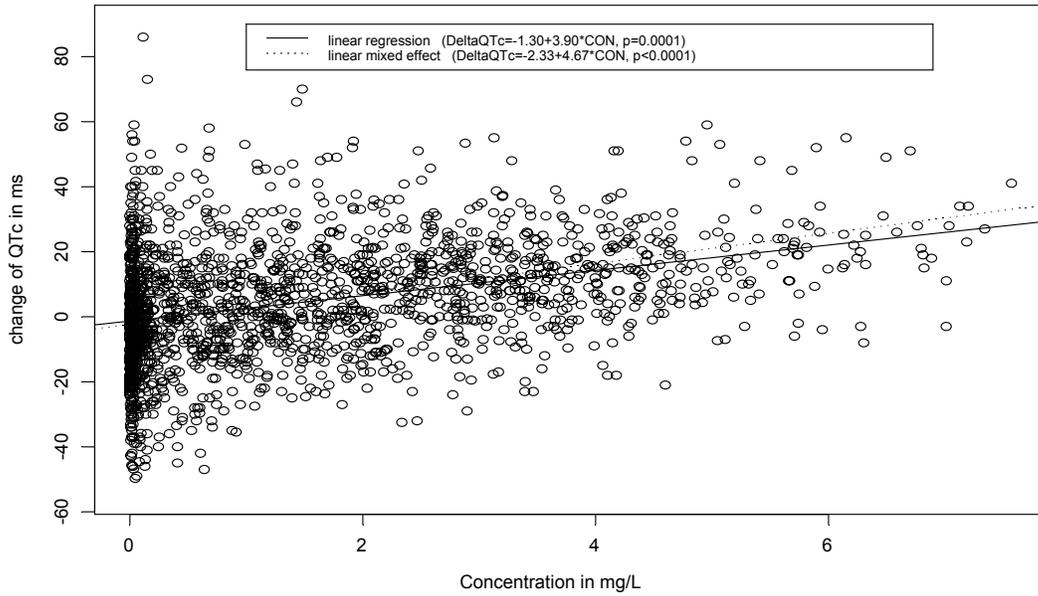
C = Telithromycin 800 mg once daily for 5 days and ketoconazole 400 mg once daily for 7 days

D = Placebo

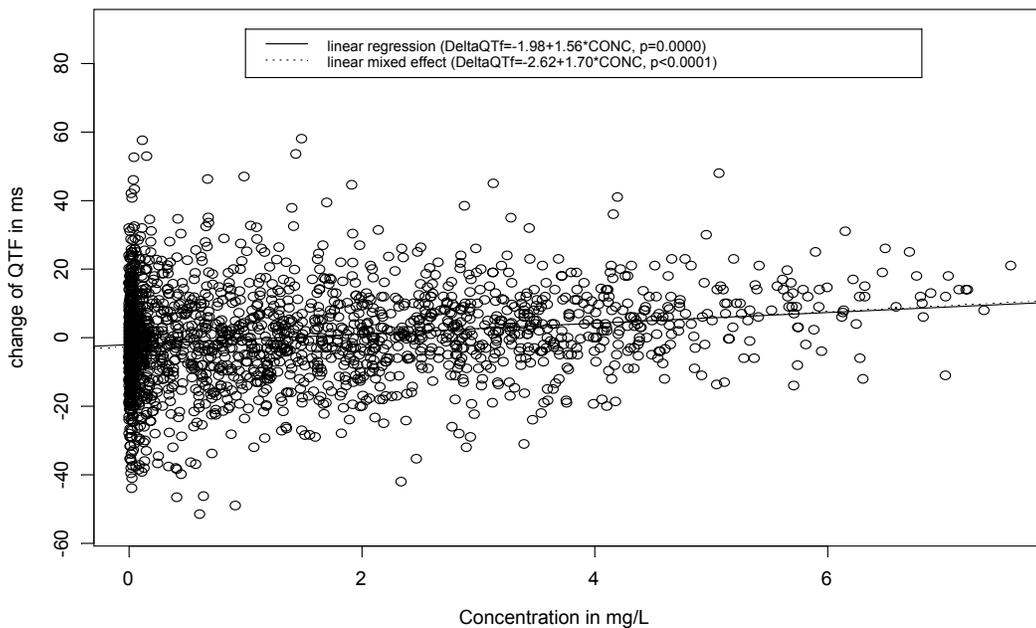
### 7. Summary: Pharmacokinetics

Phase 1 studies showed that telithromycin is associated with concentration-dependent  $QT_c$  prolongation. In some studies, there was a lag between the time of maximal serum telithromycin concentration and the time of the maximal effect on  $QT_c$ . Telithromycin concentrations are affected by several factors such as age, hepatic function, and coadministration of CYP 3A inhibitors. Observed telithromycin concentrations were variable. The maximal concentration observed in Phase 3 studies was 9.9 mg/L.

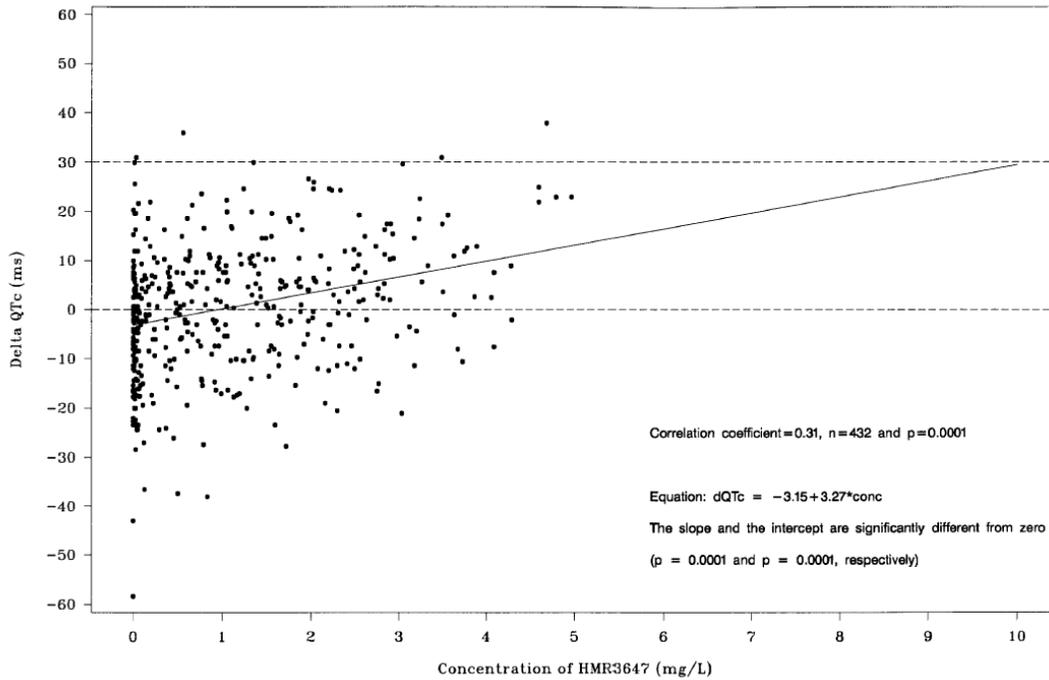
**Figure 1. Regression analysis of  $\Delta QT_c$  vs. concentration by linear and linear mixed effect models (Data are from 7 phase 1 studies)**



**Figure 2. Regression analysis of  $\Delta QT_f$  vs. concentration by linear and linear mixed effect models (Data are from 7 phase 1 studies)**



**Figure 3. Correlation between plasma concentration and  $\Delta QT_c$  when 800 mg and 1600 mg telithromycin were administered as a single doses**



**Figure 4. Correlation between clarithromycin concentration and  $\Delta QT_c$  after 500 mg bid administration for 1 day**

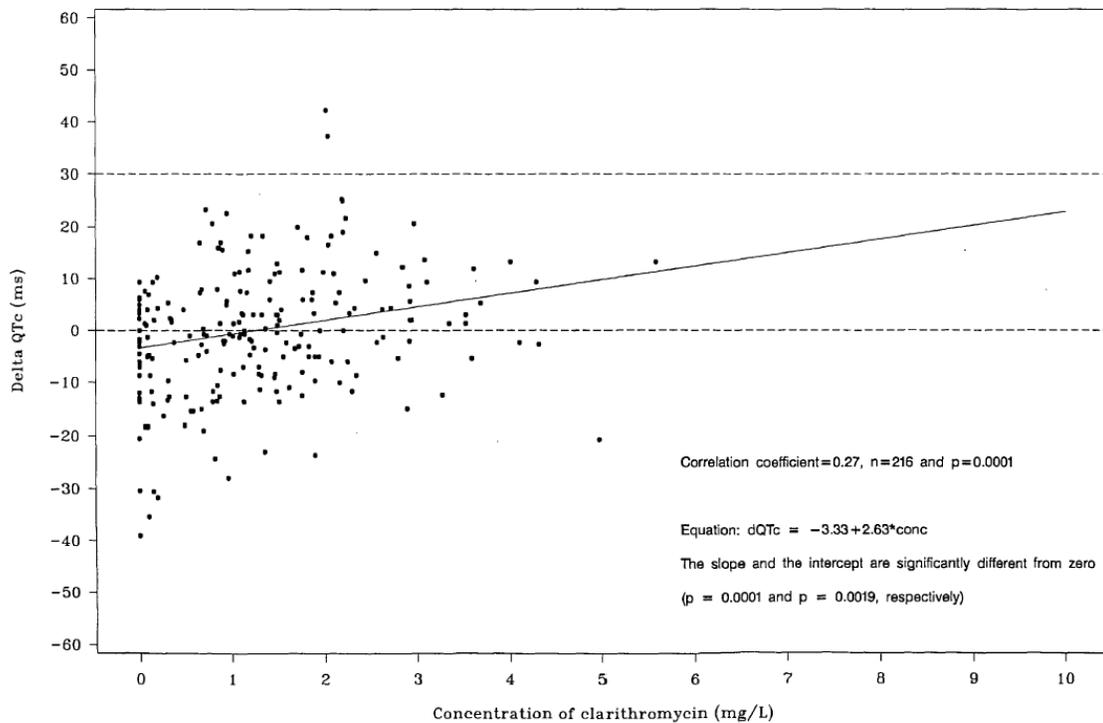


Figure 5.  $\Delta QT_c$  vs. time after dosing

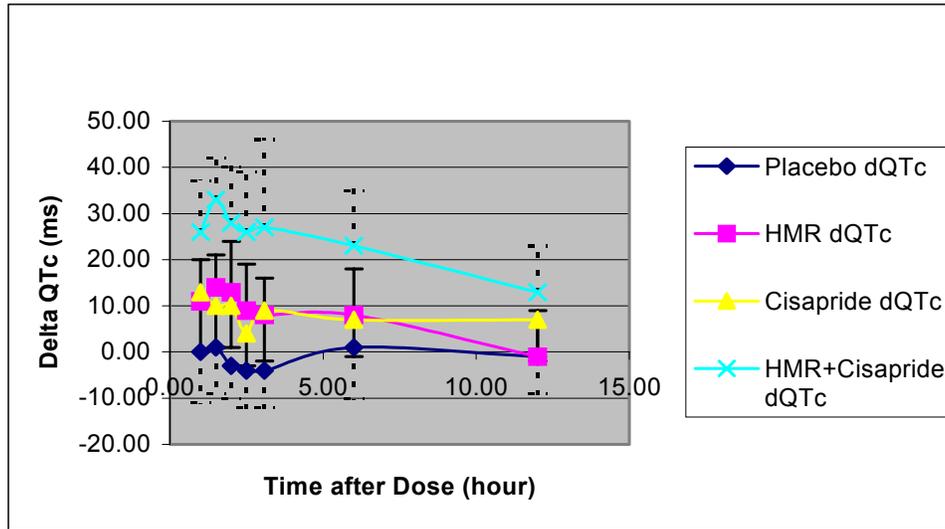
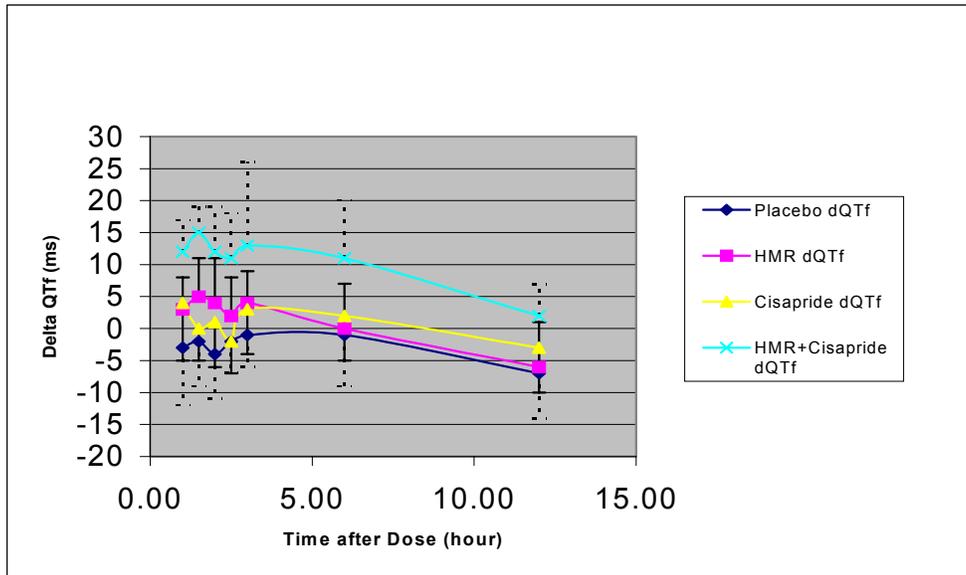


Figure 6.  $\Delta QT_f$  vs. time after dosing



## 8. Phase III Studies: Cardiac Safety

### a) Deaths and adverse events related to the cardiovascular system

There were 11 deaths in phase 3 trials (7 telithromycin, 4 comparators). All deaths except for one occurred in trials of community-acquired pneumonia; the exception was a tonsillopharyngitis patient who died of acute lymphoid leukemia.

Of deaths in telithromycin-treated patients, 6/7 were associated with cardiovascular adverse events or electrocardiographic abnormalities as follows:

A telithromycin-treated patient with a baseline QT<sub>c</sub> of 473 msec (measured using the longest lead) died on study day 2. The cause of death was stated to be a myocardial infarction that was assessed as having occurred on the day of study entry (prior to receiving study drug), on the basis of an entry EKG showing absent R waves in V2 and V3; however, serum concentrations of troponin I, creatinine phosphokinase, and the MB fraction of CPK were within normal limits.

A telithromycin-treated patient who had a QT<sub>c</sub> prolongation of 35 msec while on therapy died on day 5 of therapy. The stated cause of death in the case report form was acute aspiration. The patient had acute respiratory distress followed by an asystolic cardiac arrest. Of note, the patient had been receiving concomitant theophylline (a medication potentially interacting with telithromycin via the cytochrome P450 system) during the study period, and had complained of nausea and vomiting, which can be symptoms of theophylline toxicity.

A telithromycin-treated patient with a history of coronary artery disease, atrial fibrillation, cerebrovascular disease, diabetes mellitus and liver disease died on study day 10 of heart failure. EKGs obtained on therapy showed nonspecific anterior, lateral and inferior ST-T wave abnormalities, atrial fibrillation, sinus tachycardia and irregular rhythm. No QT<sub>c</sub> data were available due to the presence of atrial fibrillation.

A telithromycin-treated patient with a history of chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, and diabetes died 20 days after completion of therapy; Gram-negative septicemia was listed as the primary cause of death, with acute myocardial infarction and congestive heart failure as secondary causes of death. Of note, this patient developed a leukocytoclastic vasculitis involving the skin 2 days after completion of therapy.

A telithromycin-treated patient with a history of coronary artery disease and chronic obstructive pulmonary disease died on study day 4 of circulatory failure, respiratory failure, and kidney failure. Sputum cultures grew *S. pneumoniae*,  $\beta$ -lactamase-producing *H. influenzae*, and telithromycin-resistant *S. aureus*. This patient was considered a therapeutic failure because of the need to change her therapy from telithromycin to intravenous ceftriaxone and gentamicin.

A telithromycin-treated patient died 5 days after completion of therapy from respiratory failure, cardiomyopathy, liver failure, and immunosuppression due to HIV.

There were no deaths associated with cardiovascular adverse events or electrocardiographic abnormalities in comparator-treated patients.

### **b) Cardiovascular serious adverse events (SAEs)**

There were ten treatment-emergent cardiovascular SAEs in telithromycin-treated patients and seven in comparator-treated patients. SAEs included myocardial infarction, heart failure, cardiomyopathy, vasculitis, pulmonary embolism, pericardial effusion, hypertension, hypotension, angina, and chest pain. As would be predicted in a database of this size, there were no SAEs representing torsades de pointes. There were no arrhythmias representing SAEs. One cardiovascular SAE (vasculitis) in a telithromycin-treated patient was felt to be related to study drug; this was the patient who developed leukocytoclastic vasculitis and died of Gram-negative septicemia. Four of the cardiovascular SAEs occurred in telithromycin-treated patients who died. There were no cardiovascular SAEs in comparator-treated patients who died.

### **c) Cardiovascular adverse events (AEs)**

Of patients in all phase 3 trials, 82/3265 (2.5%) of telithromycin-treated patients and 53/1672 (3.2%) of comparator-treated patients had cardiovascular treatment-emergent AEs (TEAEs). 20/3265 (0.6%) of telithromycin-treated patients and 12/1672 (0.7%) of comparator-treated patients had cardiovascular TEAEs assessed as being related to study drug. Of these patients, one telithromycin-treated patient had drug-related supraventricular extrasystoles. One comparator-treated patient who received amoxicillin/clavulanate had drug-related extrasystoles, and another comparator-treated patient who received trovafloxacin had drug-related supraventricular tachycardia. No patient with drug-related arrhythmias received counteractive medication.

### **d) Electrocardiographic data**

Because of the preclinical and phase I data showing an effect of telithromycin on QTc interval, the applicant collected electrocardiographic data during all controlled phase III trials. (For studies 3004 and 3011, paired pre-therapy and on-therapy EKG data was collected for only three and one patients, respectively.) EKGs were obtained during the following time windows:

- Pretreatment: Day -2 to 1 (before first dose of active treatment)
- On-treatment: Last EKG on active treatment (2-3 h after study drug administration)
- Posttreatment: First EKG after cessation of active treatment

All EKGs were overread by a board-certified cardiologist in a blinded fashion, who made corrected machine readings of QT intervals and heart rate as appropriate before data were entered into the NDA database. QT<sub>c</sub> was calculated by averaging the corrected QT intervals for leads with the longest and shortest QT intervals.

Before discussing these data, general caveats regarding analysis of QT<sub>c</sub> effects should be mentioned.

- Because of the relative rarity of ventricular arrhythmias associated with QT prolongation, such as torsades de pointes, it would be unusual to detect such events even in a large NDA database. It is worth noting that no such events were detected at the time of approval for either terfenadine or cisapride, drugs now well known to be associated with torsade. This effect becomes even more important when specific

high-risk subgroups are underrepresented in a database, further decreasing its power to detect a signal.

- Effects on QT<sub>c</sub> prolongation may be diluted by normal inter-individual variability, obscuring clinically important effects. Such variability may be increased in a population containing ill patients rather than healthy volunteers. Again, this problem may be markedly exacerbated if there is underrepresentation of specific high-risk subgroups.
- Small changes in QT<sub>c</sub> interval may become significant in the setting of coexisting factors that can contribute to QT<sub>c</sub> prolongation, such as pharmacokinetic variability or concomitant administration of an interacting drug. For example, terfenadine causes a mean increase in QT<sub>c</sub> interval of only 6 msec<sup>3</sup>; however, when administered with an inhibitor of CYP3A4 such as ketoconazole, terfenadine concentrations increase, leading to significantly lengthened QT intervals and increasing the risk of torsade.
- The increase in risk represented by a given increase in QT<sub>c</sub> is difficult to determine. Conventionally, an increase of less than 30 msec is assumed to represent normal variability, an increase of 30 to 60 msec is thought to represent a possibly significant effect, and an increase of 60 msec or more is thought to represent a clearly significant effect. However, as just discussed, even a small increase in QT<sub>c</sub> may be associated with an increased risk of torsade, as with terfenadine.

In addition to these general considerations, some specific limitations of the applicant's database should be noted.

- EKGs were to be obtained 1-3 h after dosing. As noted above, in a number of Phase I studies maximal changes in QT<sub>c</sub> in telithromycin-treated patients occurred at 4 h after dosing. Thus, the peak effect of telithromycin on cardiac repolarization may have occurred after EKGs were obtained.
- In practice, EKGs were obtained at different times after dosing, increasing the heterogeneity of the population of observations and potentially dilution of changes in QT<sub>c</sub>.
- Exclusion criteria designed to prevent enrollment of subjects who might be at increased risk for QT<sub>c</sub> prolongation or torsade; these included concomitant administration of potentially interacting medications and severe hypokalemia. This necessarily restricted the representation of such subjects in the safety database. For example, in controlled Phase 3 trials there were only thirteen patients with hypokalemia at baseline; of these, only two had EKG data allowing assessment of the effects of telithromycin on cardiac repolarization. As discussed above, this severely limits the conclusions that can be drawn from Phase 3 data regarding possible effects of telithromycin in such subjects.

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<sup>3</sup> Pratt CM *et al.* Dose-response relation between terfenadine (Seldane) and the QT<sub>c</sub> interval on the scalar electrocardiogram: distinguishing a drug effect from spontaneous variability. *Am Heart J* 1996; **131**:472-80.

- EKGs in phase 3 trials were obtained at a resolution of 25 mm/sec; a resolution of at least 50 mm/sec has generally been used in studies of QT prolongation.
- No data were collected on serum magnesium concentrations, preventing an assessment of the effects of telithromycin in patients with hypomagnesemia, a well-recognized risk factor for torsades de pointes.

To minimize the effects of QT<sub>c</sub> variability, the FDA analysis of telithromycin's effects on repolarization focused on patients from controlled trials. Data from telithromycin-treated patients were compared to data from patients drawn from the same randomized trials.

The NDA safety database comprised 4937 patients (3265 telithromycin and 1672 comparator) who received at least one dose of drug (either telithromycin or comparator) and had follow-up safety information; another 48 patients were excluded from the database because of lack of follow-up safety information. The FDA analysis of EKG data focused on 3717 patients in controlled Phase 3 trials (2045 telithromycin and 1672 comparator). Of these, EKG data allowing analysis of on-therapy QT<sub>c</sub> values were available for 2791 patients (1515 telithromycin and 1276 comparator). **Table 33** shows mean changes in QT<sub>c</sub> for telithromycin and comparators during therapy in controlled trials for representative groups. **Table 34** shows mean changes in QT<sub>c</sub> for telithromycin and clarithromycin during therapy for studies 3006 and 3008, the two controlled studies comparing these two agents. **Table 35** shows mean changes in QT<sub>c</sub> for telithromycin in uncontrolled studies.

**Table 33. Mean ± SD changes in QT<sub>c</sub> (msec) in controlled telithromycin Phase 3 trials.**

Group	Telithromycin	Comparators
All (controlled trials)	2.0 ± 20.2 (n=1515)	-0.7 ± 20.7 (n=1276)
F	2.3 ± 18.6 (n=805)	-0.4 ± 20.7 (n=665)
M	1.6 ± 21.9 (n=710)	-1.1 ± 21.9 (n=611)
Age 13-18	3.3 ± 16.1 (n=43)	-4.0 ± 28.1 (n=55)
19-64	2.0 ± 20.4 (n=1251)	0.1 ± 19.9 (n=994)
≥65	1.6 ± 20.2 (n=221)	-3.5 ± 21.8 (n=227)

**Table 34. Mean ± SD changes in QT<sub>c</sub> (msec) in pooled studies 3006 and 3008.**

Group	Telithromycin	Clarithromycin
All (Studies 3006 and 3008)	3.5 ± 18.2 (n=433)	2.8 ± 18.2 (n=431)
F	3.7 ± 18.1 (n=246)	2.3 ± 17.8 (n=239)
M	3.2 ± 18.4 (n=187)	3.4 ± 18.6 (n=192)
Age 13-18	3.1 ± 15.4 (n=27)	0.8 ± 20.7 (n=41)
19-64	3.4 ± 18.3 (n=377)	3.1 ± 17.9 (n=353)
≥65	5.3 ± 20.2 (n=29)	1.6 ± 18.2 (n=37)

**Table 35. Mean ± SD changes in QT<sub>c</sub> (msec) in uncontrolled phase 3 studies.**

Group	Telithromycin
All uncontrolled	-0.5 ± 28.3 (n=787)
F	0.4 ± 24.6 (n=356)
M	-1.3 ± 31.1 (n=431)
Age 13-18	-4.0 ± 26.1 (n=18)
19-64	-0.3 ± 27.8 (n=707)
≥65	-2.5 ± 34.5 (n=62)

Mean changes in QT<sub>c</sub> were significantly different between telithromycin treated patients from controlled and uncontrolled trials (p = 0.014), suggesting that these patients should not be pooled for comparison with comparator-treated patients.

Telithromycin patients receiving concomitant medications metabolized by CYP3A4 or CYP2D6 showed increases in QT<sub>c</sub> relative to patients who did not receive such medications, as shown in **Tables 36** and **37**.

The analyses in Tables 36 and 37 should be regarded as exploratory and interpreted cautiously, since patients were not randomized on the basis of CYP3A4 or CYP2D6 substrate intake.

**Table 36. Mean ± SD changes in QT<sub>c</sub> (msec) in patients receiving medications metabolized by CYP3A4 and/or 2D6.**

Group	Telithromycin	Comparators
No concomitant 3A4 substrate	1.3 ± 20.3 (n=972)	-1.1 ± 21.3 (n=787)
Concomitant 3A4 substrate	3.2 ± 20.1 (n=543)	-0.2 ± 19.7 (n=489)
No concomitant 2D6 substrate	1.4 ± 20.4 (n=1315)	-1.0 ± 21.1 (n=1082)
Concomitant 2D6 substrate	5.3 ± 18.6 (n=200)	0.7 ± 28.1 (n=194)
Concomitant 3A4 and 2D6 substrates	6.9 ± 17.8 (n=110)	3.0 ± 16.7 (n=111)

**Table 37. Mean ± SD changes in QT<sub>c</sub> (msec) in patients receiving medications metabolized by CYP3A4 and/or 2D6 in studies 3006 and 3008.**

Group	Telithromycin	Clarithromycin
No concomitant 3A4 substrate	3.1 ± 18.2 (n=276)	2.7 ± 18.9 (n=266)
Concomitant 3A4 substrate	4.1 ± 18.3 (n=157)	2.9 ± 17.0 (n=165)
No concomitant 2D6 substrate	2.6 ± 18.4 (n=378)	2.6 ± 18.3 (n=359)
Concomitant 2D6 substrate	9.4 ± 15.8 (n=55)	3.6 ± 17.5 (n=72)
Concomitant 3A4 and 2D6 substrates	11.5 ± 16.3 (n=31)	5.4 ± 16.0 (n=44)

Thus, in controlled Phase 3 trials, telithromycin appeared to show a small but consistent effect on mean QT<sub>c</sub> duration, with evidence that interactions with drugs metabolized by CYP3A4 and 2D6 further affected QT<sub>c</sub> duration. In contrast, telithromycin-treated patients from uncontrolled studies showed a decrease in mean QT<sub>c</sub> duration. The difference between telithromycin-treated patients from controlled studies and uncontrolled studies is statistically significant (p=0.015), arguing against pooling patients from uncontrolled and controlled trials.

Because of the inherent variability of QT<sub>c</sub> intervals and the potential for measures of central tendency such as mean values to mask clinically important changes, outliers were also examined. **Figure 7** shows the frequency distribution of QT<sub>c</sub> changes for telithromycin and comparator-treated patients in controlled Phase 3 trials; **Figure 8** shows the corresponding distribution for studies comparing telithromycin to clarithromycin. There was a higher frequency of QT<sub>c</sub> increases of more than 30 msec in telithromycin treated patients than in comparators, both for all controlled trials as well as for trials in which telithromycin was compared to clarithromycin; the difference was not statistically significant.

Of the 114 telithromycin-treated patients in controlled trials with an increase of QT<sub>c</sub> on-therapy of more than 30 msec, the maximum QT<sub>c</sub> on-therapy was 531 msec (median, 423 msec). For the 76 comparator-treated patients, the maximum QT<sub>c</sub> was 504 msec (median, 423 msec). The maximum increase in QT<sub>c</sub> for telithromycin-treated patients was 90 msec (median, 38 msec) and for comparator-treated patients 106 msec (median, 38 msec).

3/114 (2.6%) telithromycin-treated patients with an increase of QT<sub>c</sub> on-therapy of more than 30 msec had an on-therapy QT<sub>c</sub> of greater than 470 msec. For these patients, increases from baseline to on-therapy were 50 msec (425 msec to 475 msec); 43 msec (488 to 531 msec); and 40 msec (431 msec to 471 msec). 2/76 (2.6%) comparator-treated patients had an on-therapy QT<sub>c</sub> of greater than 470 msec. The increases for these patients were 106 msec (398 msec to 504 msec) and 41 msec (453 msec<sub>2</sub> to 494 msec).

Of the 190 patients who had an increase in QT<sub>c</sub> of more than 30 msec, none died. 3/114 (2.6%) of telithromycin-treated patients had a cardiovascular treatment-emergent adverse event (TEAE), versus 4/76 (5.5%) comparator-treated patients. One cardiovascular TEAE (left heart failure) in the telithromycin group was categorized as a serious adverse event; two TEAEs in the comparator group (heart failure and angina) were categorized as serious. No cardiovascular TEAE was assessed as being causally related to either telithromycin or comparator. There were no episodes of torsades de pointes or other ventricular tachycardias in these 190 patients.

Because of the incidence of dizziness in telithromycin-treated patients and the potential connection with cardiac arrhythmias, this adverse event was analyzed in connection with QT<sub>c</sub> prolongation. Of telithromycin-treated patients in controlled trials who had dizziness reported as an adverse event, 6/91 (6.6%) had an increase in QT<sub>c</sub> of more than 30 msec, compared to 2/48 (4.2%) of comparator-treated patients who reported dizziness.

#### e) **Summary: Cardiac Safety**

Phase I data from controlled studies in humans show that telithromycin causes QT<sub>c</sub> prolongation in a dose- and concentration-dependent fashion; the magnitude of the effect is comparable to that of cisapride. The effect is enhanced by coadministration of a CYP3A4 inhibitor. Telithromycin shows considerable pharmacokinetic variability, particularly in populations such as the elderly and subjects with hepatic impairment. The concentration dependence of telithromycin-associated QT<sub>c</sub> prolongation in combination with potential drug interactions and pharmacokinetic variability suggest that significant

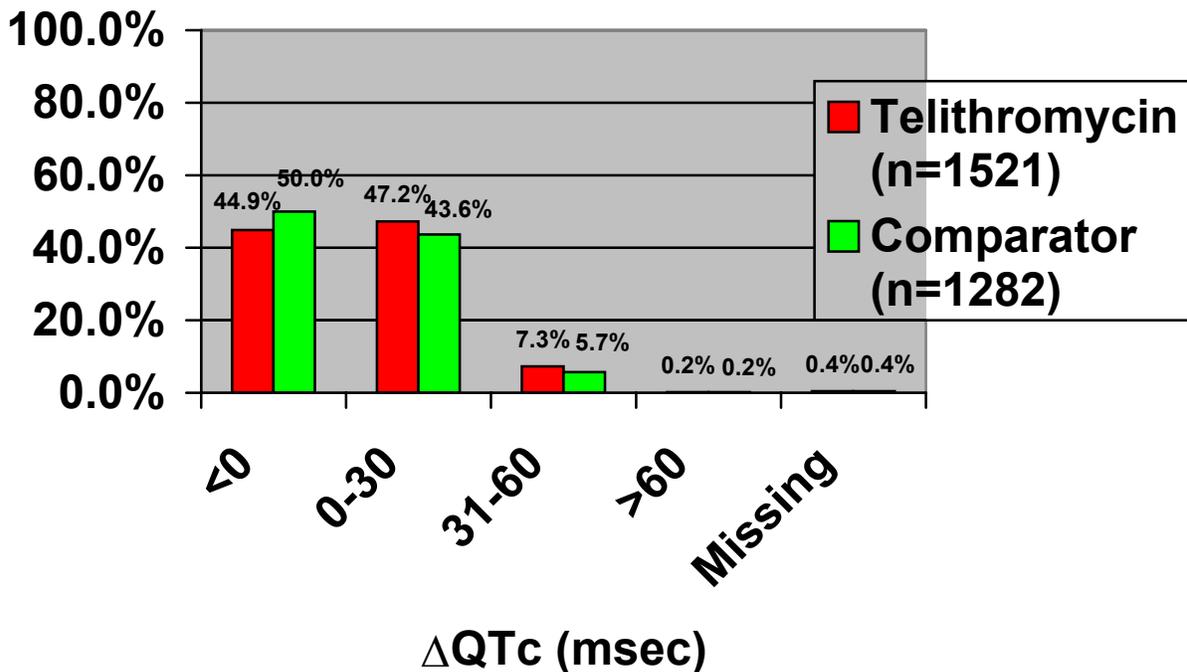
QTc prolongation may occur in at-risk patients receiving concomitant interacting medications.

For patients who died in phase 3 trials, 6/7 deaths in telithromycin-treated patients had cardiovascular causes, while 0/4 deaths in comparator-treated patients had cardiovascular causes. As would be predicted in a database of this size, there were no occurrences of torsades de pointes.

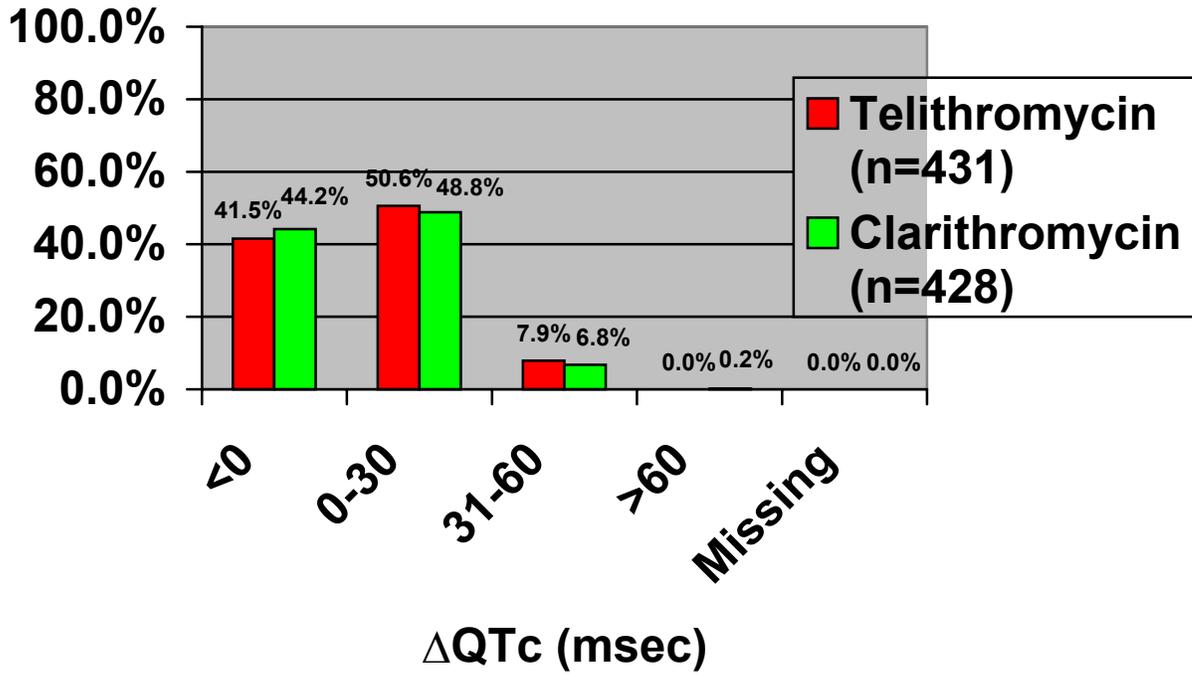
Phase 3 data on QT<sub>c</sub> changes in controlled studies must be interpreted cautiously because of limitations in the database; however, these data show a small but consistent increase in QT<sub>c</sub> in telithromycin-treated patients, greater than changes in either comparator-treated patients or comparable clarithromycin-treated patients. This effect may be enhanced by coadministration of drugs metabolized by 3A4 or 2D6.

Taken together, these findings suggest a potential for telithromycin to cause clinically significant effects on cardiac repolarization.

**Figure 7. Frequency of  $\Delta$ QTc changes**



**Figure 8. Frequency of  $\Delta$ QTc changes  
Studies 3006 and 3008**



## C. Hepatic Safety

### 1. Preclinical liver abnormalities

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. The results from the preclinical studies regarding hepatic findings and the calculated human equivalent doses are provided in **Table 38**. 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.

**Table 38. Liver-Related Findings for Telithromycin from the Preclinical Studies**

Study	NOEL	HED*	Liver-Related Findings
4 Week Rat Oral	50 mg/kg/d	8 mg/kg AUC/Cmax increased but not proportional to dose but widely variable results	-increased ALT -increased AST (2-15xULN) -increased leucine aminopeptidase -histopathologic findings of moderate to severe hepatic necrosis at doses of 150 & 300 mg/kg/d -phospholipidosis
4 Week Dog Oral	50 mg/kg/d	27 mg/kg AUC/Cmax marked increases between Days 1-30 that are not proportional to dose	-increased ALT -increased AST- up to 6xULN -one premature decedent with liver and renal failure
4 Week Rat IV	10 mg/kg/d	1.62 mg/kg	-no treatment-related hepatic findings
13 Week Rat Oral	50 mg/kg/d (NOAEL)	8 mg/kg	-increased ALT -increased AST (up to 3.6xULN) -histopathologic findings of increased inflammatory cell foci in liver at doses of 150 mg/kg/d -phospholipidosis
6 Month Rat Oral	20 mg/kg/d	3.2 mg/kg	-increased ALT (2-3x ULN) -increased AST -increased Alk. Phos. -increased liver weights -histopathologic findings of bile duct epithelial vacuolation
4 Week Dog IV	30 mg/kg/d	16.2 mg/kg	-histopathologic findings of hepatocyte hypertrophy
13 Week Dog Oral	50 mg/kg/d	27 mg/kg	-increased ALT -increased AST (up to 4.7xULN) -histopathologic findings of hepatocyte hypertrophy
4 Week Monkey	60 mg/kg/d	19 mg/kg	-increased ALT -increased AST (up to 4xULN) -increased total bilirubin -no histopathologic lesions

\*Note a dose of 800 mg of Telithromycin per day in a 70 kg human is 11.4 mg/kg

## 2. Phase I liver abnormalities

In phase I studies, several telithromycin treated patients experienced hepatic adverse events. There was a clustering of subjects with elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) laboratory values in 3 of 8 elderly subjects receiving a single 2000 mg dose of telithromycin (the highest dose received by elderly subjects). The elevation occurred between 8 and 14 days after the last dose of telithromycin. All three of these 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 three had a serology for CMV that was positive for IgG and IgM with a subsequent CMV serology 2-weeks later positive for IgG and negative for IgM. The second of the three had a transiently positive serology for EBV IgG with a negative serology for EBV IgM (antibody specificity not further described) and a positive IgG antibody to Epstein-Barr nuclear antigen (EBNA). The third had a positive IgG and IgM EBV serology (antibody specificity not further described) followed 11 days later by a positive IgG antibody to Epstein-Barr nuclear antigen (EBNA) and negative IgM antibodies to virus capsid antigen (VCA) and “EBV”. No baseline information regarding serologic status for EBV or CMV for these patients was available. 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 (**Table 39**).

The clustering of events in the elderly subjects with hepatic adverse events in a single dose study using a dose of telithromycin at 2000 mg suggests the possibility that higher doses of telithromycin may be provoking hepatic adverse events in this population of elderly patients. However, the serologic information with regards to CMV and EBV raises the possibility that other potential causes may be involved.

In the highest doses studied in multiple dose studies of telithromycin (1600 mg qd in healthy young subjects and 1200 mg po qd in elderly subjects), no hepatic adverse events were noted. A summary of the number of hepatic adverse events by dose from the phase I studies is provided in **Table 39** and the types of hepatic adverse events reported in the phase I studies single-dose studies are presented in **Table 40**.

**Table 39. Frequency of Hepatic TEAEs in Single and Multiple Oral Dose Phase I Studies of Telithromycin by Dose Level**

Ketek Dose (mg)	Single-Dose Studies			Multiple-Dose Studies		
	Number of Hepatic TEAEs (n)	Number of Dosing Periods (N)	TEAEs/Period (n/N)	Number of Hepatic TEAEs (n)	Number of Dosing Periods (N)	TEAEs/Period (n/N)
50	0	6	(0.0)	-	-	-
100	0	6	(0.0)	0	8	(0.0)
200	0	7	(0.0)	0	8	(0.0)
400	0	24	(0.0)	0	26	(0.0)
600	0	40	(0.0)	0	27	(0.0)
800	5	401	(1.2)	1	170	(0.6)
900	-	-	-	0	8	(0.0)
1200	0	8	(0.0)	0	10	(0.0)
1600	0	74	(0.0)	0	24	(0.0)
2000	3 <sup>†</sup>	16	(18.8)	-	-	-
2400	0	47	(0.0)	-	-	-
3200	1	24	(4.2)			
<b>Total</b>	<b>9</b>	<b>653</b>	<b>(1.4)</b>	<b>0</b>	<b>281</b>	<b>(0.4)</b>
Placebo	1 <sup>††</sup>	98	(1.0)	0	42	(0.0)

“-” signifies no patients exposed to this dose  
<sup>†</sup>In this table Subject 005 from Study 1030 AEs of “AST increased” and “ALT increased” are counted as one event  
<sup>††</sup>This subject’s AE of liver damage (subject 12 from Study 1030) is attributed to placebo because his liver AE was first detected Day 8 after placebo which is also Day 15 after his 2000 mg dose of telithromycin.  
 Adapted from the applicant’s Table ISS-ISE/s09/0000612t.1<sup>st</sup> 22 March 2001

**Table 40. Frequency of Hepatic AEs per Dosing Period for Telithromycin – Phase I Single-Dose Studies**

Coded Term for Hepatic AE	Ketek Periods = 653 n/N	Placebo Periods = 98 n/N
Liver Damage <sup>a</sup>	2/653	1/98 <sup>†</sup>
Increased AST	3/653 <sup>††</sup>	0
Increased ALT	2/653 <sup>††</sup>	0
Liver Function Test Abnormal	2/653	0
Increased Alk. Phos.	1/653	0
Total No. of Hepatic AEs	10	1
Total No. of Subjects with Hepatic AEs	9	1

Note: the unit of analysis is the dosing period not per subject. A subject may have more than one hepatic AE.  
<sup>†</sup>This subject’s (subject 12 from Study 1030) AE of liver damage is attributed to placebo because his liver AE was first detected Day 8 after placebo which is also Day 15 after his 2000 mg dose of telithromycin.  
<sup>††</sup> Subject 5 from Study 1030 had 2 hepatic TEAEs “Increased AST” and “Increased ALT”. She is recorded under both categories in the table above (i.e., her event is one of the 3 events under the category of “Increased AST” and also one of the 2 events under the category of “Increased ALT”). She is the only subject represented in more than one hepatic AE category within this table.  
<sup>a</sup> Liver Damage refers to asymptomatic increases in ALT and AST.

### 3. Phase III liver abnormalities and clinical outcome

In the comparative phase III clinical studies, the proportion of subjects experiencing hepatic adverse events was similar between telithromycin and its comparators (**Table 41**). This was true for both “All Treatment Emergent Adverse Events (TEAEs)”<sup>a</sup> and for “Possibly-Related TEAEs”. In the non-comparative studies on telithromycin, hepatic TEAEs were reported more frequently than in the comparative studies. This was largely the result of a higher rate of hepatic events in one of the three non-comparative CAP studies (Study 3000). The absence of a comparator group in these studies limits the extent to which any conclusions regarding causality can be made.

**Table 41. Hepatic TEAEs (coded terms) in all Completed Controlled Phase III studies**

Coded term	Number (%) of Subjects			
	All TEAEs		Possibly Related TEAEs	
	Ketek	Comparator	Ketek	Comparator
	<b>N=2045</b>	<b>N=1672</b>	<b>N=2045</b>	<b>N=1672</b>
Liver function test abnormal	32 (1.6)	25 (1.5)	23 (1.1)	18 (1.1)
SGPT/ALT increased	14 (0.7)	14 (0.8)	9 (0.4)	11 (0.7)
Alkaline phosphatase increased	5 (0.2)	3 (0.2)	1 (0.05)	3 (0.2)
SGOT/AST increased	5 (0.2)	2 (0.1)	4 (0.2)	1 (0.1)
Lactic dehydrogenase increased	4 (0.2)	3 (0.2)	1 (0.05)	1 (0.1)
Liver damage	2 (0.1)	3 (0.2)	2 (0.1)	0 (0.0)
Cholestatic jaundice	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Jaundice	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Bilirubinemia	1 (0.05)	1 (0.1)	1 (0.05)	1 (0.1)
Hepatitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
GGT Increased	5 (0.2)	4 (0.2)	1 (0.05)	3 (0.2)
Liver tenderness	1 (0.05)	0 (0.0)	1 (0.05)	0 (0.0)
<b>Total Number of Hepatic Events<sup>a</sup></b>	<b>71</b>	<b>57</b>	<b>45</b>	<b>39</b>
<b>Total Number of Patients with Hepatic Events</b>	<b>58 (2.8)</b>	<b>49 (2.9)</b>	<b>40 (2.0)</b>	<b>33 (2.0)</b>

<sup>a</sup> A subject may have had more than one hepatic TEAE.

Adapted from applicant’s Table from NDA 21-144 8:v251:p188, Table 8-276, 8:v253:p043, Table 170 from the Study 3011 Study Report p. 0532, and the applicant’s SAS.txp files for NDA 21-144 (Excludes patients from Study 3005 Centers 150, 164, and 191; Study 3007 Centers 63 and 104, and Study 3009 Center 301 and 281)

\* 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.

In the comparative 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 what was observed in the comparative studies.

### **Serious hepatic adverse events**

In the comparative studies, there were 2 serious hepatic AEs reported in telithromycin treated subjects and one serious hepatic AE reported in a comparator treated patient. In the non-comparative studies, there was one additional serious hepatic AE in a telithromycin treated patient. (Case narratives for the four patients with serious hepatic AEs are provided in Appendix C.) There were reasonable alternative explanations for one of the serious hepatic AEs in the telithromycin treated patients and for the only comparator treated patient with a serious hepatic AE. It was quite plausible to consider that the two other telithromycin treated subjects with serious hepatic AEs were possibly related to telithromycin therapy. The first of these two events was 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. The other serious hepatic AE that was plausibly associated with telithromycin is described in the next 2 paragraphs.

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<sup>6</sup>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<sup>6</sup>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.

The deaths that occurred in subjects in the telithromycin clinical studies were reviewed. There were no deaths that appeared to be primarily the result of a telithromycin induced hepatic event. While there were patients that had hepatic abnormalities that died, these events were attributed to causes other than study drug (e.g., acute leptospirosis or multiorgan failure in an HIV-positive patient with pneumonia and respiratory distress and markedly elevated ALT and AST at baseline).

Laboratory abnormalities for ALT, AST, T. Bili., and Alkaline Phosphatase (Alk. Phos.) were analyzed in a number of analyses. The summary findings derived from the multiple analyses were as follows. For patients with normal ALT, AST, and T. Bili. at baseline, there was a greater proportion of telithromycin treated patients than comparator treated patients from the comparative CAP studies with low-level (between 1x to 3x ULN) elevations in AST (**Table 42B**). This difference was present during the On-Therapy and Post-Therapy visits and absent during the Late Post-Therapy visit. For ALT, there is a slightly greater proportion of patients from the comparative CAP studies with low-level ALT elevations during On-Therapy and Post-Therapy (**Table 42A**). For patients from the comparative CAP studies with normal ALT, AST, and T. Bili. at baseline, T. Bili. elevations were infrequent in both telithromycin and comparator treated patients (**Table 42C**). The number of patients experiencing elevations of in the categories in excess of 3xULN are small in both treatment groups.

**Table 42A. Changes in ALT by Visit in Controlled Phase III CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline**

Changes in ALT	On-Therapy				Post-Therapy <sup>a</sup>				Late Post-Therapy <sup>b</sup>			
	Ketek N=320		Comp N=314		Ketek N=296		Comp N=293		Ketek N=152		Comp N=152	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≤ ULN	279	(87.2)	283	(90.1)	256	(86.5)	265	(90.4)	141	(92.8)	143	(94.1)
> ULN to ≤ 2x ULN	35	(10.9)	28	(8.9)	36	(12.2)	27	(9.2)	8	(5.3)	7	(4.6)
> 2 to ≤ 3x ULN	5	(1.6)	2	(0.6)	4	(1.4)	0	(0.0)	2	(1.3)	2	(1.3)
> 3 to ≤ 5x ULN	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.7)	0	(0.0)
> 5 to ≤ 8x ULN	0	(0.0)	1	(0.3)	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	(0.0)
Number of patients lacking lab data for visit	19		21		43		42		187		183	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.

Note: Percentages exclude subjects with missing values.

<sup>a</sup> Days 17-21.

<sup>b</sup> 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 42B. Changes in AST by Visit in Controlled Phase III CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline**

Changes in AST	On-Therapy				Post-Therapy <sup>a</sup>				Late Post-Therapy <sup>b</sup>			
	Ketek N=320		Comp N=314		Ketek N=296		Comp N=293		Ketek N=152		Comp N=152	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≤ ULN	284	(88.8)	293	(93.3)	275	(92.9)	287	(98.0)	144	(94.7)	142	(93.4)
> ULN to ≤ 2x ULN	33	(10.3)	18	(5.7)	18	(6.1)	6	(2.0)	7	(4.6)	9	(5.9)
> 2 to ≤ 3x ULN	1	(0.3)	1	(0.3)	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
> 3 to ≤ 5x ULN	2	(0.6)	2	(0.6)	1	(0.3)	0	(0.0)	1	(0.7)	0	(0.0)
> 5 to ≤ 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)
> 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	19		21		43		42		187		183	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.

Note: Percentages exclude subjects with missing values.

<sup>a</sup> Days 17-21.

<sup>b</sup> 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 42C. Changes in T. Bili. by Visit in Controlled Phase III CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline**

Changes in T. Bili.	On-Therapy				Post-Therapy <sup>a</sup>				Late Post-Therapy <sup>b</sup>			
	Ketek N=316		Comp N=305		Ketek N=289		Comp N=286		Ketek N=151		Comp N=150	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≤ ULN	315	(99.7)	304	(99.7)	286	(99.0)	284	(98.0)	150	(99.3)	150	(100.0)
> ULN to ≤ 2x ULN	1	(0.3)	1	(0.3)	3	(1.0)	1	(0.3)	1	(0.7)	0	(0.0)
> 2 to ≤ 3x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 3 to ≤ 5x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 5 to ≤ 8x ULN	0	(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	(0.0)
Number of patients lacking lab data for visit	23		30		50		49		188		185	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.

Note: Percentages exclude subjects with missing values.

<sup>a</sup> Days 17-21.

<sup>b</sup> 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 T. Bili. between treatment groups similar with the following exception; at the Late Post-Therapy visit there was a greater proportion of comparator treated patients with low-level elevations in AST. **Tables 43A-C** provide the results of these analyses.

**Table 43A. Changes in ALT by Visit in Controlled Phase III Non-CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline**

Changes in ALT	On-Therapy				Post-Therapy <sup>a</sup>				Late Post-Therapy <sup>b</sup>			
	Ketek N=1132		Comp N=839		Ketek N=936		Comp N=738		Ketek N=402		Comp N=314	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≤ ULN	1060	(93.6)	799	(95.2)	878	(93.8)	674	(91.3)	382	(95.0)	293	(93.3)
> ULN to ≤ 2x ULN	68	(6.0)	36	(4.3)	56	(6.0)	61	(8.3)	17	(4.2)	19	(6.1)
> 2 to ≤ 3x ULN	3	(0.3)	4	(0.5)	1	(0.1)	1	(0.1)	2	(0.5)	0	(0.0)
> 3 to ≤ 5x ULN	0	(0.0)	0	(0.0)	1	(0.1)	2	(0.3)	1	(0.2)	2	(0.6)
> 5 to ≤ 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 8x ULN	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Number of patients lacking lab data for visit	62		50		258		151		792		575	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.

Note: Percentages exclude subjects with missing values.

<sup>a</sup> Days 17-21.

<sup>b</sup> 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 43B. Changes in AST by Visit in Controlled Phase III Non-CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline**

Changes in AST	On-Therapy				Post-Therapy <sup>a</sup>				Late Post-Therapy <sup>b</sup>			
	Ketek N=1133		Comp N=840		Ketek N=296		Comp N=293		Ketek N=152		Comp N=152	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≤ ULN	1089	(96.1)	811	(96.5)	913	(97.6)	717	(97.2)	397	(98.5)	299	(95.2)
> ULN to ≤ 2x ULN	42	(3.7)	28	(3.3)	19	(2.0)	19	(2.6)	3	(0.7)	15	(4.8)
> 2 to ≤ 3x ULN	1	(0.1)	1	(0.1)	1	(0.1)	0	(0.0)	3	(0.7)	0	(0.0)
> 3 to ≤ 5x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 5 to ≤ 8x ULN	1	(0.1)	0	(0.0)	2	(0.2)	1	(0.1)	0	(0.0)	0	(0.0)
> 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Number of patients lacking lab data for visit	61		49		259		151		791		575	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.

Note: Percentages exclude subjects with missing values.

<sup>a</sup> Days 17-21.

<sup>b</sup> 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 43C. Changes in T. Bili. by Visit in Controlled Phase III Non-CAP Studies in Subjects with Normal ALT, AST, and T. Bili. at Baseline**

Changes in T. Bili.	On-Therapy				Post-Therapy <sup>a</sup>				Late Post-Therapy <sup>b</sup>			
	Ketek N=1113		Comp N=825		Ketek N=920		Comp N=729		Ketek N=392		Comp N=313	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≤ ULN	1106	(99.4)	822	(99.6)	907	(98.6)	725	(99.5)	386	(98.5)	311	(99.4)
> ULN to ≤ 2x ULN	7	(0.6)	3	(0.4)	13	(1.4)	4	(0.5)	6	(1.5)	2	(0.6)
> 2 to ≤ 3x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 3 to ≤ 5x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 5 to ≤ 8x ULN	0	(0.0)	0	(0.0)	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	(0.0)
Number of patients lacking lab data for visit	81		64		274		160		802		576	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.

Note: Percentages exclude subjects with missing values.

<sup>a</sup> Days 17-21.

<sup>b</sup> 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.

From the population of patients in the phase III studies with normal ALT & AST & T. Bili. at baseline, there were 5/2358 telithromycin treated patients with concurrent elevations of ALT & AST & T. Bili. in the category >ULN and ≤ 2x ULN (where the category is chosen based upon the lowest multiple of the ULN from among the analytes). There were an additional 5/2358 telithromycin treated patients with concomitant elevations in ALT and T. Bili. in the category >ULN and ≤ 2x ULN and one additional



**Table 44B. Alkaline Phosphatase Lab Values During Treatment\* in Patients with a Normal Alkaline Phosphatase at Baseline – Non-CAP Studies**

Analysis Category	Controlled Non-CAP Studies				Uncontrolled Non-CAP Studies	
	Ketek†		Comparator††		Ketek†	
	n/N	(%)	n/N	(%)	n/N	(%)
Baseline Alk. Phos. Normal and Follow-up Alk. Phos. is						
≤ ULN	1342/1364	(98.4)	992/1010	(98.2)	304/306	(99.3)
> ULN & ≤ 2x ULN	22/1364	( 1.6)	18/1010	( 1.8)	2/306	( 0.7)
> 2x ULN & ≤ 3x ULN	0/1364	( 0.0)	0/1010	( 0.0)	0/306	( 0.0)
> 3x ULN & ≤ 5x ULN	0/1364	( 0.0)	0/1010	( 0.0)	0/306	( 0.0)
> 5x ULN & ≤ 8x ULN	0/1364	( 0.0)	0/1010	( 0.0)	0/306	( 0.0)
> 8x ULN	0/1364	( 0.0)	0/1010	( 0.0)	0/306	( 0.0)

\*During Treatment = from pretherapy/entry through end of treatment + 7 days      ULN= upper limit of normal for the analyte being evaluated  
† The Ketek regimen for the Controlled Non-CAP (comparative) studies were Ketek 800 mg po QD x 5 days (Studies 3003, 3004, 3307, 3008, and 3011) and Ketek 800 mg po QD x 5 days and Ketek 800 mg po QD x 10 days (in Study 3005 a 3-arm study). The Ketek regimen for the uncontrolled Non-CAP study was Ketek 800 mg po QD x 5 days vs Ketek 800 mg po QD x 10 days (Study 3002).  
†† Comparators for the controlled Non-CAP studies were: cefuroxime axetil 500 mg po BID x 10 days (Studies 3003 and 3007); Amoxicillin/clavulanic acid 500/125 mg po QD x 10 days (Study 3005); penicillin VK 500 mg po TID x 10 days (Study 3004), clarithromycin 250 mg po BID x 10 days (Study 3008), and cefuroxime axetil 250 mg po BID x 10 days.  
Adapted from the applicant's Table v10/0000087t.1<sup>st</sup> 5February 2001  
(Excludes patients from Study 3005 Centers 150, 164, and 191; Study 3007 Centers 63 and 104, and Study 3009 Center 301 and 281)

#### 4. Summary: Hepatic Safety

In summary, the findings from the preclinical studies demonstrate hepatotoxic effects for telithromycin in dogs, rats, and monkeys. In the single dose phase I studies in humans there was a clustering of hepatic adverse events in elderly subjects at a dose of 2000 mg. Whether factors other than study drug were causally related to these events is unclear. Hepatic adverse events were not reported from younger subjects receiving single doses of 2400 mg or from the multiple dose studies which used doses of 1600 mg in healthy young subjects. In younger patients receiving single doses of 3200 mg of telithromycin there was one hepatic AE reported.

In phase III studies, the proportion of patients experiencing hepatic adverse events or treatment discontinuation because of a hepatic adverse event were similar between telithromycin and comparator treatment groups. In the comparative studies there were 2 serious hepatic AEs in the telithromycin treated patients and 1 serious hepatic AE in comparator treated patients. There was one additional serious hepatic AE from the noncomparative telithromycin studies. One of these serious adverse events in the telithromycin treated group was a patient with a liver biopsy showing centrilobular necrosis and eosinophilic infiltration, strongly suggestive of drug-induced liver disease (the patient's baseline labs included an ALT of 81 U/L (NR<49 U/L) and an eosinophil count of 774 cells/10<sup>-6</sup> L (NR not available)). (Note: Erythromycin estolate, ethylsuccinate, and propionate have been associated with cholestatic hepatitis, sometimes

accompanied by fever and eosinophilia.<sup>4,5,6</sup> The pathologic changes for some of the cases of trovafloxacin-associated hepatitis were described as centrilobular necrosis and eosinophilic infiltration on liver biopsy<sup>7,8</sup>). Several months later this patient went on to have an episode of asymptomatic elevations in his ALT and AST and a liver biopsy showing changes consistent with chronic hepatitis, probably autoimmune.

Analysis of liver function tests from the comparative phase III studies in patients who were normal at baseline shows a greater proportion of patients with low level elevations of AST and to a lesser extent ALT in the telithromycin treated patients limited to the CAP studies. The AST and ALT elevations from patients in the CAP studies is present during the On-Therapy and Post-Therapy visits. Patients with concomitant elevations in AST and ALT and T. Bili were infrequent, but only found in telithromycin treated patients and were categorized as low level elevations between 1x and 2x the ULN.

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<sup>4</sup> Steigbigel NH. Macrolides and Clindamycin. In Principles and Practices of Infectious Diseases, 5<sup>th</sup> Ed. Mandell GL, Bennett JE, and Dolin R. Churchill Livingstone. Philadelphia. 2000. p. 366-382

<sup>5</sup> Pessayre D, Larrey D. Acute and chronic drug induced hepatitis. Bailliere's Clinical Gastroenterology. 1988;(2):385-422.

<sup>6</sup> Diehl AM, et al. Cholestatic hepatitis from erythromycin ethylsuccinate: report of two cases. Am J Med. 1984;(76); 931-4.

<sup>7</sup> Chen HJL, Bloch KJ, Maclean JA. Acute eosinophilic hepatitis from trovafloxacin. NEJM 2000, 342 (5):359.

<sup>8</sup> Lucena MI, Andrade, RJ, Rodrigo L, Salmeron J, et. al. Trovafloxacin-induced acute hepatitis. Clin Infect Dis. 2000. 30(2):400-1.

**VI. Appendices**  
**A. FDA Cardio-Renal Consult**

MEMORANDUM

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of CardioRenal Drug Products

Consultation

Date: 10-2-00

To: Mercedes Albuerne, MD  
Division Director, HFD-520

From: Maryann Gordon, MD  
Medical Reviewer, HFD-110

Through: Norman Stockbridge, MD, PhD  
Medical Team Leader, HFD-110

Raymond Lipicky, MD  
Division Director, HFD-110

Subject: Telithromycin NDA#21,144  
QT interval review in protocol HMR3647A/1049

**Conclusion**

The antibiotic telithromycin, compared to placebo, was shown in protocol 1049 to increase the corrected<sup>9</sup> QT interval in a dose-related manner. However, the interpretation of this finding is somewhat confounded by data showing that telithromycin did not change mean heart rate (although the placebo group showed a decrease) and its effect on the uncorrected QT interval was not statistically significant.

That stated, it can be concluded from the results of this study that there is most likely a drug effect on cardiac repolarization manifested by a concentration related lengthening of the QTc interval. Further exploration of this issue with higher doses and longer duration of treatment is strongly encouraged.

The following points need to be considered by your review division:

1) Since the study was conducted using only single doses, the effect on the QTc with multiple dosing could be even greater than what was shown here. Examining ECG data collected from large controlled trials should be done, but, since the peak effect of telithromycin on QTc interval was about 4 hours after dosing, ECGs recorded after that could underestimate the effect.

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<sup>9</sup> Corrected using Bazett's formula

2) It is unclear if there are drugs that, if used concomitantly, will cause the concentration of telithromycin to increase substantially. The drug is metabolized by cytochrome P450 3A4 and it is also excreted unchanged in the urine. This will need to be explored in depth, as will the effect of food and concomitant diseases on drug levels. As you know, drugs such as terfenadine and cisapride are clearly more dangerous when used concomitantly with drugs that inhibit their metabolism.

3) The philosophy of our Division is that if a drug has a defined risk that is not shared by other drug(s) in its class/indication, the sponsor needs to demonstrate unequivocally that the drug has an additional benefit that outweighs the additional risk. The benefit should be something in the order of demonstrating that telithromycin is effective when other similar treatments fail. The use of this drug to treat mild or trivial infections should be re-evaluated.

4) Although the sponsor claims that only the telithromycin 800 mg dose will be prescribed, it is not unusual for patients to receive twice the recommended dose. Therefore, a 2-fold safety margin gives one no comfort. It is important for the sponsor to explore the effect of doses of telithromycin higher than 1600 mg.

5) It would be interesting to know what effect increasing concentration of this drug has on cardiac ion channels such as  $I_{Kr}$ , the rapidly-activating delayed-rectifier potassium current.

## Introduction

Telithromycin is a member of a new macrolide subclass called ketolides. This class possesses a mode of action similar to the macrolide-lincosamide-streptogramin (MLS) compounds. The sponsor designed the present study to evaluate the effect of a single dose (800 mg and 1600 mg) of telithromycin on cardiac repolarization compared to placebo and clarithromycin. There are reports<sup>10,11</sup> that the macrolide clarithromycin, alone as well as in combination with other drugs, causes prolongation of the QT interval and episodes of torsades de pointes (TdP).

## 1. Protocol HMR3647A/1049

Title: Safety, tolerability and pharmacokinetics of single doses of telithromycin (800, 1600 mg) versus clarithromycin (500 mg bid) in patients with underlying cardiovascular diseases.

Objective: to assess the effect of 2 single doses of telithromycin on cardiac repolarization, as determined by changes in QT interval, in subjects with underlying cardiovascular disease. In addition, the study examined the relationship between antibiotic plasma concentrations and the ECG findings.

Design: single center, double-blind, randomized, placebo-and active-controlled, 4-way crossover study. All subjects received, in a randomized sequence, telithromycin 800 mg and telithromycin 1600 mg as single oral doses, clarithromycin 500 mg twice daily for one day, and placebo as single dose treatment. There was a 7-day washout period between each of the treatments.

Subject type: patients with cardiac disease defined as either -ischemic heart disease, stable on medical treatment and not revascularized,

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<sup>10</sup> Kamochi H et al, Clarithromycin associated with torsades de pointes. Jpn Circ J 1999 May ;63(5):421-2

<sup>11</sup> Lee KL et al, QT prolongation and torsades de pointes associated with clarithromycin. Am J Med 1998 Apr;104(4):395-6.

- ischemic heart disease, revascularized (angioplasty or bypass grafting) with, at most, mild ventricular impairment,
- hypertension with left ventricular hypertrophy,
- arrhythmia including: atrial fibrillation, non life-threatening arrhythmia, e.g. frequent premature atrial or ventricular complexes,
- grade II and III heart failure, or
- mild to moderate stable valvular heart disease with good left ventricular function. (Subjects who had had valvular repair were allowed.)

Study procedures: times for obtaining 12-lead ECGs, Holter monitoring, and blood samples for drug plasma concentrations are shown below.

	Screening	Day -2	Day -1	Day 1												Day 2		Day 3	Day 8 <sup>c</sup>
				- 0.5h	0 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	12 h	24 h	36h	48h		
Informed consent form		X																	
Medical -history	X																		
Physical examination	X		X															X	
Blood pressure + heart rate	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oral temperature	X			X														X	
ECG	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Holter 24 h	X	X	X	X															
Hematology	X		X											X				X	
Biochemistry	X		X											X				X	
Serology	X																		
Pregnancy test	X		X																
Urinalysis	X		X											X				X	
Drug screen	X																		
Adverse event questioning		X	X	X										X			X	X	
Drug administration					X								X						
Plasma sample				X <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X		
Meals													X <sup>b</sup>						

<sup>a</sup> just before dosing

<sup>b</sup> after second dosing

<sup>c</sup> end of study visit only

Statistical plan: all analyses were to be descriptive. The resting ECG was to be analyzed only with the QT and RR intervals obtained from expert over-reading. Changes from baseline for QTc, QTf, RR, QT, and HR were to be analyzed using ANOVA, with a mixed model. The fixed effects in the model are period, treatment, time and treatment x time. The effect of the repeated measurements was to be taken into account in the analysis.

Results: a total of 24 white subjects (14 males and 10 females ) were enrolled and randomized. Age and weight ranges were 53 to 77 years (mean 63.1 years) and 50 to 116 kg (mean 78.0 kg), respectively. All 24 subjects completed the trial, meaning all subjects received all 4 treatments. In one case, a subject treated with 1600 mg telithromycin in the morning did not take the required dose of study medication (placebo) in the afternoon because of an adverse event. This subject remained in the trial and received the other 3 treatments. All 24 subjects were included in the pharmacokinetic and safety analyses.

Of the 24 subjects enrolled in the study, 8 had ischemic heart disease with revascularization, 7 had an arrhythmia, 5 had valvular heart disease, 5 had ischemic heart disease stable on treatment and without revascularization, 3 had hypertension and left ventricular hypertrophy, and 3 had congestive heart failure.

Pharmacokinetics: the pharmacokinetic variables for the study drugs are shown below.

**Pharmacokinetic characteristics of single doses of 800 and 1600 mg HMR3647 and 500 mg bid clarithromycin administered on 1 day (N = 24)**

Parameter	Statistic	HMR3647		Clarithromycin <sup>a</sup>
		800 mg	1600 mg	500 mg bid
C <sub>max</sub> (mg/L)	Mean (CV%)	1.81 (48)	3.12 (32)	2.50 (48)
	[min-max]	[0.793-4.086]	[1.641-4.970]	[1.100-5.581]
t <sub>max</sub> (h)	Median	1.5	2.0	2.0
	[min-max]	[1.0-3.0]	[0.5-4.0]	[1.0-6.0]
AUC (0-12h) (mg.h/L)	Mean (CV%)	NA	NA	15.7 (41)
	[min-max]			[7.8-31.5]
AUC (0-24h) (mg.h/L)	Mean (CV%)	8.11 (58)	20.5 (41)	NA
	[min-max]	[2.60-19.55]	[10.92-47.77]	

<sup>a</sup> Pharmacokinetic parameters for clarithromycin were determined after the first dosing with clarithromycin. NA = Not applicable

When the dose of telithromycin was doubled, mean C<sub>max</sub> increased about 1.7 times, mean AUC<sub>0-24h</sub> increased 2.5 times, and median T<sub>max</sub> remained almost unchanged (1.5-2 hrs). Plasma telithromycin concentration profiles are shown in figure 1 (see attachment).

Heart rate: figure 9 (see attachment) shows the mean heart rate changes from baseline at various time points, by treatment group. All 4 treatment groups had at least a small decrease from baseline, with the placebo group showing the largest decrease. However, the p-value for the correlation between change in heart rate and the concentration of telithromycin 1600 mg (but not the lower dose or clarithromycin) was statistically significant (p=0.001, appendix b.3.4 faxed 9-19-00).

QT interval: adjusted changes from baseline in QTc and QT intervals for all treatment groups are shown in figure 7 (see attachment) and the following tables.

Adjusted+ mean changes from baseline QTc (msec)

Time after dose (hr)	Placebo	Tel 800 mg	Tel 1600 mg	Clarithro
0.5	-1.67	-5.39	-7.40	-4.59
1	-5.71	-5.56	-2.19	-3.84
1.5	-6.75	-0.10	0.81	-3.51
2	-9.42	-0.51	7.73	0.03
3	-4.17	-2.68	8.98	3.16
4	2.29	4.90	11.6	6.62
8	-9.29	-3.51	3.40	-1.51
24	-0.50	-3.43	-1.40	4.03
48	-5.75	0.53	-4.6	-2.51

+ANOVA using a mixed model—fixed effects in the model are period, treatment, time and treatment x time.

Standard error was 2.58 for all changes

Adjusted+ placebo subtracted adjusted mean changes from baseline QTc (msec)

Time after dose (hr)	Tel 800 mg	Tel 1600 mg	Clarithro
0.5	-3.72	-5.73	-2.92
1	0.15	3.52	1.87
1.5	6.65	7.56*	3.24
2	8.90*	17.15***	9.45**
3	1.49	13.15***	7.33*
4	2.61	9.31**	4.33
8	5.78	12.69***	7.78*
24	-2.93	-0.90	4.53
48	6.28	1.15	3.24

+ANOVA using a mixed model—fixed effects in the model are period, treatment, time and treatment x time.

\*p<0.05 for comparison to placebo.

\*\*p<0.01 for comparison to placebo.

\*\*\*p=0.001 for comparison to placebo.

**Most of the differences between placebo and telithromycin 1600 mg were statistically significant.**

Adjusted+ mean changes from baseline QT (msec)

Time after dose (hr)	Placebo	Tel 800 mg	Tel 1600 mg	Clarithro
0.5	-0.88	-3.11	-0.57	-2.29
1	7.62	1.18	6.18	3.42
1.5	13.37	3.76	7.26	8.54
2	17.12	4.56	7.39	11.04
3	22.71	3.85	10.43	13.46
4	22.92	8.51	8.06	20.42
8	6.67	4.43	4.64	8.50
24	12.29	8.06	10.43	7.29
48	3.58	6.60	6.89	3.13

+ANOVA using a mixed model—fixed effects in the model are period, treatment, time and treatment x time.

Standard error was 2.83 for all changes

The changes from baseline for uncorrected QT interval in the placebo group were greater at nearly all time points compared to the 3 active treatment groups. This is probably a reflection of the decreased heart rate when subjects were on placebo.

Correlation between QTc, QTf<sup>12</sup>, and QT intervals and blood concentration for the 3 treatments are shown below.

Drug	No. of observations	Correlation delta QTc/conc	p-value	Correlation delta QTf/conc	p-value	Correlation delta QT/conc	p-value
Tel 800 mg	216	0.01977	0.7727	-0.04472	0.5133	-0.12956	0.0573
Tel 1600	216	0.47502	0.0001	0.42994	0.0001	0.01488	0.8279
Clarith	216	0.27211	0.0001	0.26776	0.0001	0.11391	0.0949

Appendix B.3.4 faxed 9-19-00

**There were statistically significant correlations for changes in QTc (and QTf) interval and blood concentration for telithromycin 1600 mg and clarithromycin.**

Attached figures show the relationship between changes in QTc and blood concentration and changes in QT and blood concentration for low and high doses of telithromycin as well as for clarithromycin.

Outliers

Examining outliers in this very small sample size is not very informative. However, while there were no patients with a QTc ≥ 500 msec, there were 2 female patients (telithromycin 800 mg and 1600 mg) with QTc ≥ 470 msec and 1 male patient (clarithromycin) with QTc ≥ 450 msec.

Holter monitoring reports

While there were reports of abnormalities, particularly episodic abnormal heart rates and rhythms that are not unexpected in this diseased population, there were no reports of TdP.

Serious adverse events

There was 1 report of nausea, diarrhea, and syncope in patient #19 taking telithromycin 1600 mg. The holter monitor recorded an episode of sinus bradycardia. There was no evidence of QT prolongation or TdP. She recovered within 2 minutes of the event, but did not take the evening dose of medication (placebo). She remained in the study and received the other 3 treatment arms without incident.

cc

Orig.

HFD-110/NStockbridge

HFD-520/ADavidson/JCitron

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<sup>12</sup> Fridericia's formula

Figure 1 : Mean (± SD) HMR3647 plasma concentrations (ng/L) after single oral administration of HMR3647 (linear plot)

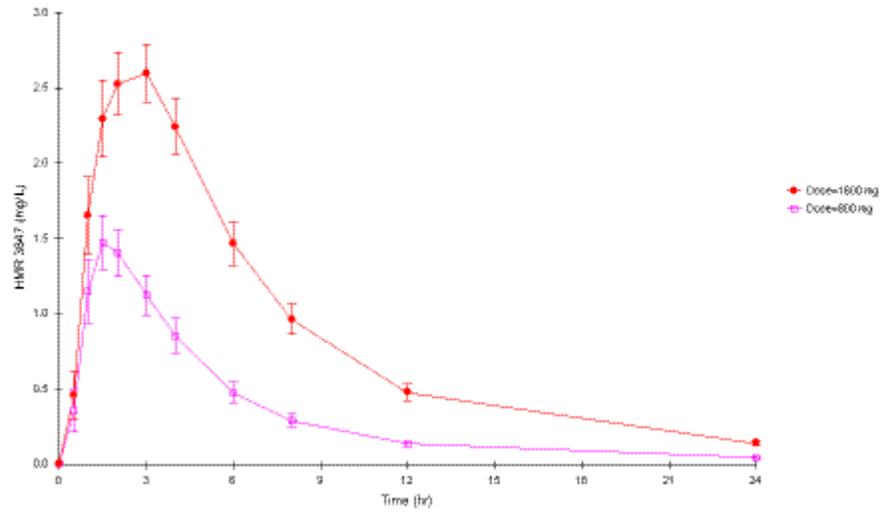


Figure 9: Evolution over time of delta HR (bpm) by treatment

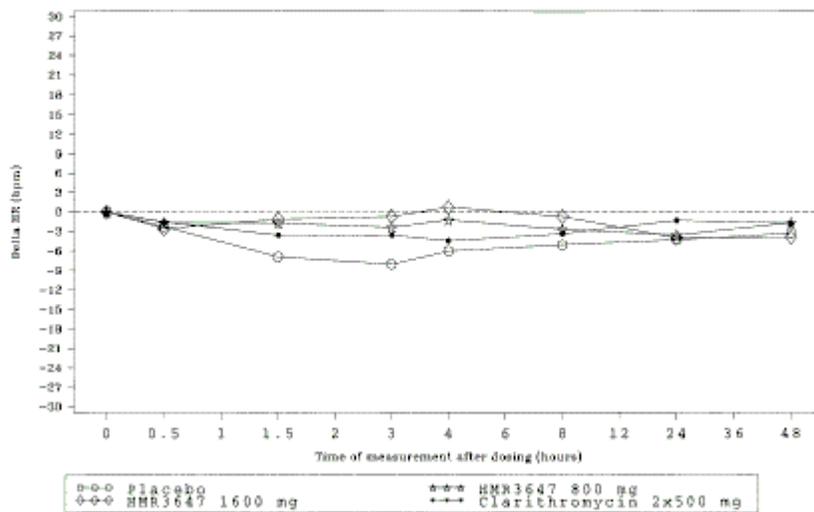


Figure 9 : Evolution over time of Delta QTc (ms) by treatment

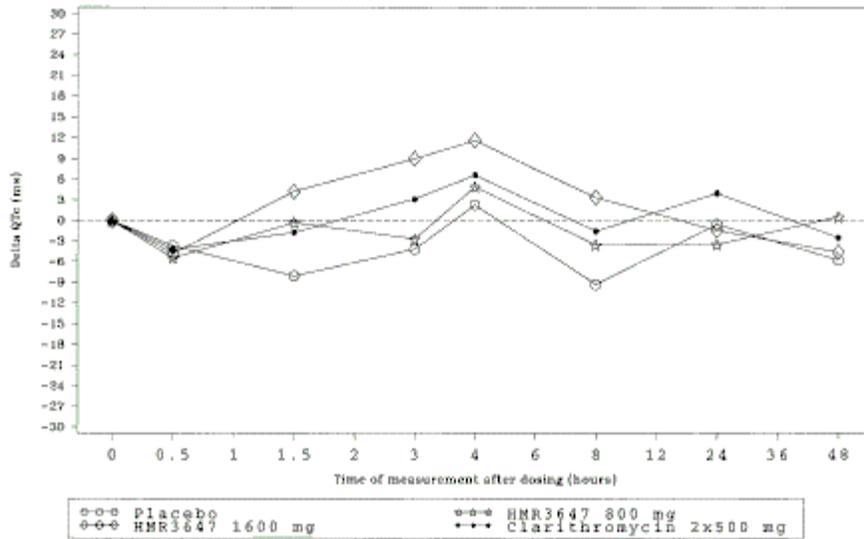


Figure 10 : HMR3647 800 mg - Predictability of Delta QTc (ms) from plasma concentration of HMR3647

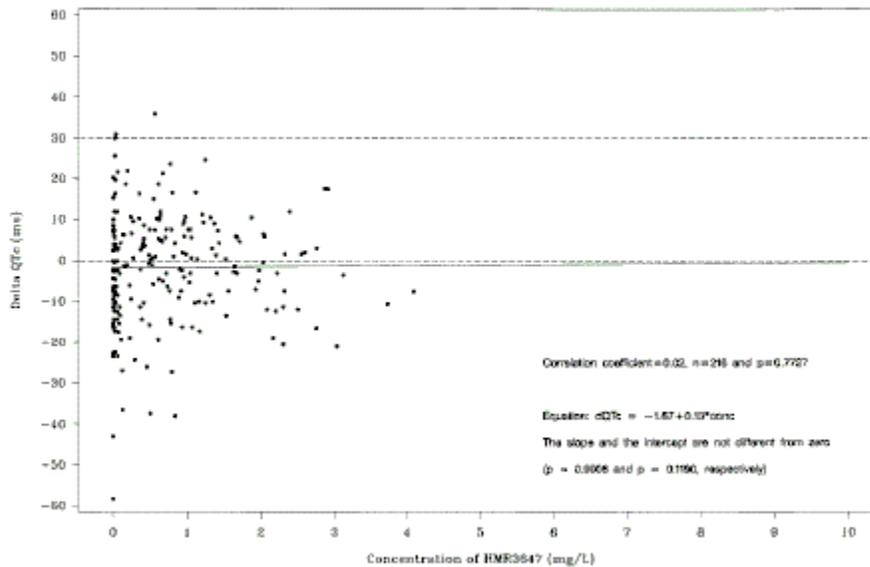
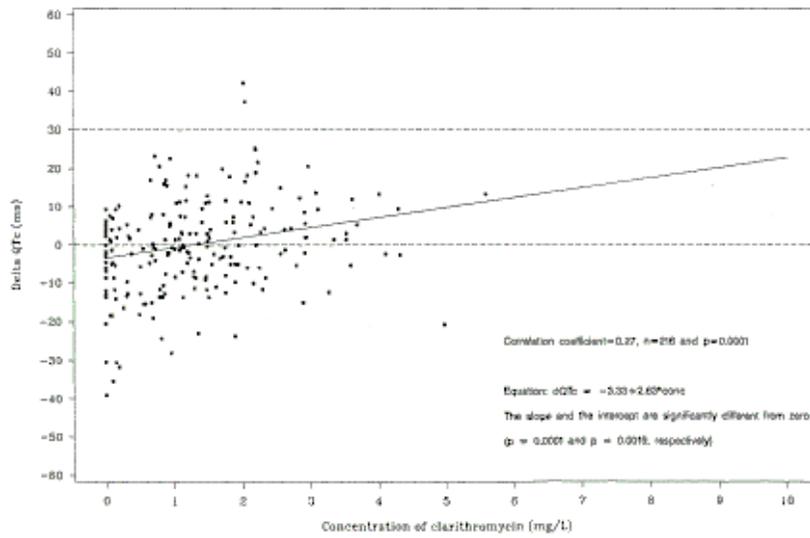


Figure 12 : Clarithromycin - Predictability of delta QTC (ms) from plasma concentration of clarithromycin



## B. Patient Narratives: Efficacy Section

### Brief Narratives of Subjects (3) with PRSP and ERSP who were classified as Failures:

- Subject 6051091:** 78-year old female with history of hypertension, anxiety, malnutrition, gastroesophageal reflux, and bilateral deafness was hospitalized on February 3, 1999 for moderately severe CAP. Pretherapy chest X-ray showed unilateral left multiple lobar consolidation. On visit 1, mouth mycosis was reported as a nonserious adverse event and treated locally with miconazole. The local laboratory isolated *S. pneumoniae*, *Haemophilus influenzae* (negative beta-lactamase assay) and *Moraxella catarrhalis*, all susceptible to telithromycin, from a bronchial aspirate sample taken on the same day of enrollment. Blood culture was obtained which isolated *S. pneumoniae* susceptible to telithromycin. The central lab identified *S. pneumoniae* susceptible to telithromycin (MIC 0.03 mg/L), and resistant to penicillin G (MIC 2 mg/L) and resistant to erythromycin (MIC >32 mg/L). The Fine category calculated a posteriori was III. WBC count was 10,280/mm<sup>3</sup>. Telithromycin was prescribed for 10 days. The MIC determination at the central lab, performed a posteriori, isolated *S. pneumoniae* from BAL with same pattern of susceptibility as the baseline blood sample (the MIC values found were very similar) and *H. influenzae* susceptible to telithromycin (MIC 1.0 mg/L), no data for ampicillin were recorded. The central lab identified *M. catarrhalis* susceptible to telithromycin (MIC 0.12 mg/L) and resistant to amoxicillin in the baseline sputum sample. On Visit 2, the pneumonia-related signs and symptoms had improved but the chest X-ray findings were reported as unchanged, *Citrobacter freundii* was isolated from sputum culture and considered as colonization by the investigator. On Visit 3, pneumonia-related signs and symptoms and chest X-ray findings had improved. Repeat blood culture was sterile. Fever (38.9°C-oral) and leukocytosis (WBC count 13,320/mm<sup>3</sup>) were noted during that visit. A urine culture was obtained which grew *Staphylococcus aureus*. Patient was administered amikacin and piperacillin on day 15 (5 days after completion of a 10-day course of telithromycin) for six days; then vancomycin was administered on day 16 for 5 days. After the courses of amikacin, piperacillin and vancomycin, pristnamycin was administered for six additional days. On Visit 4, the patient's clinical status was reported as improved and discharged from the hospital. The clinical outcome at TOC visit was assessed as Failure due to the requirement for additional antibiotics to treat pneumonia and urinary tract infection. At late posttherapy visit (LPT), patient developed another respiratory infection and suspicion of pulmonary embolism, which required another hospitalization. Patient received ofloxacin for ten days. The clinical outcome at LPT was considered failure. Bacteriological outcomes were unsatisfactory at TOC and LPT with presumed persistence for all three pathogens.
- Subject # 1002/027:** A 71 year old woman with a history of chronic obstructive pulmonary disease (since 1990), coronary artery disease (since 1994), dorsal scoliosis, and surgical intervention for squamous carcinoma right cheek (1994), was enrolled in the study on September 14, 1998, with moderately severe CAP. On the same day, the subject was admitted at entry to a frail care nursing unit for the pneumonia, general care and meals. Pretherapy chest X-ray showed single lobe consolidation on the right side. Sputum samples contained  $\geq 25$  PMN and  $< 10$  SEC. Sputum cultures were positive for *S. pneumoniae* (susceptible to telithromycin [MIC: 0.03 mg/L] and resistant to amoxicillin [MIC: 2 mg/L], penicillin G [MIC: 2 mg/L], erythromycin A [MIC: 32 mg/L], clindamycin, cefuroxime and oxacillin), beta-lactamase positive *Haemophilus influenzae* (susceptible to telithromycin and cefuroxime [both MIC: 1 mg/L] and resistant to amoxicillin [MIC:16 mg/L]) and *Staphylococcus aureus* (susceptible to cefuroxime and oxacillin, but resistant in central laboratory [MIC : 2 mg/L and 32 mg/L respectively] and resistant to telithromycin [MIC: 0.12 mg/L], penicillin G and amoxicillin [MIC for both: 8 mg/L], , erythromycin A [MIC: 32 mg/L] and clindamycin. Central laboratory serological analysis, performed a posteriori, was negative for atypical infection. Telithromycin was prescribed for 10 days and the first dose was administered on September 14, 1998. The subject was also noted to be hypotensive at this visit (BP: 95/70 mm Hg). On September 15, 1998 (D2), the subject's clinical condition worsened (severe lobar pneumonia,

with associated hypotension, cyanosis and altered mental state that was not related to study medication). This was reported as a serious adverse event because it was considered medically important and prolonged hospitalization. No beds were available in either an intensive care unit or state hospital. On September 15, 1998, intravenous gentamicin (80 mg x 2) and Rocephin (1 g x 1) were started in view of the bacteriological results and the deterioration of the subject. The clinical outcome on study medication was considered to be failure because of the requirement for additional antibiotics. On September 16, 1998 (D 3), severe multiorgan failure was reported as a serious adverse event not related to study medication. The event had sign and symptoms of circulatory failure, kidney failure and respiratory failure. The subject remained in a frail care nursing unit, as no beds had become available in the state hospital. Right lung sounds had improved from the previous day. On the morning of that day, the subject responded verbally and took food by mouth. However, in the afternoon, the subject developed oliguria and edema of the legs and was treated with furosemide (80 mg) i.v. and oxygen. There was no response to the treatment. At 23.00h on the same day, the subject's condition deteriorated. Urinary output was 60 mL/10 h and the subject developed generalized and pulmonary edema. Cyanosis was present even on oxygen treatment and patient was reported as still hypotensive. Furosemide treatment was given without response and the subject died at 02.00h on September 17, 1998 (Day 4). The subject had not received any study medication on that day. The cause of death was reported as multiorgan failure. No autopsy was performed. ECG data: On September 14, 1998 (D 1), the pretherapy/entry ECG showed a QTc value of 324.7 msec (Bazett) and 278.1 msec (Fridericia), with sinus tachycardia and an atrial flutter with 2<sup>nd</sup> degree block. No post baseline ECG data was available. Adverse events: serious lobar pneumonia (severe, not related), from September 15, 1998; serious multi-organ failure leading to death (severe, not related) from September 16 to 17, 1998. Concomitant medication: tilazem (60 mg x 3) p.o., for coronary artery disease, from 1994 to September 15, 1998; bisolvon linctus (10 mL x 3) p.o., for cough, from September 14 to 16, 1998; Lasix (80 mg stat) i.v., for edema, on September 16, 1998; ringer lactate (1000 ml x 2) i.v., for hypotension and circulatory failure, from September 15 to 17, 1998; Rocephin (1 g x 1) i.v., for lobar pneumonia, from September 15 to 16, 1998; gentamicin (80 mg x 2) i.v., for lobar pneumonia, from September 15 to 16, 1998. Investigator's assessment of SAE: lobar pneumonia and multi-organ failure not associated with study medication.

Applicant's comment on SAE: lobar pneumonia and multi-organ failure not related to study medication.

Investigator's assessment of event: severe lobar pneumonia and severe multi-organ failure not related to study medication. Clinical outcome (Investigator's assessment): failure at TOC and LPT. Bacteriological outcome was unsatisfactory at TOC and LPT (presumed persistence for all three pathogens).

- **Subject #0369/105:** 37 year-old female, without major medical history, non-smoker, enrolled into the study on Sept. 7, 1999, completed a 5-day course of telithromycin (7-10 days) for CAP. Investigator assessment of current infection was moderate-Fine category II. Baseline chest-X-ray showed dense pneumonic changes in the posterior segment of right lower lobe and also in the adjacent lung segments and around the hilum with bronchial wall thickening. Baseline (Visit 1) sputum grew *S. pneumoniae* resistant to penicillin G and erythromycin. Blood culture was positive for *S. pneumoniae* resistant to penicillin G (MIC 2.000 µg/mL) and erythromycin (MIC=4.000 µg/mL). No sputum was obtained from the patient on Visit 2 (Day 3). Instead a repeat blood culture was obtained which was still positive for *S. pneumoniae* resistant to penicillin G and erythromycin. On Visit 3, patient's pneumonia signs and symptoms were not improving, so the investigator stopped the study medication and changed antibiotic treatment to penicillin G 1.2 million units every 6 hours I.V. and cefoxitin 1 gram every 8 hours. Patient was withdrawn from the study due to failure to respond to study drug.

Investigator assessment: Clinical failure and bacteriologic persistence at EOT visit.

### C. Patient Narratives: Serious Hepatic Adverse Events

The 4 patients experiencing serious hepatic Adverse Events (AEs) are identified in Table AC1. Narratives for the 4 patients are provided in the sections that follow.

**Table AC1. Serious Hepatic Adverse Events for Subjects in Phase III Clinical Studies**

Coded Term	Indication and Study No.	Subject No.	Treatment
<b>Controlled Studies</b>			
Liver damage	CAP 3006	0060/039	Ketek 800 mg po qd x 10 d
Liver damage	TONS/PHAR 3008	0259/005	Ketek 800 mg po qd x 5 d
Jaundice	CAP 3006	0425/011	Clarithromycin 500 mg po BID x 10 d
<b>Uncontrolled Studies</b>			
Hepatitis	CAP 3000	502/1069	Ketek 3647 800 mg po qd x 7-10 d

Adapted from applicant's table from 8:v251:p195

**Subject 0060/039 from Study 3006 (CAP, telithromycin):** A 76-year-old female cigarette smoker with a history of hypercholesterolemia since 1992, hyperuricemia since 1997, s/p amygdectomy (1928), was enrolled in Study 3006 and started on telithromycin 800 mg po qd on 11 Feb 1999 for treatment of community-acquired pneumonia. Sputum culture at pretherapy/entry yielded group A streptococci. During study she was also maintained on her other chronically used medications, pravachol (pravastatin sodium) 20 mg po qd for hyperlipidemia (since 1997) and allopurinol 200 mg po qd for hyperuricemia (since 1997). On 15 Feb 1999, she returned for Visit 2 and was noted to be clinically improved. Also noted during Visit 2 was asymptomatic elevation of her AST, ALT, and alkaline phosphatase. This led to discontinuation of telithromycin on 16 Feb 1999, and withdrawal from the study on 17 Feb 1999. Therapy was changed to Cefitin (cefuroxime axetil) 500 mg twice daily on 16 Feb 1999. Selected laboratory test results are presented in the following table.

Laboratory analyte	Day 1 11 Feb 99	Day 5 15 Feb 99	Day 7 17 Feb 99	Day 12 22 Feb 99
AST/SGOT (NR 9-34 U/L)	37	295	66	24
ALT/SGPT (NR 6-32 U/L)	24	418	200	64
Alk phos (NR 35-115 U/L)	79	146	131	–
T. Bilirubin (NR 3-21 mmol/L)	17	22	10	–
Eosinophils (NR < 570 cells/10 <sup>6</sup> L)	30	190	110	–

NR= normal range

Both the investigator and the applicant assessed the “liver injury” (verbatim term) (coded as “liver damage”) as possibly related to telithromycin. At the time of the elevated transaminases (15 Feb 1999) the patient reported mild diarrhea and associated abdominal pain. Her event resolved without sequelae.

**Subject 0259/005 from Study 3008 (Tonsillopharyngitis, telithromycin):** A 19-year-old white male with no significant past medical history experienced liver damage (verbatim term “drug-induced hepatic toxicity”) characterized by increased AST (SGOT), ALT (SGPT), and lactate dehydrogenase (LDH) on 10 Apr 1999 after treatment with telithromycin for tonsillitis. The patient was diagnosed with tonsillopharyngitis (with a throat culture subsequently yielding group A  $\beta$ -hemolytic streptococci) and was enrolled in Study 3008. He began his course of

telithromycin 800 mg po qd on 29 March 1999. He completed a 10-day course of telithromycin on 7 April 1999. On 10 April 1999, at the End of Therapy visit, subject 0259/005 was noted to have elevations in his transaminases (AST = 273 U/L and ALT 124 U/L). The subject had no associated signs or symptoms, but stated that he had ingested an excessive amount of alcohol during the previous evening. By 18 April 1999, his AST, ALT and LDH had decreased to near baseline values and by 28 April 1999 had returned to baseline values. Relevant laboratory values for subject 0259/005 are presented in the following table.

Laboratory Analyte	29 Mar 99 Pretherapy /entry	1 Apr 99 On-therapy	10 Apr 99 End of therapy	18 Apr 99 TOC	28 Apr 99 LPT
AST/SGOT (NR=11-36 U/L)	23	ND	273	29	19
ALT/SGPT (NR=6-43 U/L)	27	ND	124	44	28
Alk. Phos. (NR<250 U/L)	93	ND	79	79	79
T. Bilirubin NR= 3-21 µmol/L	21	ND	14	22	15
SGGT(NR= 10-61 U/L)	31	ND	37	39	35
LDH (NR= 53-234 U/L)	192	ND	592	133	108
Eosinophils (NR < 570 cells/10 <sup>6</sup> L)	180	ND	40	ND	ND

ND = not done, NR = normal range, TOC = posttherapy/test of cure, LPT = late posttherapy

The investigator considered the observed transaminase elevation as possibly related to study medication but suspected the patient's reported excessive alcohol intake as the most probable cause of the patient's elevated AST, ALT, and LDH. The applicant noted that it is not known if the subject has early alcoholic liver disease or a history of chronic alcohol abuse.

Review of the patient's concomitant medications reveals that the patient took a dose of zinc-echinacea (amount of dose unknown) on 29 March 1999 and 17 April 1999 and a dose of Vitamin C (amount of dose unknown) on 28 March 1999 and 18 April 1999.

**Subject 0425/011 from Study 3006 (CAP Clarithromycin):** A 61-year-old white male with a history of CHF treated with digoxin, alcoholism (1970 through 5/1999), smoking (1952 until May 1999), melena (5/1999), and s/p amygdectomy (1942) was enrolled in study 3006 and received clarithromycin 500 mg po bid from 05 August 1999 to 14 August 1999 for treatment of CAP. On 17 August 1999 the patient was noted to have an "icteric syndrome" (verbatim term) (coded term jaundice) with choluria (T. Bilirubin 103 µmol/L (NR 3-21 µmol/L), alkaline phosphatase (658 U/L) [NR <121 U/L] and GGT (457 U/L) [NR 7-74 U/L]). The subject was withdrawn from the study on 17 Aug 1999 because he "no longer wished to continue". On 19 Aug 1999, a "disseminated neoplasm was found, with associated lung nodule, adrenal nodule, Douglas space nodule." increased The patient's case report forms note that his primary care physician and oncologist performed an abdominal ultrasound and a CT scan of the chest and abdomen. These studies revealed the anatomic findings described above. A renal or hepatic source for the subject's apparent malignancy was suspected by the patient's physicians.

Laboratory Analyte	5 Aug 99 Pretherapy /entry	9 Aug 99 On-therapy	17 Aug 99 End of Therapy
AST/SGOT (NR<45 U/L)	21	14	41
ALT/SGPT (NR<48 U/L)	18	20	40
Alk. Phos. (NR<121 U/L)	89	136	658
T. Bilirubin (NR= 3-21 µmol/L)	5	5	103
Eosinophils (NR < 560 cells/10 <sup>6</sup> L)	320	0	830

NR = normal range

The investigator assessed the icteric syndrome and disseminated neoplasm as not related to study medication, but rather attributed the event to “underlying/concomitant illness”. The events had not resolved at the time of the report, but further follow-up within the study was not deemed necessary by the investigator. Further care of the patient for his suspected disseminated neoplasm was transferred to his primary care physician and oncologist.

**Subject 502/1069 from Study 3000 (CAP telithromycin):** A 53-year-old white male with a history of asthma (since 1975) and diabetes mellitus (since 1982) was enrolled in Study 3000 at center 502 in Tampere, Finland on 02 Feb 1999 with community-acquired pneumonia (CAP). He received telithromycin from 3 Feb 1999 through 12 Feb 1999, with a clinical outcome of cure. The investigator noted that the patient was feeling “quite well” after completing therapy for his CAP. Three days after the last dose (15 Feb 1999), he reported exposure to family members suffering from a gastroenteritis-like illness. Jaundice was not noted in the affected family members. Four days after his last dose of telithromycin (16 Feb 1999) he developed an acute illness with symptoms of fever, vomiting, and diarrhea. The vomiting and diarrhea resolved, but at visit 4 (22 Feb 1999) he still complained of fever (temperature 38.1°C tympanic; reportedly the patient had fevers to 39°C). At visit 4 he had an elevated ALT of 354 U/L (local laboratory). Of note is that the patient’s ALT at baseline was elevated (81 IU/L [NR 0-49]) when tested at the local laboratory and when tested at the central laboratory (69 IU/L [NR 6-43 IU/L]). On 25 Feb 1999, three days after visit 4, his ALT was 1529 U/L (local laboratory). The subject was hospitalized with a diagnosis of hepatitis. Serologic testing for “Hepatitis A, B, and C was negative.” EBV and CMV serologies were positive for IgG consistent with past infection. A percutaneous liver biopsy was performed on 02 March 1999. The pathologic material was reviewed at the Armed Forces Institute of Pathology (AFIP). The AFIP reading for this biopsy was: *Recent zone 3 (“centrilobular”) necrosis with numerous tissue eosinophils, strongly suggestive of drug-induced liver disease.* The patient also had an abdominal ultrasound examination with findings consistent with fatty liver. The subject was discharged from the hospital on 10 March 1999. The table below shows the patient’s laboratory values for selected analytes.

Lab	Date*																		
	Laboratory Analyte	2/2	2/5	2/15	2/22	2/25	2/26	2/27	2/28	3/1	3/2	3/3	3/5	3/8	3/10	3/15	3/16	4/9	5/7
<b>Local Laboratory</b>																			
AST (NR<49 U/L)	38	-	-	-	-	<b>170</b>	-	-	-	-	-	-	-	-	-	-	-	-	-
ALT (NR<49 U/L)	<b>81</b>	-	-	<b>354</b>	<b>1529</b>	<b>947</b>	<b>694</b>	<b>550</b>	<b>454</b>	<b>456</b>	<b>463</b>	<b>519</b>	<b>518</b>	<b>362</b>	<b>130</b>	-	<b>53</b>	<b>53</b>	
Alk Phos (NR 60-275 U/L)	-	-	-	-	169	164	194	260	242	259	-	-	261	251	-	-	169	28	
T. Bilirubin (NR 2-20 mmol/L)	9	-	-	-	<b>29</b>	<b>31</b>	<b>26</b>	<b>24</b>	18	18	-	-	15	13	-	-	16	16	
<b>Central Laboratory</b>																			
AST (NR 11-36 U/L)	36	29	35	<b>167</b>	-	-	-	-	-	-	-	-	-	<b>193</b>	-	-	-	-	-
ALT (NR 6-43 U/L)	<b>69</b>	<b>69</b>	<b>69</b>	<b>280</b>	-	-	-	-	-	-	-	-	-	<b>463</b>	-	-	-	-	-
Alk Phos (NR 31-110 U/L)	78	73	74	60	-	-	-	-	-	-	-	-	-	104	-	-	-	-	-
T. Bilirubin (NR 3-21 mmol/L)	7	6	9	10	-	-	-	-	-	-	-	-	-	10	-	-	-	-	-
<b>Other Lab Values from the Local Laboratory</b>																			
INR for PT (NR <1.20)	0.97	0.95	0.90	-	-	-	-	-	-	-	-	-	-	1.04	-	-	-	-	-
Absol. Eosinophils (cells/ $\mu$ L)†	<b>774</b>	-	-	<b>960</b>	<b>1062</b>	-	-	-	-	-	-	-	<b>1729</b>	<b>2856</b>	-	-	-	-	-
Hemoglobin (NR 13.0-18.0 g/dL)	14.4	-	-	14.9	<b>12.5</b>	<b>12.0</b>	<b>11.9</b>	<b>11.2</b>	<b>11.4</b>	<b>11.4</b>	<b>10.6</b>	-	-	-	-	<b>12.9</b>	-	-	
ESR (NR 0-20)	<b>87</b>	<b>92</b>	17	-	-	-	-	-	-	-	-	-	-	<b>69</b>	-	-	-	-	-
C-Reactive Protein (mg/L)	-	-	-	<b>68</b>	<b>170</b>	-	-	-	-	-	-	-	-	-	-	-	-	-	-
<b>Other Lab Values from the Central Laboratory</b>																			
Albumin (NR 33-49)	<b>31</b>	33	36	36	-	-	-	-	-	-	-	-	-	<b>31</b>	-	-	-	-	-
Total Protein (NR 61-84)	67	74	71	70	-	-	-	-	-	-	-	-	-	74	-	-	-	-	-
Absolute Eosinophils (NR 0.00-0.57 GI/L)	-	<b>0.65</b>	0.00	<b>0.78</b>	-	-	-	-	-	-	-	-	-	<b>2.54</b>	-	-	-	-	-
C-React. Prot. (NR 0-8mg/L)	<b>120</b>	<b>77</b>	5	<b>66</b>	-	-	-	-	-	-	-	-	-	8	-	-	-	-	-

NR = normal range  
 Lab values shown in Bold type are outside of the normal range  
 Central laboratory lab values are derived from the applicant's LAB\_MEGA.xpt file for Study 3000. Normal ranges for central laboratory lab values are derived from laboratory reports and summaries whenever available.  
 \*All dates are from the year 1999.  
 †Normal range for absolute eosinophils is typically considered as < 500 cells/uL  
 Normal ranges are provided whenever available

The patient's previous and concomitant medications as listed in the case report forms included:

- Fluticasone 2 puffs (1000  $\mu$ g) inhaled bid for asthma which he had been taking since 1995
- Salbutamol inhaler used prn for asthma since 1979
- Atrovent 1 mL inhaled 5 x a day from 01 March 1999 to 10 March 1999
- Nasonex aerosol 200  $\mu$ g nasal inhalation "x 1" started on January 1999
- Calcichew one 500 mg tablet "x1" started on 04 March 1999 for hypocalcemia
- Acetaminophen 500 mg tablets orally, frequency unknown started on 15 February 1999 to an unknown subsequent date in February 1999. The investigator notes in the previous and concomitant medication case report forms describe the acetaminophen use as "all together 6 tablets in one week". In the Serious adverse event CRF, the investigator notes "Pat. has also taken paracetamol 6 tbl's for treatment of fever (500mg/tab.)"

The patient had not taken any herbal products of any kind.

Subject 1069 also had urinalyses performed on 02 February 1999, 05 February 1999, and 15 February 1999; all were negative for proteinuria, glycosuria, blood, and WBCs. There are no

results for subsequent urinalyses (from the time period when subject 1069's transaminases were known to be elevated).

Additional diagnostic evaluations included serologic studies that were negative for HIV, *Toxoplasma*, "F-para-O", Tularemia (x2), *Legionella*, *Brucella*, *Mycoplasma*, *Coxiella burnetii*, *Fasciola hepatica*, and *Toxocara canis*. Serologic testing for EBV, CMV, and HSV was "low positive" with a negative IgM class antibody consistent with previous infection. He also had serologic testing for Ebola virus which returned with results of "low-positive", the significance of which is unclear. Stool examination for parasites was negative. The patient also had the following additional results from testing performed on 07 May 1999: CH50=68 U/mL; IgA=3.1g/L, IgG=12.7 g/L, (IgG1=4.53, IgG2=3.93, IgG4=3.34) [laboratory normal ranges not provided, typical normal ranges;<sup>13, 14</sup> CH50 (63-145 U/mL); IgA (0.5-3.5 g/L); IgG (5.0-12.0 g/L)].

Additional information from the patient's medical history revealed that prior determinations of ALT had shown "ALT was slightly increased up to 58 U/L in September 98 and to 51 U/L in October 98" [normal ranges not provided]. Prior to the episode of February 1999 described above, there was no known prior history of liver or autoimmune disease. The patient had no prior history of a liver biopsy or other diagnostic testing prior to the biopsy of 02 March 1999 and tests described above.

Additional history obtained from the patient related that he had previously been treated with macrolides: in August of 1998 he was treated with roxithromycin for 10 days. The patient was treated with azithromycin for "respiratory signs and sinusitis" on 13 October 1998 and 22 December 1998 (dosage and duration unknown). ALT was not measured during these courses of macrolide therapy.

The patient underwent a routine check-up on 12 November 1999 and was found to have an ALT=1331 U/L, T.Bili=25 umol/L (NR <20 umol/L). Eosinophilia was not present. Serologic tests for hepatitis A antibodies, HbsAg, Hbc antibodies, and HCV antibodies, were negative. EBV and CMV serology results were consistent with old inactive infection. Antinuclear and anti-mitochondrial antibodies were negative. A serology for anti-smooth muscle antibodies yielded a titer of 1:1000. Serum immunoglobulin levels were IgG=18.1 g/L, IgA=5.48 g/L, IgM=2.07 g/L, IgE=471 kU/L [normal range not provided, typical normal ranges for IgA and IgG as noted, for IgM (0.3-2.3 g/L)<sup>13</sup>; IgE (0-380 kU/L<sup>15</sup>)]. An ultrasound examination of the liver was reported as normal. The only medication that the patient reported taking was acetaminophen for headache. A percutaneous liver biopsy was performed on 27 December 1999. The liver biopsy material was reviewed at the Armed Forces Institute of Pathology. The AFIP reading on the liver biopsy was: *chronic hepatitis, probably autoimmune, with marked activity and extensive bridging fibrosis*. His ALT reportedly normalized rapidly and was 43 U/L on 03 February 2000.

<sup>13</sup> System International (SI) units table. JAMA 1996;276:24-26.

<sup>14</sup> Kratz A, Lewandrowski KB. Normal reference laboratory values. NEJM 1998;339(15):1063-1072.

<sup>15</sup> Elin RJ. Reference intervals and laboratory values (Ch. 523). In *Cecil Textbook of Medicine*. Eds. Goldman L, Bennett JC. 21<sup>st</sup> Ed, Vol. 2. W.B. Saunders Co. Philadelphia. 2000. pp. 2299-2308.

On 19 July 2000, the patient reportedly had normal LFTs, a negative ANA, and negative serologic tests for anti-smooth muscle, anti-microsomal, and anti-thyroglobulin antibodies. At a subsequent follow-up visit on December 14, 2000, follow-up information notes that the patient's "LFTs normalized."

**D. Review and Evaluation of Pharmacology and Toxicology Data  
Division of Anti-Infective Drug Products, HFD-520**

**NDA 21144**

**Reviewer:** Terry S. Peters, D.V.M.

**Number of Volumes:** 27

**Date Review Started:** 2/22/01

**Date 1<sup>ST</sup> Draft Completed:** 3/16/01

**KEY WORDS:** Ketek®, Biaxin®, telithromycin, clarithromycin

**Applicant:** Aventis

**Manufacturer:** Abbott Pharmaceuticals, Abbott Park, IL

**Relevant INDs/NDAs/DMFs:** Biaxin, NDA 50662

**Introduction and Drug History:** The purpose of this review is to compare and contrast the preclinical findings for clarithromycin with those for telithromycin with emphasis on cardiovascular and hepatic effects. Sources for this information include the original submissions to all INDs and NDAs for clarithromycin as well as telithromycin.

Metabolism of clarithromycin: Three principal pathways:

- 1) N-demethylation of the dimethylamino group on the desosamine sugar to produce N-desmethylclarithromycin
- 2) Hydroxylation at the 14 position of the erythromolide ring to produce 14-hydroxylclarithromycin
- 3) Hydrolytic cleavage of the cladinose sugar to produce descladinosylclarithromycin

Both N-demethylation and hydroxylation are mediated by the P450 system. Hydroxylation of clarithromycin is stereo-specific. The applicant contends that the monkey is the best animal model for clarithromycin as they use the 14-hydroxylation as the major route of biotransformation, as does the human. Hydrolysis of the cladinose sugar is the primary pathway in the rat but only a minor pathway in the human.

Metabolism of telithromycin: Three principal pathways:

- 1) RU 76363- Loss of aryl rings
- 2) RU 72365- N-desmethyl desosamine derivative
- 3) RU 76584- N-oxide pyridine

From Dr. J. Zheng's review of human metabolism of HMR 3647:

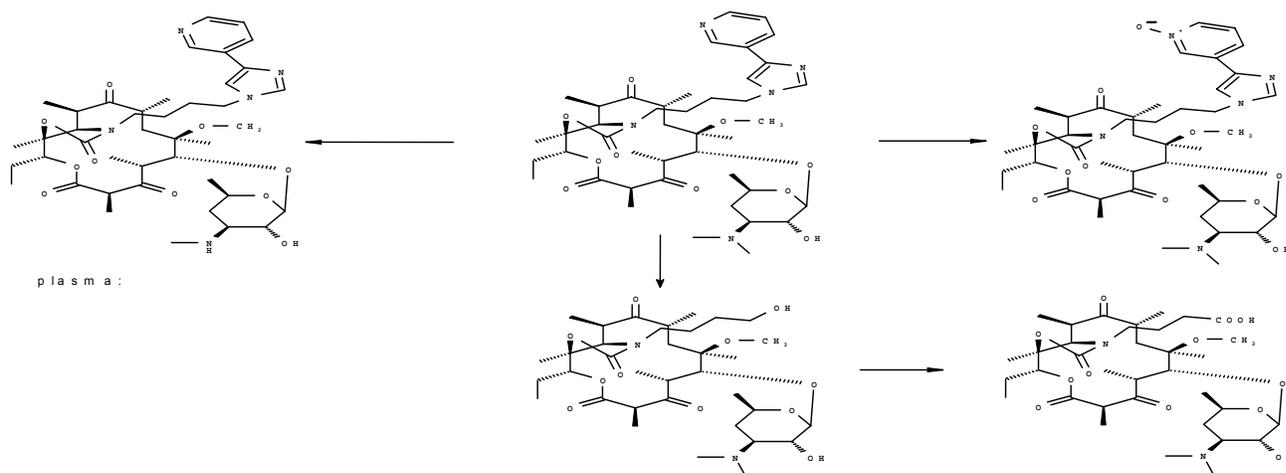
Figure 5. Metabolic pathway of HMR 3647 in human

RU 72365	HMR 3647	RU 76584
plasma : 2.97%*		Plasma: 2.03*

urine : <0.1% dose  
 feces : < 1% dose

urine : <0.1% dose  
 feces : 2% dose

urine : 12% dose  
 urine : 0.1% dose  
 feces : 20% dose



plasma : 2.22%\*  
 urine : 0.6% dose

\* : metabolite AUC / HMR 3647 AUC (%)

feces: 11.5% dose

**RU 76363**  
 plasma : 12.6%\*

urine : 1.2% dose

feces : 2.7% dose

How is HMR 3647 metabolized in humans? How is HMR 3647 excreted?  
 1. The metabolism pathway and recovered radioactivity after single dose of HMR 3647 are shown in

The recovered radioactivity in urine and feces in % of dose

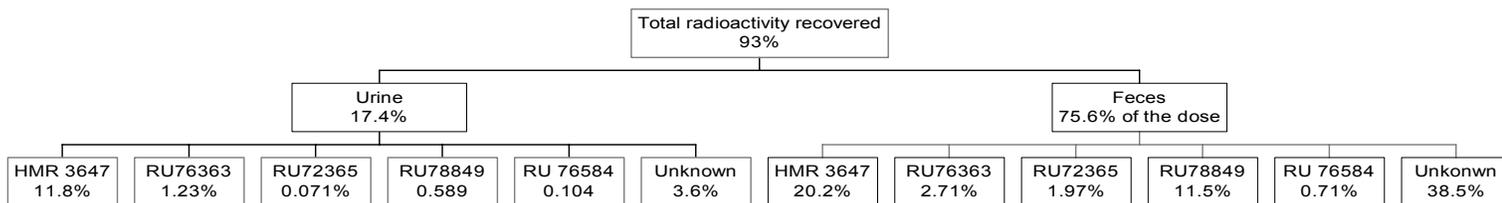


figure 5 and the chart.

2. In feces, a total of 76% of ingested dose is recovered. The most abundant compound was HMR 3647 and its  $\alpha$ -epimer, comprising 29% of the radioactivity recovered in feces (22% of ingested dose). The remaining characterized compounds were RU 76363 (3.86% the radioactivity recovered in the feces), RU 78849 (16.5%), RU 76584 (1.0%), and RU 72365 (2.79%). The remaining radioactivity in feces was comprised of several other metabolites, background, and individual peaks below 0.5% of dose. Therefore, only about 53% of radioactivity recovered in feces had structure identified and 47% of the radioactivity unknown.
3. In urine, 17% of ingested dose is recovered. The most abundant compound in urine was HMR 3647 and its  $\alpha$ -epimer, comprising 69% of the radioactivity recovered in urine (11.7% of the ingested dose). The remaining characterized compounds were the same as those found in feces, RU 76363, RU 78849, RU 76584, and RU 72365 comprising 7.28%, 3.51%, 0.63%, and 0.41% of the radioactivity recovered in the urine, respectively. The remaining radioactivity in urine was comprised of several other metabolites, background, and individual peaks below 0.05% of dose. Therefore, about 81% of radioactivity recovered in urine had structure identified with 19% of the radioactivity unknown.
4. HMR 3647 and its four main metabolites were also found in plasma. The main circulating compound in plasma was HMR 3647, with its mean total AUC representing 57% of total radioactivity AUC. The next most prevalent compound was RU 76363 whose mean AUC represented 12.6% that of HMR 3647. The three other metabolites were also quantitated in plasma however each of their mean AUC's represented less than 3% the AUC of HMR 3647.
5. Metabolism is considered the principle route of elimination of HMR 3647. Only 34% of dosed HMR 3647 was recovered as unchanged compound (22% in feces, 12% in urine)

In vivo, the parent drug represented the major portion. The compound after loss of aryl rings represented 13% of the circulating metabolite in man but is present at very low levels in dogs and rats. In monkeys, this metabolite represents ~1.4x the parent levels. In rat and human liver microsome studies, CYP3A1/3A2 was the major pathway for the rat and CYP3A4/3A5 was the major pathway for humans with CYP1A and CYP2B6 contributing. Protein binding was variable between species: 90, 60, 45, 50, and 70% in mouse, rat, dog, monkey and man, respectively.

#### **Clarithromycin studies reviewed within this submission:**

- 1) Chronic toxicity in monkeys at Huntingdon Research, Cambridgeshire, U.K.
- 2) Subacute toxicity in Wistar rats at Taisho Pharmaceutical, Japan
- 3) Effect on liver metabolizing enzymes in rats at Taisho Pharmaceutical, Japan
- 4) Effect on cytochrome P450 in rats at D. Passayre, at hospital laboratory, Clichy, France
- 5) Effect on liver in vitro at Taisho Pharmaceutical, Japan
- 6) Six Week Oral Toxicology Study in the Rat at Roussel Uclaf, Romainville, France
- 7) 30 Day Oral Toxicity Study in the Rat at Roussel Uclaf, Romainville, France
- 8) Chronic toxicity in rats at Taisho Pharmaceutical, Japan
- 9) Subacute oral toxicity study of TE-031 in rats for 28 days at Taisho Pharmaceutical, Japan.
- 10) Chronic toxicity study of TE-031 in oral administration to dogs for 6 months, Taisho Pharmaceutical, Japan.
- 11) Subacute oral toxicity study of TE-031 in rats for 28 days at Taisho Pharmaceutical, Japan
- 12) Subacute oral toxicity of TE-031 in dogs for 28 days at Taisho Pharmaceutical, Japan
- 13) Three month toxicity study of TE-031 administered orally to dogs with one month interim kill at Abbott Laboratories, Abbott Park, IL
- 14) TE-031 Toxicity to Cynomolgus monkeys by repeated oral administration over 28 days at Huntingdon Research Center, UK
- 15) Six week toxicity of Abbott 56268 administered orally to immature rats at Abbott Laboratories, Abbott Park, IL
- 16) 28 Day oral toxicity of TE-031 and erythromycins in rats at Taisho Pharmaceutical, Japan

**TOXICOLOGY**

1) Chronic toxicity study in *M. fascicularis* performed at Huntingdon Research, Cambridgeshire, U.K. This study was initiated on 10/16/86. Doses: 0, 25, 50 or 100 mg/kg/d for 26 weeks by gavage suspended in 5% gum arabic. Five or six monkeys/sex/group, aged 2-4 years at study initiation. One/control and high dose were assigned to recovery (4 weeks)

Results: Vomiting and salivation at all doses. Increased red cell fragility at high dose. Significant decreases in serum globulin at high dose. Significantly increased serum albumin (Week 25) in high dose. Increased liver and adrenal weights. No comment as to LFTs. Liver weights were significantly increased at 50 and 100 mg/kg/d.

Histopathology: Minimal cytoplasmic rarefaction of centrilobular hepatocytes in all high dose animals. All findings were reversible during recovery period (1 animal/sex from control and 100 mg/kg/d group for 26 weeks). No electron micrographic abnormalities were found. NOEL for this study was set at 50 mg/kg/d.

2) Subacute toxicity in Wistar rats at Taisho Pharmaceutical, Japan. Study was initiated on 3/22/86. Doses: 20, 100 or 200 mg/kg/d by gavage suspended in 5% gum arabic. Six female rats/group, aged 5 weeks at study initiation.

Results: Increased urinary volume, decreased urine specific gravity, increased urinary LDH, ALP (alkaline phosphatase) and NAG (N-acetyl- $\beta$ -glucosamidase) in all doses. At the high dose, increased relative kidney weight with mild degeneration of renal epithelial cells in collecting ducts. Decreased serum albumin, increased serum NAG, GGT in all doses.

3) Effect on liver metabolizing enzymes in rats at Taisho Pharmaceutical, Japan. Study was initiated on 10/16/86. Doses: 100 or 500 mg/kg/d of clarithromycin and 100 mg/kg/d phenobarbital by gavage suspended in 5% gum arabic. 6 male Wistar rats/group treated once/day for 1, 3, 7 or 14 days. Liver homogenate was evaluated for aniline hydroxylase, aminopyrine N-demethylase, UDP-glucuronyltransferase and cytochrome P450.

Results: 500 mg/kg/d clarithromycin elicited increased relative and absolute liver weights and increased P450 and cytochrome b5 at all time periods.

4) Effect on cytochrome P450 in rats at D. Passayre, at hospital laboratory, Clichy, France. Doses of dexamethasone at 50 mg/kg, macrolides (clarithromycin, roxithromycin, troleandomycin, erythromycin and erythromycin estolate) at 0.5 mmol/kg by gavage suspended in 5% gum arabic.

Results: Dexamethasone pre-treated rats showed increased P450-Fe complexes with all macrolides (clarithromycin=roxithromycin<erythromycin base<erythromycin estolate<troleandomycin).

Without pre-treatment, neither clarithromycin nor roxithromycin elicited P450 increases. All other macrolides elicited increased total P450 and P450-Fe complexes (erythromycin base<erythromycin estolate<<troleandomycin).

5) Effect on liver in vitro at Taisho Pharmaceutical, Japan. Study was initiated on 4/12/86. Test system was isolated hepatocytes from male Wistar rats. Doses of clarithromycin and its primary metabolite (M1) were  $10^{-4}$  to  $5 \times 10^{-5}$  M. Control drugs were erythromycin stearate and erythromycin estolate.

Results: Increased SGOT, SGPT and LDH were released at the highest concentration. The control macrolides elicited increases (erythromycin stearate<clarithromycin and M1<<erythromycin estolate).

6) Six Week Oral Toxicology Study in the Rat at Roussel Uclaf, Romainville, France. Study was initiated on 4/22/91. Doses of 400 or 1000 mg/kg/d in 10 male Sprague-Dawley OFA rats/dose by gavage. 2/10 rats died from the 400 mg/kg/d group and 8/10 rats died from the 1000 mg/kg/d group (2 survivors sacrificed on Day 10). Deaths were from Day 4-9.

Results: No significant clinical chemistry alterations including evaluation of ALT, AST and LDH. Moderate decrease in albumin. Marked increase in absolute and relative liver weight, moderate increase kidney weight (high dose).

Histopathology: Microvacuolar hepatic steatosis with/without necrosis at 1000 mg/kg/d. Renal lesions, more pronounced in the 400 mg/kg/d group (probably due to survival) included tubulonephritis. No degree of severity noted.

7) 30 Day Oral Toxicity Study in the Rat at Roussel Uclaf, Romainville, France. Study was initiated on 10/16/91. Doses of 600 or 800 mg/kg/d in 10 Sprague-Dawley OFA rats/dose by gavage. 8/10 died in the 600 mg/kg/d group and 10/10 from the high dose group.

Results: Increases in AST, ALT, leucine aminopeptidase, LDH and bilirubin in the surviving animals. Group means only are presented. Increases in 600 mg/kg/d animals were approximately 5x control values. No high dose animals were evaluated.

Histopathology: Diffuse microvacuolar steatosis with hepatocellular necrosis and increased lipid in Kupffer cells. Renal tubular and glomerular lipidosis with necrosis were found in most animals. No degree of severity is noted.

8) Chronic toxicity in rats at Taisho Pharmaceutical, Japan. Study was initiated on 4/15/85. 20 male and 27 female Wistar rats were administered 0, 1.6, 8, 40 or 200 mg/kg/d for 6 months by gavage. 7/sex from control and high dose groups were allowed a 63 day recovery period.

Results: There were no premature deaths. The 2 highest dose groups showed decreased rbc counts, decreased hematocrit and increased red cell parameters (MCV, MCH, MCHC). The same groups showed increased ALP, and males only showed increased SGOT and SGPT (2-3x, not reversible). Liver weights were increased in high dose females only, but their LFTs were lower in treated animals than in controls.

Histopathology: Increased multinucleated hepatocytes in two top dose groups (no quantitation) with focal hepatic necrosis. Electron microscopy: "Confirmatory information relating to the above changes." NOEL set at 8 mg/kg/d.

9) Subacute oral toxicity study of TE-031 in rats for 28 days at Taisho Pharmaceutical, Japan. This study was initiated on 10/3/84. Doses of 12.5, 50, 200 or 800 mg/kg/d for 28 days by gavage. 20 SPF Wistar rats/sex/dose. 13/20 males and 18/20 females at 800 mg/kg/d died within 14 days of initiation. Extensive renal cortical tubular epithelial necrosis was noted at necropsy. Three to ten animals/group were retained for 28 day recovery groups.

Results: "Slightly decreased" hemoglobin and hematocrit values were reported in high dose males. "Increased GOT and GPT values" for males at 2 highest doses (not reversible- still 2-3x increases at the end of the recovery period) and females (~2-3x). Increased liver weights in 200 and 800 mg/kg/d females.

Histopathology: Hepatocyte necrosis with inflammation and multinucleated hepatocytes (dose-related increases in incidence and severity) at 200 and 800 mg/kg/d in both sexes. Fatty metamorphosis noted at high dose. Electron microscopy: "Membranous cytoplasmic bodies, autophagic vacuoles and dense bodies in hepatocytes and bile duct epithelial cells in liver of males and females at 800 mg/kg/d and in kidneys." NOEL for this study was set at 12.5 mg/kg/d.

10) Chronic toxicity study of TE-031 in oral administration to dogs for 6 months, Taisho Pharmaceutical, Japan. This study was initiated on 8/12/85. Doses: 0.8, 4, 20 or 100 mg/kg/d for 6 months by gavage. Five beagles/sex/dose were treated. A 1 month recovery period for 1/sex from control and two highest dose groups.

Results: 1 high dose male died on Day 174. High dose animals showed decreased albumin, increased GOT (2.3x), GPT (~2x) and ALP activities (~2x). Increases were greater in males than females. These increases "tended" to return to normal during the recovery period.

Histopathology: Livers from high dose animals showed degeneration and fatty metamorphosis and deposition of yellow pigments and proliferation of bile duct epithelium. Electron microscopy: "Changes in microstructure that correspond to the findings in the liver." These included increases in myelin structures in hepatocytes and bile duct epithelial cells, lysosomes and granular substances in Kupffer cells, and dilated SER (smooth endoplasmic reticulum) in hepatocytes. Similar alterations were not noted in the recovery animals. NOEL was set at 4 mg/kg/d.

11) Subacute oral toxicity study of TE-031 in rats for 28 days at Taisho Pharmaceutical, Japan. This study was initiated on 10/3/86. Doses: 0, 12.5, 50, 200, or 800 mg/kg/d for 28 days by gavage. 20 Sprague-Dawley rats/sex/dose were treated for 28 days, 10 rats/sex/dose (except 12.5 mg/kg/d) were recovery animals (28 days). However, examinations were limited to 10/sex/dose from all but the high dose where 4 sacrificed males and 3 recovery males and 2 females and 9 recovery females were examined biochemically and histologically.

Results: 13/20 males and 18/20 females from the high dose group died or were sacrificed prematurely. Most of these animals showed severe necrosis in the renal cortical tubular epithelium. Increased SGOT and SGPT (2-3x) were reported for males at >50 mg/kg. These alterations remained throughout the recovery period. No significant biochemical changes were reported in females. However, only 3 males and 2 females were evaluated.

Histopathology: Livers from mid and high dose males and high dose females showed hepatocyte necrosis (minimal to mild in controls and low dose animals) with inflammatory infiltrates and multinucleated hepatocytes as well as bile duct epithelial swelling and fatty metamorphosis (high dose only) [Dose-related increase in incidence and severity]. Only the multinucleated hepatocytes remained at the end of the recovery period. Electron microscopy: Membranous cytoplasmic inclusion bodies, autophagic vacuoles and dense bodies were found in hepatocytes and bile duct epithelial cells in all high dose animals. Dense bodies and autophagic vacuoles were also found in renal tubular epithelial cells. The NOEL was set at 12.5 mg/kg/d.

12) Subacute oral toxicity of TE-031 in dogs for 28 days at Taisho Pharmaceutical, Japan. This study was initiated on 5/8/85. Doses: 0, 6.25 (Low), 25 (mid), 100 (mid-high) or 400 (high) mg/kg/d for 28 days by capsule. Four beagles/sex/dose were treated. One/sex/control and 100 and 400 mg/kg/d were added as 28 day recovery animals.

Results: At doses >6.25 mg/kg/d, vomiting, lacrimation and decreased locomotor activities were noted. One female and 2 males at 400 mg/kg/d died prematurely.

Time	CM	LM	MM	MHM	HM	CF	LF	MF	MHF	HF
Bili										
Wk2	.17	.18	.15	.13	.89	.04	.05	.04	.03	.08
Wk4	.21	.21	.23	.21	1.64	.13	.13	.21	.19	.25
Rec	.11			.14	.14	.16			.19	.10
SGOT										
Wk 2	26	26	21	24	262	31	32	30	35	128
Wk 4	34	35	31	36	347	29	27	30	34	93
Rec	29			30	32	27			30	25
SGPT										
Wk2	37	42	32	53	423	33	44	37	50	288
Wk4	41	32	31	52	335	35	39	46	49	128
Rec	32			25	67	37			29	57

Histopathology: Livers showed degeneration and deposition of yellow pigments, inflammatory cell infiltrates, and bile duct epithelial vacuolation and bile duct hyperplasia at 400 mg/kg/d.

Electron microscopy: "Cytoplasmic organella changes corresponding to the above microscopic lesions in the 400 mg/kg/d group." These changes included membranous cytoplasmic bodies, hyperplasia of the SER in hepatocytes, Kupffer cells at the 400 mg/kg/d. At 100 mg/kg/d, the cytoplasmic bodies were found in Kupffer cells but not in hepatocytes. No significant findings were reported in the recovery animals. The NOEL was set at 6.25 mg/kg/d.

13) Three month toxicity study of TE-031 administered orally to dogs with one month interim kill at Abbott Laboratories, Abbott Park, IL. This study was initiated on 4/6/85. Doses: 0, 10, 30 or 100 mg/kg/d for 3 months at 8 mL/kg/d by gavage. 4/sex/dose were for the 3 month sacrifice, 3 for the 1 month sacrifice. This report addresses the 1 and 3 month sacrifice animals.

Results: No significant EKG effects were reported. One high dose male was sacrificed on Day 69 due to moribund condition. At necropsy, this animal had severe bile duct hyperplasia, hepatocellular necrosis, cholestasis, cholecystitis, pericholangitis with necrosis of intrahepatic bile duct epithelium, bone marrow hypoplasia, and moderate pneumonia. Emesis was noted at doses  $\geq 10$  mg/kg/d. Increased ALT (2-3x in males, up to 10x in females), ALP (20x in males, 5x in females) and GGT (3x in males, 3-5x in females) were reported for high dose animals and some mid dose animals. No differences from controls were found in AST levels.

Histopathology: Treatment-related mild diffuse pericholangitis, with mild necrotic changes in the bile duct epithelium were reported in the high dose animals. Moderate biliary hyperplasia and mild intrahepatic cholestasis were also noted. Multifocal hepatocellular necrosis and Kupffer cell hyperplasia were increased in these animals as well. One 30 mg/kg/d animal showed similar changes. The NOEL for this study was set at 10 mg/kg/d.

14) TE-031 Toxicity to Cynomolgus monkeys by repeated oral administration over 28 days at Huntingdon Research Center, UK. This study was initiated in 1986. Doses: 0, 25, 100 or 400 mg/kg/d for 28 days by gavage. Wild caught cynomolgus monkeys were used, 4/sex/dose.

Results: All high dose monkeys were found dead/sacrificed in extremis. Clinical signs included lethargy, ataxia and/or subdued behavior with significant decreases in feed consumption and body weights. No significant differences from controls were noted in hematology, clinical chemistries or urinalyses except in the high dose where increased BUN, creatinine, GPT, GOT

and LDH were reported.

Histopathology: Vacuolated cells were noted in multiple organs, primarily within macrophages. These were found in all high dose but also some mid dose animals. Increased lipid droplets were found in hepatocytes with hepatocellular necrosis and renal proximal convoluted tubular cells. Electron microscopy: electron dense material in liver, kidney, cornea and pancreatic cells, corresponding to the vacuolation noted on light microscopy. The NOEL was set at 25 mg/kg/d.

15) Six week toxicity of Abbott 56268 administered orally to immature rats at Abbott Laboratories, Abbott Park, IL. This study was initiated in 1986. Doses: 0, 15, 50 or 150 mg/kg/d for 6 weeks by gavage. Animals were 15 days old at study initiation and were weaned on Day 13 of dosing. 10 Crl:CD(SD)BR rats/sex/dose were used.

Results: No premature decedents were reported. LFTs were not individually reported in this study and only appear in the statistical analysis portion.

Histopathology: Control and high dose animals only were evaluated. Although statistically significant increases in liver and kidney weights in both sexes at the high dose were reported, no histologic correlates were noted. The NOEL was set at 50 mg/kg/d.

16) 28 Day oral toxicity of TE-031 and erythromycins in rats at Taisho Pharmaceutical, Japan. This study was initiated in 1984. TE-031 was dosed at 50, 150 or 450 mg/kg/d and erythromycin stearate (Em-S) was dosed at 208 or 625 mg/kg/d (Study 1). In Study 2, TE-031 was dosed at 37.5, 75 or 150 mg/kg/d and Em-S was dosed at 204 or 613 mg/kg/d. Erythromycin base (Em-B) was dosed at 147 or 441 mg/kg/d and erythromycin estolate was at 212 or 636 mg/kg/d. These doses were chosen to approximate equimolar amounts of active drug.

Results: In Study 1, total bilirubin was increased with TE-031 at 450 mg/kg/d and with Em-S at both doses. SGOT and SGPT were also significantly increased at both doses of TE-031 and high dose Em-S (1.3-3.6x control values). In Study 2, erythromycin estolate elicited the most SGOT and SGPT change (10x control values at 30 days and 4x after 30 days of recovery).

A peer review was performed by Abbott's pathologist and the following comments were made: "The Taisho pathologists have understated the multifocal, severe hepatic necrosis induced by erythromycin estolate and failed to point out that the estolate lesion was qualitatively different from that induced by TE-031, Em-B and Em-S."

Overall Toxicology Summary for Clarithromycin:

Liver:

Rats: 30 days of dosing at 12.5, 50, 200 and 800 mg/kg/d in adults resulted in reversible hepatocyte necrosis at >50 mg/kg/d. 90 days of dosing at 15, 37.5 in adults resulted in males showing dose-related increase in multinucleated hepatocytes at >15 mg/kg/d. 180 days of dosing at 1.6, 8, 40 or 200 mg/kg/d in adults resulted in increased ALT, AST and ALP and dose-related increases in multinucleated hepatocytes with minimal necrosis at >8 mg/kg/d. Steatosis was noted in most of the rats treated with clarithromycin. Neonatal rats dosed for 2 weeks at 15, 55 or 200 mg/kg/d showed mild, multifocal degeneration of the bile duct. NOELs for hepatic effects were 12.5, 15, 8, and 55 mg/kg/d for the respective studies.

Dogs: 30 days of dosing at 6.25, 25, 100 or 400 mg/kg/d in adults elicited hepatocyte degeneration, biliary hyperplasia, membranous cytoplasmic inclusion bodies in hepatocytes and increases in LFTs at the highest dose tested. 30 day dosing at 10, 30 or 100 mg/kg/d in adults elicited increased LFTs, moderate pericholangitis and biliary hyperplasia in the bile duct at >10 mg/kg/d. 90 days of dosing at 10, 30 or 100 mg/kg/d in adults elicited similar findings with necrosis and increased mitotic activity in bile duct epithelium at >10 mg/kg/d. 180 days of dosing at 0.5, 4, 20 or 100 mg/kg/d in adults elicited similar findings with deposition of bile pigments and bile duct proliferation at >4 mg/kg/d. Juvenile dogs (3 weeks of age) dosed at 30, 100 or 300 mg/kg/d showed fatty deposition in centrilobular hepatocytes, inflammatory cells in portal areas and fatty metamorphosis at >100 mg/kg/d. NOELs for hepatic effects were 6.25, 10, 10, 4 and 100 mg/kg/d for the respective studies. Recovery times (whenever assessed) appeared to be directly related to dosing duration. From the metabolism studies, it appears that the dog achieves 3-5x blood levels compared to humans. This may explain the extreme sensitivity in this species to the test compound.

Monkeys: 7 days of dosing at 20, 80 or 320 mg/kg/d elicited increased LFTs and severe centrilobular fatty change at 320 mg/kg/d. 14 days of dosing at 50, 100, 200 or 300 mg/kg/d in adults elicited increased LFTs and diffuse hepatocellular swelling at >100 mg/kg/d. 30 days of dosing at 15, 35, 75 or 150 mg/kg/d in adults elicited reversible increased LFTs and centrilobular fatty metamorphosis at >35 mg/kg/d. 30 days of dosing at 25, 100 or 400 mg/kg/d elicited increased LFTs at >100 mg/kg/d with necrosis and vacuolation of hepatocytes at >25 mg/kg/d. 180 days of dosing at 25, 50 or 100 mg/kg/d in adults elicited increased liver weights and cytoplasmic rarefaction at >25 mg/kg/d. NOELs for hepatic effects were 80, 100, 35, 25 and 25 mg/kg/d for the respective studies.

#### Renal:

Rats: Adults: Necrosis of renal tubular epithelium at doses >50 mg/kg/d for 30 days. Apparently recovery reversible.

Neonates: Similar findings at >55 mg/kg/d for 14 days. Apparently recovery reversible.

Dogs: Adults: Atrophy of renal tubular epithelium at >100 mg/kg/d for 30 days. Apparently recovery reversible.

Juveniles: Increased epithelial fatty droplets at >100 mg/kg/d for 30 days. Apparently recovery reversible.

Monkeys: Adults: Increased epithelial fatty droplets at >80 mg/kg/d for 7 days. After 14 days of dosing, vacuolization of cortical tubules, mineralization, dilated basophilic tubules and degenerate/necrotic tubules with fatty deposition at >100 mg/kg/d. No recovery groups.

#### Cardiovascular:

Rats: No information available

Dogs: Moderate hypotensive effect at 100 and 300 mg/kg orally. An i.v. dose of 5 mg/kg produced no effects and at 30 mg/kg i.v., increases in pulmonary arterial wedge pressure and left ventricular end-diastolic pressure were noted. At 10 and 30 mg/kg i.v., a transient decrease in blood pressure, cardiac contractile force and femoral blood flow were reported, as well as a moderate increase in heart and respiratory rates.

Cats: Essentially no effects after one dose with intra-arterial administration at 1-10 mg/kg.

## OVERALL SUMMARY AND EVALUATION:

Introduction: The purpose of this review was to evaluate the original source data submitted to the FDA in support of any and all clarithromycin applications. This was done as the current NDA 21144 for telithromycin compares the hepatic and cardiac effects to those with clarithromycin.

Side by side comparisons of pivotal preclinical studies with clarithromycin vs. telithromycin

	<b>Clarithromycin</b>		<b>Telithromycin</b>	
<b>Type of Study</b>	<b>Findings</b>	<b>NOEL/HED</b>	<b>Findings</b>	<b>NOEL/HED</b>
14-15 day monkey Clari doses: 0, 50, 100, 200, 300 mg/kg/d Ketek doses: 0, 100, 200, 300 mg/kg/d	Inc. LFTs, hep. Swelling >100 mg/kg/d	NOEL= 100 mg/kg/d  HED=32.4	Inc. LFTs, inc. total bili. mid & high dose, mod. renal tubular atrophy	NOEL= 100 mg/kg/d  HED= 32.4
4 week rat oral  Clari doses: 0, 12.5, 50, 200, 800 mg/kg/d  Ketek doses: 0, 50, 150, 300 mg/kg/d	Sig. inc. LFTs- males primarily (2-3x), multinuc. hepatocytes, hepatic necrosis >50 mg/kg/d, EM- inclusion bodies	NOEL= 12.5 mg/kg/d  HED= 2 mg/kg	Sig. inc. LFTs (2-15x- AST, ALT, leucine aminopeptidase), phospholipidosis, mod- sev. hepatic necrosis >50 mg/kg/d	NOEL= 50 mg/kg/d  HED= 8 mg/kg
4 week dog oral  Clari doses: 0, 6.25, 25, 100, 400 mg/kg/d  Ketek doses: 0, 50, 150, 300 mg/kg/d	Marked inc. LFTs (4-5x), hyperbilirubinemia, biliary hyperplasia, sev. hep. degener., bile duct prolif. – all > 25 mg/kg	NOEL= 6.25 mg/kg/d  HED= 3.4 mg/kg	Marked inc. LFTs (ALT- 6x, AST- 3.4x), inc. HR, one premature decedent with acute liver & renal failure, phospholipidosis mid & high dose	NOEL= 50 mg/kg/d  HED= 27
4 week monkey oral Clari doses: 0, 15, 35, 75, 150 mg/kg/d or 0, 25, 100, 400 mg/kg/d Ketek doses: 0, 30, 60, 120 mg/kg/d	Inc. LFTs (normal after 2 wk rec.), sev. centrilob. fatty swelling >25 mg/kg	NOEL= 25 or 35 mg/kg/d  HED= 8 or 11 mg/kg	Inc. LFTs (~4x)- high dose, increased total bilirubin (1.8- 2.3x), no histo. lesions	NOEL= 60 mg/kg/d  HED= 19 mg/kg

13 week rat oral Clari doses: 0, 15, 37.5, 75, 150 mg/kg/d Ketek doses: 0, 20, 50, 150 mg/kg/d	Multinucleated hepatocytes at >15 mg/kg/d in males	NOEL= 15 mg/kg/d HED= 2.4	Inc. LFTs (3.6x), inc. NAGs (3x) in urine, inc. inflamm. cells in liver, phospholipidosis	NOAEL= 50 mg/kg/d HED= 8 mg/kg (Impt. to note is NOAEL, not NOEL)
13 week dog oral Clari doses: 0, 10, 30, 100 mg/kg/d Ketek doses: 0, 20, 50, 150 mg/kg/d	Inc. LFTs, hyperbilirubin, biliary hyperplasia, hepatic degen.- all at >10 mg/kg/d	NOEL= 10 mg/kg/d HED= 5.4 mg/kg	Inc. LFTs (4.7x), inc. HR, no path. narrative but hep. hypertrophy noted in high dose	NOEL= 50 mg/kg/d HED= 27 mg/kg
6 month rat oral Clari doses: 0, 1.6, 8, 40, 200 mg/kg/d Ketek doses: 0, 20, 50, 150 mg/kg/d	Inc. LFTs >8 mg/kg/d (2-3x) (no return to baseline after 1 mo. rec.), inc. multinucl. hepatocytes, min. hepatic necrosis >8 mg/kg	NOEL= 8 mg/kg/d HED= 1.2 mg/kg	Inc. LFTs (2x), inc. BUN, inc. NAG in urine, vacuol. In bile duct epithel., phospholipidosis	NOEL= 20 mg/kg/d HED= 3.2 mg/kg
6 month dog oral Clari doses: 0, 0.8, 4, 20, 100 mg/kg/d	Inc. LFTs, degen. & nec. of hep. parenchyma, bile duct prolif.	NOEL= 4 mg/kg/d HED= 2.2	None performed	
6 month oral monkey Clari doses: 0, 25, 50, 100 mg/kg/d	No LFT differences from controls, minimal rarefaction of hepatocytes at high dose	NOEL= 50 mg/kg/d HED= 16.2 mg/kg		

<b>QT Evaluations</b>				
Dogs- telemetry- single dose Clari dose: 15 mg/kg/d Ketek dose: 15 mg/kg/d Erythromycin dose: 15 mg/kg/d			Ketek: +30 msec, inc. HR, stat. sign. inc. QT Clari: +17 msec, no change in HR, insign. inc. QT Erythro: +17 msec, inc. HR (less than Ketek), insign. inc. QT	
Dogs- oral dosing (30 days)-telemetry Clari doses: 0, 10, 30, 100 mg/kg/d Ketek doses: 0, 10, 30, 90 mg/kg/d	No drug-related changes		↑QT at high dose (27-30 msec), markedly ↑ HR	
Dogs- oral dosing (3 months) Clari doses: 0, 10, 30, 100 mg/kg/d Ketek doses:	No drug related changes			

Dr. John Koerner, HFD 110, has reviewed much of the preclinical data submitted in support of the Ketek application and has made the following statements: "HMR 3647 demonstrated a potential to affect ventricular repolarization." As an overall summary for the application, he stated: "In the absence of 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 Aventis (sponsor for Ketek) is advocating that their drug is no worse than clarithromycin, it is critical to consider the effects in each species evaluated. The sponsor of clarithromycin considered the monkey the most appropriate animal model. After 2 weeks of dosing, the findings were increased LFTs with both compounds. Additionally, Ketek elicited renal tubular atrophy and increased total bilirubin levels. After 4 weeks of dosing in the monkey, both compounds elicited increased LFTs, but more significantly with telithromycin. Ketek continued to increase total bilirubin levels.

In the rat after 4 weeks of dosing, although both drugs increased LFTs (clarithromycin- 2-3x, Ketek- 2-15x), the degrees of effect were quite different. Clarithromycin's effect was primarily multinucleated hepatocytes (significance to humans unknown) with minimal to mild hepatic

necrosis at >50 mg/kg/d. Telithromycin's effect was 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 Ketek elicited increased LFTs, increased NAGs (3x) in urine and phospholipidosis.

In the dog, 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. When EKGs were performed, no drug-related differences from controls/baseline were recognized with clarithromycin but telithromycin caused a markedly increased heart rate and increased QT interval (27-30 msec). In the only comparative study performed, clarithromycin and erythromycin each increased the QT interval by 17 msec while telithromycin increased it by 30 msec.

While the clarithromycin sponsor (Abbott) contended that dogs were more sensitive than any other species to the effects of clarithromycin, it appears that the incidence and severity of significant changes to LFTs, histopathology and QT intervals were increased in the telithromycin-treated animals when compared to the clarithromycin-treated animals. Additionally, more species appeared to be adversely affected by telithromycin treatment than by clarithromycin treatment.

**RECOMMENDATIONS:** This review should be submitted to the Advisory Committee package for Ketek® (telithromycin).

**Terry S. Peters, D.V.M.**

Veterinary Medical Officer, HFD-520

Orig. NDA  
cc:  
HFD-520  
HFD-520/Pharm/Peters  
HFD-520/MO/Ross, Davidson, Cox  
HFD-520/Chem/Yu  
HFD-520/CSO/Cintron  
HFD-520/Micro/Marsik

Concurrence Only:  
HFD-520/REOsterberg  
HFD-520/LGavrilovich