

Aventis Pharma



KETEK™ (telithromycin)

**Briefing Document
for the FDA Anti-Infective Drug Products
Advisory Committee Meeting**

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EXECUTIVE SUMMARY

Telithromycin, the first ketolide, has been developed by Aventis Pharmaceuticals for the treatment of outpatient respiratory tract infections (RTIs). The proposed indications for telithromycin are:

- Community-acquired pneumonia (CAP)
- Acute exacerbation of chronic bronchitis (AECB)
- Acute sinusitis (AS)

On 26 April 2001, Aventis presented the findings of the telithromycin clinical studies to the FDA's Anti-infectives Advisory Committee. The FDA subsequently issued an approvable letter (01 June 2001) for the indications of CAP, AECB, and AS and requested further data from Aventis to support these indications.

A large clinical program was designed in cooperation with the FDA to support these indications, which included obtaining additional data in elderly subjects with impaired renal and metabolic elimination pathways, in subjects with *S. pneumoniae* resistant to penicillin G or the macrolides (erythromycin A), and in a large comparative study performed in a usual care setting that focused specifically on hepatic, cardiac, visual, and vasculitic adverse events.

Since July 2001, telithromycin has been approved and marketed in a number of countries, including: Germany, France, Italy, Spain, Brazil, and Mexico. As of 01 October 2002, postmarketing data are available on approximately 1 million exposures. The postmarketing reports confirm the safety profile of the Phase III studies, with no new safety signals identified.

This briefing document is a review of the information gathered during the clinical development and early postmarketing experience with telithromycin.

Current medical need

RTIs are among the most frequent infectious diseases encountered in outpatients and can lead to significant morbidity and, occasionally, mortality if inadequately treated. The key pathogens associated with these infections include common bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Streptococcus pyogenes*, as well as atypical pathogens such as *Mycoplasma pneumoniae*, and intracellular pathogens such as *Legionella pneumophila* and *Chlamydia pneumoniae*. In the outpatient setting, RTIs are frequently treated empirically; thus, it is critical that antibiotics administered to these patients should demonstrate a spectrum of activity that is specifically targeted against these key pathogens.

Many penicillins and oral cephalosporins are inactive against β -lactamase-producing strains of *H. influenzae* and *M. catarrhalis* as well as atypical and intracellular pathogens. In addition, the efficacy of these compounds is increasingly threatened by the emergence of resistance among strains of *S. pneumoniae* (approximately 25% across the US in 2000-2001 PROTEKT US). The escalating prevalence of macrolide resistance now jeopardizes the utility of this class. In 2000-2001 in the US, about 30% of *S. pneumoniae* strains tested were resistant to erythromycin A and other macrolides (PROTEKT US). The clinical significance of such resistance is increasingly being appreciated. For macrolide resistance, the antibiotic MICs for the more resistant strains (8 to 512 $\mu\text{g/mL}$) are generally

significantly higher than the drug concentrations achieved in blood and most tissues (extracellular fluid) by currently available macrolides. Therefore, the contribution of these drugs to the eradication of antibiotic-resistant isolates of *S. pneumoniae* from RTIs is expected to be very low, threatening the utility of the entire class of macrolides. Therapeutic failure of macrolides in the treatment of patients with bacteremia caused by non-susceptible strains of *S. pneumoniae* have recently been reported [30, 31]. As the majority of macrolide-resistant *S. pneumoniae* are co-resistant to most β -lactams, co-trimoxazole, and the tetracyclines, choices of highly effective drugs against these pathogens are increasingly limited.

Fluoroquinolones have demonstrated activity against *S. pneumoniae*, but resistance to these antibiotics, although still generally low across the US (<1%), is emerging with rates > 2% in several cities. More importantly, their antibacterial spectrum is not targeted to the pathogens involved in outpatient RTIs, encompassing in particular enteric gram-negative pathogens responsible for the more severe infections for which this class of drugs was initially developed. Evidence of evolving resistance among strains of *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* is now being reported, representing a real concern for the medical community.

Therefore, there is a clear medical need for new antibiotics with a spectrum of activity focused on respiratory pathogens encountered in outpatients, including the emerging antibiotic-resistant strains. Telithromycin is the first in a new chemical class of antibacterial agents, the ketolides. It is derived from erythromycin A, but has 3 structural features (a 3-keto function [that replaces the α L-cladinose moiety], a C₁₁-C₁₂ carbamate, and an aryl alkyl side chain) that endow it with a novel mechanism of action. Unlike the macrolides, telithromycin binds to domain II of the 23S rRNA of the 50S ribosomal subunit, interfering with protein synthesis. Additionally, it exhibits the classic ribosomal activity associated with macrolides, binding to domain V of the 23S rRNA and disrupting assembly of the 50S ribosomal subunit.

Microbiology (see Section 3, Microbiology)

Telithromycin has an antibacterial spectrum focused on the pathogens encountered in RTIs from outpatients, including *S. pneumoniae* (regardless of antibiotic resistance phenotype), *H. influenzae* and *M. catarrhalis* (irrespective of β -lactamase production), *S. aureus*, *S. pyogenes*, most species of oropharyngeal anaerobic bacteria, atypical pathogens such as *M. pneumoniae*, and intracellular pathogens such as *L. pneumophila* and *C. pneumoniae*. Telithromycin is typically inactive against members of the Enterobacteriaceae and non-fermentative gram-negative bacilli. The focused in vitro activity of telithromycin against the pathogens most frequently causative of these infections is presented in the table below.

Table ES -1. MIC values for telithromycin against pathogens associated with community-acquired RTIs ^a

Pathogen	N	MIC (µg/mL)		
		MIC ₅₀	MIC ₉₀	Range
<i>S. pneumoniae</i>	16672	0.015	0.5	0.002 – 8
<i>H. influenzae</i>	8064	1.0	2.0	0.002 – 32
β-lactamase positive	1631	2.0	4.0	0.008 – 16
<i>M. catarrhalis</i>	1156	0.06	0.12	0.004 – 0.5
β-lactamase positive	1071	0.06	0.12	0.008 – 0.5
<i>S. aureus</i>	2676	0.06	≥64	≤0.008 – ≥64
<i>S. pyogenes</i>	3918	0.03	0.03	≤0.015 – ≥16
<i>C. pneumoniae</i>	19	0.0625	0.25	0.031 – 2
<i>L. pneumophila</i>	26	0.008	0.015	≤0.004 – 0.015
<i>M. pneumoniae</i>	47	0.008	0.008	0.008 – 0.06

^a PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) international respiratory tract pathogen surveillance program: includes organisms collected from 1999 to 2001 worldwide, except for *M. pneumoniae* and *C. pneumoniae*

Telithromycin is highly active in vitro against *S. pneumoniae*, exhibiting strong concentration-dependant bactericidal activity against this pathogen. Telithromycin is active against almost all *S. pneumoniae*, including penicillin G-resistant, macrolide-resistant (MLS_B and/or efflux-type of resistance), and fluoroquinolone-resistant strains.

Table ES-2. MIC values for telithromycin against *S. pneumoniae* strains ^a

Strain of <i>S. pneumoniae</i> :	N	MIC (µg/mL)		
		MIC ₅₀	MIC ₉₀	Range
Erythromycin susceptible/intermediate	11384	0.015	0.015	≤0.002 – 1
Erythromycin A resistant	5288	0.12	1.0	0.008 – 8
Genotype <i>erm</i> (B) ^b	657	0.06	0.5	0.008 – 8
Genotype <i>mef</i> (A) ^b	436	0.12	0.5	0.008 – 1
Genotype <i>mef</i> (A) and <i>erm</i> (B) ^b	71	0.5	0.5	0.06 – 1
Penicillin G resistant ^c	4027	0.12	1	0.004 – 8
Levofloxacin-resistant	154	0.03	0.5	0.004 – 1
Multidrug resistant ^d	1500	0.12	1.0	0.008 – 8

^a PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) international respiratory tract pathogen surveillance program: includes organisms collected from 1999 to 2001 worldwide.

^b Only a subset of erythromycin resistant strains were genotyped for their mechanism of resistance.

^c Includes macrolide-resistant strains.

^d Includes strains concomitantly resistant to penicillin G, the macrolides, trimethoprim-sulfamethoxazole, and tetracycline

A thorough evaluation of the potential for selection of telithromycin-resistant strains of bacteria was conducted, including comparative in vitro and in vivo clinical studies. The potential appears to be lower with telithromycin than with other compounds in the MLS family of antibiotics. In a serial passage experiment, telithromycin selected mutants of *S. pneumoniae* at a very low frequency that was lower than that seen for clarithromycin and azithromycin. In 2 controlled studies in healthy subjects, telithromycin appeared to have less impact on the protective usual flora (viridans group streptococci) than amoxicillin-clavulanic acid and clarithromycin, and does not appear to result in overgrowth with important pathogens such as *C. difficile*.

Clinical pharmacology (see Section 5, Clinical pharmacokinetics)

After oral administration, absorption of telithromycin is almost complete (90%), and the absolute bioavailability is 57% in subjects of all ages. The rate and extent of absorption are not influenced by food. Mean maximum concentration (C_{max}) of telithromycin in plasma is 1.9 $\mu\text{g/mL}$ after a single oral dose of 800 mg and 2.27 $\mu\text{g/mL}$ at steady state, attained after 2 to 3 days of oral dosing with 800 mg once daily. The pharmacokinetics of telithromycin were comparable in RTI patients (C_{max} 2.89 $\mu\text{g/mL}$). Telithromycin has a terminal half-life of 9.8 hours. It is distributed extensively in human tissues; the C_{max} in pulmonary epithelial lining fluid of patients with RTIs was 14.9 $\mu\text{g/mL}$, and C_{max} in white blood cells of healthy subjects was 83 $\mu\text{g/mL}$, with a substantial concentration (20.9 $\mu\text{g/mL}$) at 24 hours after dosing. Telithromycin is 60 to 70% bound to serum proteins.

After oral administration of an 800 mg radiolabeled dose, the main circulating compound is unchanged telithromycin (57% of radioactivity AUC). The main plasma metabolite (RU 76363) represents 13% of the AUC of telithromycin, and 3 other metabolites each represent 3% or less. None of these metabolites contribute appreciably to the clinical antibacterial activity of telithromycin.

Telithromycin has multiple pathways by which it is eliminated, as unchanged drug and several metabolites that are mediated by CYP3A4- and non-CYP3A4 pathways. Non-CYP3A4 pathways are not known to be involved in drug interactions. Due to these multiple pathways of elimination, the increase in telithromycin exposure due to impairment of these pathways is minimal. This has been observed in several studies in subjects with renal or hepatic impairment, and in subjects whose metabolic pathway was impaired by administration of a potent CYP3A4 inhibitor (exposure did not exceed 2-fold in any of these populations). In agreement with the Biopharmaceutics Division of the FDA, a study was carried out to further characterize telithromycin exposure in subjects where more than one pathway was impaired. This study was performed in subjects greater than 60 years of age who had mild-to-moderate impaired renal function and, in addition, who were administered ketoconazole to block their CYP3A4 metabolic capacity. The increase in telithromycin exposure under these conditions of multiple impairment was modestly more than that observed when the CYP3A4 pathway alone was blocked.

The potential for telithromycin to inhibit the CYP3A4 pathway is similar to that seen with clarithromycin and less than that seen with known potent inhibitors. There were no clinically relevant interactions between telithromycin and theophylline or warfarin. Telithromycin is a mild inhibitor of CYP2D6.

Telithromycin is administered for shorter treatment durations for certain RTIs compared to macrolides and is given once daily, indicating that there will be less potential for exposure increase and hence drug interactions.

Efficacy in respiratory tract infections (see Section 6, Efficacy by indication)

Fourteen Phase III clinical studies, including 9 double-blind, randomized, active controlled studies, demonstrated that telithromycin given once daily is at least as effective as a broad range of antimicrobial therapies currently used for the treatment of RTIs, all but one given more than once daily (see table below). In addition, the analysis of outcomes among CAP subjects with macrolide- or penicillin G-resistant *S. pneumoniae* includes data obtained in 2 studies conducted in Japan. These studies included 1 dose comparison study (600 mg vs. 800 mg once daily for 7 days) and one active-controlled study (600 mg once daily vs. levofloxacin 100 mg three times daily for 7 days).

Table ES-3. 14 Phase III telithromycin clinical studies ^a

Indication	Study No.	Telithromycin		Comparator		
		Dose	Duration	Drug	Dose	Duration
CAP	3000	800 mg qd	7 to 10 d	-	-	-
	3001	800 mg qd	10 d	AMX	1000 mg tid	10 d
	3006	800 mg qd	10 d	CLA	500 mg bid	10 d
	3009 ^b	800 mg qd	7 to 10 d	TVA	200 mg qd	7 to 10 d
	3009OL ^c	800 mg qd	7 to 10 d	-	-	-
	3010	800 mg qd	7 d	-	-	-
	3012	800 mg qd	7 d	-	-	-
	4003	800 mg qd	5 d/7 d	CLA	500 mg bid	10 d
AECB	3003	800 mg qd	5 d	AMC	500/125 mg tid	10 d
	3007	800 mg qd	5 d	CXM	500 mg bid	10 d
	3013	800 mg qd	5 d	CLA	500 mg bid	10 d
AS	3002	800 mg qd	5 d/10 d	-	-	-
	3005	800 mg qd	5 d/10 d	AMC	500/125 mg tid	10 d
	3011	800 mg qd	5 d	CXM	250 mg bid	10 d

CAP = community-acquired pneumonia, AECB = acute exacerbation of chronic bronchitis, AS = acute sinusitis.

AMX=amoxicillin; CLA=clarithromycin; TVA=trovafloxacin; AMC=amoxicillin-clavulanic acid; CXM=cefuroxime axetil

^a Does not include the 2 Japanese studies whose data were used only for resistant isolates of *S. pneumoniae*. See Section 6.4.1.7.1, *S. pneumoniae* isolates resistant to penicillin G and/or macrolides (Western studies and Japanese studies 2105 and 3107).

^b Study 3009 was stopped prematurely after the FDA restricted trovafloxacin to inpatient use for severe infections as a result of safety concerns that arose during postmarketing surveillance.

^c No subjects from Study 3009OL were enrolled in Study 3009.

The main efficacy analysis populations in the Phase III studies are defined as follows:

- mITT (modified intent-to-treat population): All subjects with disease who received at least 1 dose of study medication.
- PPc (per-protocol population for analysis of clinical outcome): The primary analysis group. Includes all mITT subjects excluding major protocol violators and subjects with an indeterminate response.
- PPb (per-protocol population for analysis of bacteriological outcome): All PPc subjects with a causative pathogen isolated at pretherapy/entry.

A breakdown of subjects in each population in the 14 Phase III studies by indication is given in the following table.

Table ES-4. Number of telithromycin-treated subjects in 14 Phase III study populations by indication

Indication	Population		
	mITT	PPc	PPb
CAP	2289	1925	653
AECB	612	480	136
Acute sinusitis	980	731	253
TOTAL	3881	3136	1042

mITT=modified intent-to-treat; PPc=clinically evaluable per protocol;

PPb=bacteriologically evaluable per protocol.

As shown in the following table of the 9 Phase III active-controlled studies, the clinical cure rates for evaluable telithromycin-treated subjects were equivalent to active comparators across all indications. Equivalence to active comparators was also demonstrated for clinical cure rates in the mITT population. Study 3009 was discontinued prematurely due to safety concerns with trovafloxacin, the comparator.

Table ES-5. Clinical cure rates in the PPc population of 9 Phase III active-controlled studies

Indication/Study	Treatment				95% confidence intervals	
	Telithromycin		Comparator			
	n/N	(%)	n/N	(%)		
CAP: 3001	141/149	(94.6)	137/152	(90.1)	[-2.1; 11.1]	
	3006	143/162	(88.3)	138/156	(88.5)	[-7.9; 7.5]
	3009	72/80	(90.0)	81/86	(94.2)	[-13.6; 5.2]
	4003 (5 days Tel)	142/159	(89.3)			[-9.7; 4.7]
	4003 (7 days Tel)	143/161	(88.8)	134/146	(91.8)	[-10.2; 4.3]
AECB: 3003	99/115	(86.1)	92/112	(82.1)	[-6.4; 14.3]	
	3007	121/140	(86.4)	118/142	(83.1)	[-5.8; 12.4]
	3013	193/225	(85.8)	206/231	(89.2)	[-9.9; 3.1]
AS: 3005 (5 days Tel)	110/146	(75.3)			[-9.9; 11.7] ^a	
	3005 (10 days Tel)	102/140	(72.9)	102/137	(74.5)	[-12.7; 9.5] ^b
3011					[-8.4; 13.3] ^c	
	161/189	(85.2)	73/89	(82.0)	[-7.1; 13.4] ^c	

CAP = community-acquired pneumonia, AECB = acute exacerbation of chronic bronchitis, AS = acute sinusitis. Comparators = amoxicillin (Study 3001); amoxicillin-clavulanic acid (Studies 3003 and 3005); clarithromycin (Studies 3006 and 3008); cefuroxime axetil (Studies 3007 and 3011); trovafloxacin (Study 3009).

^a Pairwise comparison between 5-day telithromycin treatment regimen and amoxicillin-clavulanic acid regimen.

^b Pairwise comparison between 10-day telithromycin treatment regimen and amoxicillin-clavulanic acid regimen.

^c Pairwise comparison between 5-day and 10-day telithromycin treatment regimens.

Telithromycin was highly effective against the key pathogens encountered in RTIs from outpatients. The clinical cure rates by pathogen in the PPb population, pooled by indication, are shown in the table below.

Table ES-6. Clinical cure rates for major pathogens in telithromycin-treated subjects - PPb population (14 Phase III studies)

Key pathogen	n/N (%) Subjects					
	CAP		AECB		Acute sinusitis	
<i>S. pneumoniae</i>	300/318	(94.3)	22/27	(81.5)	82/91	(90.1)
<i>H. influenzae</i>	206/229	(90.0)	44/60	(73.3)	57/64	(89.1)
<i>M. catarrhalis</i>	44/50	(88.0)	27/29	(93.1)	16/18	(88.9)
<i>S. aureus</i>	36/44	(81.8)	4/6		22/23	(95.6)
<i>M. pneumoniae</i>	36/37	(97.3)	3/3		NA	
<i>C. pneumoniae</i>	34/36	(94.4)	11/12	(91.7)	NA	
<i>L. pneumophila</i>	13/13	(100)	NA		NA	

NA = not applicable

In CAP, telithromycin 800 mg administered orally once daily for 7 to 10 days demonstrated comparable efficacy to a broad range of active comparators administered more than once daily for 10 days (amoxicillin high dose, 1 g three times daily; clarithromycin 500 mg twice daily) and against trovafloxacin 200 mg once daily. Particularly noteworthy results are:

- Telithromycin demonstrated efficacy in the most vulnerable patients in the community, increasingly treated in the outpatient setting: the elderly (87.4%, 243/278 cases cured) and subjects with pneumococcal bacteremia (90.2%, 74/82 cases cured). In addition, excellent results were obtained among subjects with confirmed infections caused by *S. pneumoniae* and *Legionella*, the infections most frequently associated with morbidity and mortality.
- Excellent efficacy was also obtained among subjects infected with antibiotic-resistant *S. pneumoniae* isolates: for penicillin G-resistant *S. pneumoniae*, the clinical outcome was cure in 24/27 isolates. For erythromycin A- (macrolide) resistant *S. pneumoniae*, the clinical outcome was cure in 44/50 isolates, including 8/10 subjects with macrolide-resistant *S. pneumoniae* isolated from the blood.

In AECB, telithromycin 800 mg given once daily for 5 days was effective and comparable to widely prescribed drugs considered the standards of care (cefuroxime axetil, amoxicillin-clavulanic acid, clarithromycin), given 2 to 3 times daily for 10 days. Efficacy was maintained in subjects more likely to require hospitalization such as the elderly and subjects with COPD, even with significant obstruction ($FEV_1/FVC < 60\%$).

In acute sinusitis, telithromycin 800 mg given once daily for 5 days was effective and comparable to cefuroxime axetil and amoxicillin-clavulanic acid given 2 to 3 times daily for 10 days. In this indication 2 studies also demonstrated that 5 and 10 days of treatment with telithromycin are comparable. A total of 8/10 subjects with *S. pneumoniae* resistant to penicillin G and 12/14 subjects with *S. pneumoniae* resistant to the macrolides were clinically cured with telithromycin given for 5 days.

Excellent efficacy was consistently demonstrated with telithromycin in the 3 targeted indications (CAP, AECB, and acute sinusitis). High clinical cure rates were demonstrated against all of the key pathogens causative of outpatient RTIs, including common, atypical, and intracellular pathogens, and *S. pneumoniae* resistant to penicillin G or the macrolides.

Safety (see Section 7, Safety)

There is extensive safety experience with telithromycin, including over 16,000 subjects treated in clinical studies and postmarketing exposure in approximately 1 million courses of therapy. Clinical trials included 16 Phase III studies; 14 in the claimed indications of CAP, AECB, and acute sinusitis, and 2 in tonsillitis/pharyngitis (indication not being sought for approval). In addition, a large study was performed in a usual care setting (Study 3014, see description below the following Phase III section). Significant experience has also been achieved in populations generally considered at risk for drug-related adverse events, including the elderly and those with a variety of co-morbid conditions. Safety data from these sources reinforce the favorable safety profile of telithromycin.

The following table summarizes the Phase III safety-evaluable population.

Table ES-7. Safety-evaluable population in telithromycin Phase III clinical program

Number of Subjects						
Integrated Phase III Studies					Study 3014	
All studies		Controlled		Uncontrolled		
TEL	COMP	TEL	COMP	TEL	TEL	AMC
4472	2139	2702	2139	1770	12159	11978

TEL = telithromycin; COMP = pooled active comparators; AMC = amoxicillin-clavulanic acid

Phase III studies (excluding study 3014)

The incidence and nature of the most frequently reported treatment-emergent adverse events (TEAEs) were, in general, similar between telithromycin and comparators. TEAEs of the gastrointestinal disorders system organ class (e.g. diarrhea, nausea, and vomiting) were most frequently reported and were generally mild or moderate in intensity. The most frequent TEAEs in controlled Phase III studies are summarized in the table below.

Table ES-8. Most frequent TEAEs in controlled Phase III studies

Preferred term	Number (%) of subjects	
	Telithromycin N=2702	Comparator N=2139
All TEAEs^a		
Subjects with TEAEs	1348 (49.9)	1035 (48.4)
Diarrhea NOS	292 (10.8)	184 (8.6)
Nausea	213 (7.9)	99 (4.6)
Headache NOS	148 (5.5)	125 (5.8)
Dizziness (excluding vertigo)	99 (3.7)	57 (2.7)
Vomiting NOS	79 (2.9)	48 (2.2)
Loose stools	63 (2.3)	33 (1.5)
Dysgeusia	43 (1.6)	77 (3.6)

^a Based on a frequency of all TEAEs of $\geq 2.0\%$ in telithromycin or comparator treatment groups.
NOS = not otherwise specified

Adverse events resulting in discontinuation of study medication were uncommon and balanced between treatment groups: telithromycin (119/2702, 4.4%) and comparators (92/2139, 4.3%). The most frequently reported TEAEs leading to discontinuation in both telithromycin- and comparator-treated subjects were diarrhea (0.9% vs. 0.6%, respectively), vomiting (0.8% vs. 0.5%) and nausea (0.7% vs. 0.5%).

Blurred vision, which was generally mild, transient, and fully reversible, was rare (0.4%) in Phase III clinical studies and appeared with a higher incidence in subjects under 50 years of age. The effect had a short duration (2 to 3 hours). There was no evidence of retinal toxicity or change in intraocular pressure or anterior chamber angle, as explored in Phase I studies. The mechanism of this blurred vision is consistent with a slight delay in accommodation.

The overall incidence of death was the same (0.4%) in both telithromycin and comparator groups. None of the deaths were assessed by the investigator as being possibly related to study medication.

In Phase III studies, hepatic laboratory values (such as combined total bilirubin and ALT increases, and clinically noteworthy abnormal laboratory values for ALT and AST) were balanced between telithromycin and comparators. There was 1 case of granulomatous hepatitis with eosinophilic infiltration on biopsy that resolved with an asymptomatic recurrence 9 months later without further telithromycin exposure, suggesting a pre-existing and undiagnosed autoimmune disorder as a cause.

ECG analyses showed that, at therapeutic dose, telithromycin was associated with a small (1.5 ms) mean increase in QTc interval. No excess in risk for significant QTc interval prolongation was noted, even in at-risk populations.

Study 3014

In this large study in a usual care setting, the safety profile of telithromycin was comparable to that seen in the Phase III studies, with no new significant safety signals identified.

The main focus of this study designed in consultation with the FDA was clinical safety, with the intent to exclude an increased risk of rare clinical events. Telithromycin was administered at 800 mg once daily for 5 days in the treatment of acute sinusitis, and for 7 to 10 days in CAP; in consultation with the FDA, the treatment duration for AECB was expanded from 5 days (the usual telithromycin AECB dosing duration) to 7 to 10 days in order to enhance potential safety signal detection. Telithromycin was compared with amoxicillin-clavulanic acid (AMC). AMC was administered at 875 mg amoxicillin in combination with 125 mg clavulanic acid 3 times daily for 7 to 10 days for all 3 indications, as recommended in its US labeling. Consistent with a usual care setting design, exclusion criteria were kept to a minimum. The study enrolled and treated 24140 subjects (12161 telithromycin, 11979 AMC), including 11208 subjects aged 50 years or older, and 40.1% of subjects with CAP or AECB. Adverse events of special interest (AESIs) were subject to detailed reporting and follow-up, and included hepatic (hepatitis, jaundice, worsening of pre-existing hepatic illness, and ALT >3x ULN), cardiac, visual, and vasculitic adverse events. Predefined safety endpoints were adjudicated by an independent and blinded clinical event committee (CEC).

The frequency and profile of TEAEs were similar between telithromycin (2807/12159, 23.1%) and AMC (2745/11978, 22.9%). The majority of TEAEs were of mild or moderate intensity, and discontinuation of study medication due to a TEAE was uncommon in both treatment groups (telithromycin: 467/12159, 3.8%; AMC: 557/11978, 4.7%). Gastrointestinal disorders were the most common TEAEs reported in both treatment groups (telithromycin: 1292/12159, 10.6%; AMC: 1417/11978, 11.8%). Diarrhea was the most common individual TEAE in both groups and occurred less frequently in the telithromycin group (telithromycin: 423/12159, 3.5%; AMC: 813/11978, 6.8%). An extensive review of subgroups identified no population at increased risk for adverse drug-related outcomes.

The frequency of serious TEAEs was similar between treatment groups (telithromycin: 155/12159, 1.3%; AMC: 133/11978, 1.1%). A total of 35 subjects (telithromycin: 15; AMC: 20) died during the study. None of the deaths were related to study medication.

The profile of hepatic AESIs was generally similar between groups. The incidence of CEC adjudicated hepatic safety endpoints, representing possibly drug-related clinically overt liver injury, was low and similar between treatment groups (telithromycin 3 subjects; AMC 2 subjects). Moderate increases of primarily asymptomatic ALT elevations were rare, but slightly more common with telithromycin. These laboratory abnormalities did not lead to a meaningful increase in clinically symptomatic events, and these events resolved. No episodes of fulminant hepatitis, hepatic failure, chronic immune-mediated hepatitis, liver transplantation or death due to liver injury were noted.

No CEC positively adjudicated cardiac endpoints were observed in the telithromycin group, compared with 1 event in the AMC group. All presumed arrhythmic deaths in the telithromycin group occurred distant to treatment and occurred primarily in subjects with significant baseline cardiovascular risk factors.

Positively adjudicated visual endpoints (blurred vision) occurred in 0.61% of telithromycin-treated subjects and 0.04% AMC-treated subjects. The events were consistent with a delay in accommodation, were transient, and resolved without sequelae. There were no reports of permanent visual disturbance and no reports of any adverse event that could be related to an accidental injury

associated with blurred vision. There were no cases of positively adjudicated drug-related systemic vasculitis in either treatment group.

Postmarketing surveillance

Since approval for use in the treatment of RTIs in July 2001, telithromycin has been marketed in several countries in Europe and South/Central America, including Germany, France, Italy, Spain, Brazil and Mexico. Current exposures are estimated at approximately 1 million courses of therapy as of 01 October 2002¹.

The postmarketing reports confirm the safety profile of the Phase III studies, with no new safety signals identified after approximately 1 million exposures. The most frequently reported adverse events were gastrointestinal.

There were no reports of hepatic failure, death from primary hepatic causes, injury requiring transplant, or immune-mediated hepatitis. The overall pattern of hepatic effects observed in the first year of marketing is consistent with that seen from previous clinical studies and with currently marketed antibiotics; no excess risk was identified.

No documented cases of drug-related sudden or unexplained death have been received. A single case of fatal ventricular arrhythmia reported as 'torsades de pointes' was received that lacked ECG confirmation. This case was confounded by the presence of other high risk conditions as well as the onset of prodromal symptoms 3 days prior to telithromycin therapy, and was not associated with QT interval prolongation on ECG. (Nevertheless, while this case cannot be confirmed as torsades de pointe, a single case remains within the expected background rate for this event.)

Blurred vision and related visual complaints were reported infrequently (reporting rate of 0.01%). These events were similar to those observed in the clinical studies; they were primarily mild or moderate in intensity, with rapid resolution noted and no documented reports of permanent sequelae or serious eye injury.

Conclusions

Telithromycin is the first in a new class of antimicrobial agents, the ketolides, with a novel mechanism of action, including dual binding to the bacterial ribosome (at domains II and V), as compared to the single binding site for the macrolides (at domain V).

Telithromycin has an antibacterial spectrum of activity targeted to the treatment of outpatient RTIs. It is active against all the key bacterial species encountered in RTIs, including common and atypical/intracellular pathogens as well as strains of *S. pneumoniae* that are resistant to penicillin G, the macrolides, or fluoroquinolones. Telithromycin is typically inactive against members of the Enterobacteriaceae and non-fermentative gram-negative bacilli.

The pharmacokinetic profile of telithromycin, with sustained levels in tissue and therapeutic concentrations in plasma, support a brief and convenient, once-daily oral dosing regimen. Telithromycin is eliminated by multiple pathways, hence the increase in telithromycin exposure due to impairment of metabolic pathways is minimal. The potential for telithromycin to inhibit the CYP3A4 pathway is similar to clarithromycin and less than that of known potent inhibitors. Telithromycin is

¹ From Aventis internal sales data to retail and outpatient pharmacies.

administered for shorter treatment durations for certain RTIs compared to macrolides, and is given once daily, indicating that there will be less potential for drug interactions.

Telithromycin was effective in treating RTIs, including the most vulnerable outpatients, particularly the elderly and patients with pneumococcal bacteremia in the setting of CAP. Telithromycin demonstrated efficacy in AECB and acute sinusitis, with a treatment regimen of 5 days. The brief, simple regimen should promote patient compliance, an important factor in reducing further pressure for development of antibiotic resistance which may be caused by missed doses at the end of prolonged therapy. Telithromycin was highly effective in infections due to *S. pneumoniae* resistant to penicillin G or to the macrolides.

There is now extensive safety experience with telithromycin, including over 16000 subjects treated in clinical studies (Phase III studies plus Study 3014, the large study in a usual care setting) and postmarketing exposure of approximately 1 million courses of therapy. Significant experience has also been obtained in the elderly and in subjects with a variety of co-morbid conditions.

The frequency and profile of TEAEs observed with telithromycin subjects were comparable to other commonly prescribed antibiotics for respiratory infections. The majority of TEAEs were mild or moderate in intensity, with gastrointestinal events being the most commonly reported. Rates of discontinuation for adverse events were low and similar to comparator antibiotics. Blurred vision was rarely reported (0.4%, Phase III studies, 0.6% in Study 3014), and was consistent with a transient delay in accommodation.

The hepatic safety profile seen with telithromycin is comparable to widely prescribed antibiotics. In the large safety study in a usual care setting, no excess risk in clinical hepatitis was observed compared to amoxicillin-clavulanic acid. The profile of hepatic adverse events reported from marketed use (approximately 1 million exposures since initial launch) was similar to that seen with other antibiotics. No cases of drug-related fulminant hepatic failure, deaths or transplants have been observed.

Telithromycin is associated with a minimal increase in QTc (1.5 ms). Clinical studies and postmarketing experience of approximately 1 million exposures to date have revealed no excess in sudden unexplained deaths or malignant ventricular arrhythmias.

Thus, telithromycin fulfills an important medical need for new antibiotics with a spectrum of activity focused on respiratory pathogens encountered in outpatients, including the emerging antibiotic-resistant strains of *S. pneumoniae*. It has proven to be highly effective in the treatment of outpatients with CAP, AECB, and acute sinusitis with a convenient dosing regimen, and has exhibited a safety profile comparable to marketed antibiotics used to treat RTIs. Telithromycin represents a key addition to the outpatient antimicrobial therapeutic armamentarium.

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LIST OF ABBREVIATIONS

Ae(% dose)	Amount of drug excreted unchanged in urine as a percentage of administered dose
AECB	Acute exacerbation of chronic bronchitis
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (previously SGPT)
AMC	Amoxicillin-clavulanic acid
AMI	Acute myocardial infarction
AMX	Amoxicillin
ARDS	Adult respiratory distress syndrome
AS	Acute sinusitis
AST	Aspartate aminotransferase (previously SGOT)
AUC	Area under plasma concentration-time curve
AUC ₍₀₋₂₄₎	Area under plasma concentration-time curve from time zero to 24 h after dosing
AZI	Azithromycin
bid	Two times a day
BLNAR	Beta-lactamase negative, ampicillin resistant
BLPACR	Beta-lactamase positive, amoxicillin-clavulanate resistant
bmITT	Bacteriological modified intent-to-treat (population)
bpm	Beats per minute
CAD	Coronary artery disease
C _{24h}	Plasma concentration at 24 hours
CAP	Community-acquired pneumonia
CEC	Clinical Expert Committee
CHF	Congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CLA	Clarithromycin
CL _{CR}	Creatinine clearance (mL/min)
CL/F	Apparent oral clearance (mL/min)
CL _R	Renal clearance (L/h)
CMI	Clinical Microbiology Institute, Inc.
C _{max}	Maximum concentration
C _{max,ss}	Maximum concentration at steady state
CNALV	Clinically noteworthy abnormal laboratory value
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COT	Co-trimoxazole
CRF	Case report form

CR	Constitutively resistant
CT	Computerized tomography
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CV	Coefficient of variation
CXM	Cefuroxime axetil
CYP3A4	Cytochrome P450 3A4 enzyme
CYP2D6	Cytochrome P450 2D6 enzyme
ECG	Electrocardiogram
ELF	Extracellular fluid
ENT	Ear, nose, and throat (otolaryngology)
ERSP	Erythromycin A resistant <i>Streptococcus pneumoniae</i>
ER	Emergency room
ERY A	Erythromycin A
F	Absolute bioavailability
FEV ₁ /FVC	Forced expiratory volume in 1 second/forced vital capacity
Fu	Unbound fraction
GERD	Gastroesophageal reflux disease
GGT	Gamma glutamyl transferase
GPE	Global Pharmacovigilance and Epidemiology
HARTS	Hoechst Adverse Reaction Terminology System
HERG	Human cardiac potassium channels
HIV	Human immunodeficiency virus
HTM	Haemophilus test medium
HT	Hypertension
ICH	International Conference on Harmonisation
IHD	Ischemic heart disease
IM	Intensified monitoring
iv	intravenous
IR	Inducible resistance
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LFT	Liver function test
LPCA	Last evaluation, predefined change abnormal
LVF	Levofloxacin
MBC	Minimum bactericidal concentration
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MIC	Minimum inhibitory concentration

MIC ₅₀	50% minimum inhibitory concentration
MIC ₉₀	90% minimum inhibitory concentration
mITT	Modified intent-to-treat (population)
MLS _B	Macrolide lincosamine streptogramin B
MRSA	Methicillin (oxacillin)-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin (oxacillin)-susceptible <i>Staphylococcus aureus</i>
NCCLS	National Committee for Clinical Laboratory Standards
NIDDM	Non-insulin dependent diabetes mellitus
NOAEL	No observed adverse effect level
NOS	Not otherwise specified
PCA	Predefined change abnormal
PCR	Polymerase chain reaction
PEN	Penicillin VK
PPb	Per-protocol population for analysis of bacteriological outcome
PPc	Per-protocol population for analysis of clinical outcome
PROTEKT	Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
PRSP	Penicillin G resistant <i>Streptococcus pneumoniae</i>
qd	Once daily
QT	Interval from beginning of QRS complex to end of T-wave (ms)
QTc	QT interval corrected for heart rate (ms)
QTcB	QT interval corrected for heart rate using Bazett formula (ms)
QTcF	QT interval corrected for heart rate by means of Fridericia formula (ms)
QTcN	QT interval corrected for heart rate using new formula with an exponent derived from QT and RR interval data obtained from drug-free periods of study population (ms)
Rac	Accumulation ratio
RTI	Respiratory tract infection
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
ss	Steady state
t _{1/2,λz}	Apparent terminal elimination half-life (h)
TEAE	Treatment-emergent adverse event
TEL	Telithromycin
TET	Tetracycline
tid	Three times daily
t _{max}	Time to maximum plasma concentration (h)
TOC	Test of cure

TVA	Trovafloxacin
ULN	Upper limit of normal
WBC	White blood cell

1. BACKGROUND AND OVERVIEW

Respiratory tract infections (RTIs) are among the most frequent infectious diseases encountered among outpatients, and are associated with significant morbidity and occasionally mortality when inadequately treated. The key agents associated with these infections include common bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Streptococcus pyogenes*. In addition, the atypical (*Mycoplasma pneumoniae*) and intracellular (*Legionella pneumophila* and *Chlamydophila [Chlamydia] pneumoniae*) pathogens represent important causes of community-acquired pneumonia (CAP) [32].

In the outpatient setting, most RTIs are treated empirically and antibiotics used to treat RTIs in the community should have an antibacterial spectrum specifically targeted against these key pathogens.

Many penicillins and oral cephalosporins are inactive against β -lactamase-producing strains of *H. influenzae* and *M. catarrhalis* as well as against atypical and intracellular pathogens. In addition, the efficacy of these compounds is increasingly threatened by the emergence of resistance among strains of *S. pneumoniae*. The escalating prevalence of macrolide resistance now jeopardizes the utility of this class. In 2001 in the US, 31.7% (23.2% to 40.2% depending on geographical region) of *S. pneumoniae* strains tested were resistant to erythromycin A and other macrolides (PROTEKT US 2001). As the majority of macrolide-resistant *S. pneumoniae* are co-resistant to most β -lactams, co-trimoxazole, and the tetracyclines, choices of highly effective drugs against these pathogens are becoming limited.

The clinical significance of such resistance is increasingly being understood and appreciated. Recent studies of outcome in the most severe indication of bacteremic pneumococcal pneumonia have demonstrated that infection with penicillin-nonsusceptible pneumococci is associated with an increased risk of adverse outcome [34]. Similarly, in another recent study, 31 patients with bacteremic pneumococcal infections who failed to respond to therapy with macrolides were reported to subsequently respond to other antibiotics [31]. Of importance, the antibiotic MICs for the more resistant strains, (8 to 512 $\mu\text{g/mL}$), are generally significantly higher than the drug levels achieved in blood and most tissues (extracellular fluid) by currently available macrolides. Therefore, the contribution of these drugs to the eradication of resistant isolates of *S. pneumoniae* from RTIs is expected to be very low.

Fluoroquinolones have demonstrated activity against *S. pneumoniae*, but treatment failures have recently been published [12]. Resistance to these antibiotics, although still generally low across the US (<1%), has started to emerge with rates >2% in several cities (PROTEKT US). More importantly, their antibacterial spectrum is not targeted to the pathogens involved in outpatient RTIs, encompassing in particular, enteric gram-negative pathogens responsible for infections generally more severe, for which this class of drugs was initially developed. Evidence of evolving resistance among strains of *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* is now being reported [46, 28], representing a real concern for the medical community.

Therefore, there is a clear medical need for new antibiotics with a spectrum of activity focused on respiratory pathogens encountered in outpatients, including the emerging antibiotic-resistant strains.

Telithromycin is the first in a new chemical class of antibacterial agents, the ketolides. It is derived from erythromycin A, but has 3 structural features that endow it with a novel mechanism of action. A 3-keto function (that replaces the α L-cladinose moiety long thought to be essential for antibacterial

activity), a C₁₁-C₁₂ carbamate, and an aryl alkyl side chain. Unlike the macrolides, telithromycin binds to domain II of the 23S rRNA of the 50S ribosomal subunit, interfering with protein synthesis. Additionally, it exhibits the classic ribosomal activity associated with macrolides, binding to domain V of the 23S rRNA and disrupting assembly of the 50S ribosomal subunit. This novel dual mechanism of action results in excellent activity against strains of *S. pneumoniae*, either susceptible or resistant to the macrolides.

Telithromycin is active against all the common bacterial species encountered in RTIs, including *S. pneumoniae* (regardless of resistance phenotype), *H. influenzae*, *M. catarrhalis*, *S. aureus*, *S. pyogenes*, most species of oropharyngeal anaerobic bacteria, and atypical pathogens such as *M. pneumoniae* and intracellular pathogens such as *L. pneumophila* and *C. pneumoniae*. Telithromycin is highly active in vitro against all strains of *S. pneumoniae* including susceptible, penicillin G-resistant, macrolide-resistant (MLS_B and/or efflux-type resistance), and fluoroquinolone-resistant strains. Activity against *S. pneumoniae* is particularly important for treatment of community-acquired RTIs, both because of the prevalence of this pathogen and because this pathogen is also more likely to be associated with comorbid sequelae than other respiratory pathogens. Telithromycin is typically inactive against members of the Enterobacteriaceae and non-fermentative gram-negative bacilli. Hence it has an antibacterial spectrum of activity well targeted to the treatment of outpatient RTIs.

On 26 April 2001, Aventis presented the findings of the telithromycin clinical trials to the FDA Anti-infectives Advisory Committee. Following this meeting, the FDA issued an approvable letter (01 June 2001) for the indications of CAP, AECB, and acute sinusitis and requested further data from Aventis to support these indications.

A large clinical program was designed in cooperation with FDA to support these indications that included additional data in elderly subjects with impaired renal and metabolic elimination pathways, in subjects with *S. pneumoniae* resistant to penicillin or to macrolides (erythromycin A) and a large comparative study performed in a usual care setting with special focus on hepatic, cardiac, visual, and vasculitic adverse events.

Since July 2001, telithromycin has been approved in Europe and Latin America. It has been marketed in the following countries since October 2001: Germany, Italy, Spain, Brazil, Mexico, and France. Postmarketing data are now available for the more than 1 million patients treated with telithromycin.

This briefing document is a review of the information gathered during the clinical development and early postmarketing experience with telithromycin.

2. CLAIMED INDICATIONS

Approval is being sought for telithromycin 800 mg oral dose once daily for the treatment of:

Community-acquired pneumonia (treatment duration: 7 to 10 days) due to *S. pneumoniae* (including strains resistant to penicillin G and the macrolides [erythromycin A]), *H. influenzae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, *L. pneumophila*, or *M. pneumoniae* in patients 13 years of age or older.

Acute exacerbation of chronic bronchitis (treatment duration: 5 days) due to *S. pneumoniae* (including strains resistant to penicillin G and the macrolides [erythromycin A]), *H. influenzae* (including β -lactamase producing strains), *M. catarrhalis* (including β -lactamase producing strains), *S. aureus*, *C. pneumoniae*, or *M. pneumoniae* in patients 18 years of age or older.

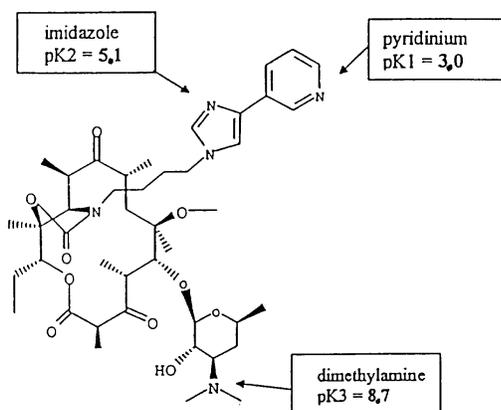
Acute sinusitis (treatment duration: 5 days) due to *S. pneumoniae* (including strains resistant to penicillin G and the macrolides [erythromycin A]), *H. influenzae* (including β -lactamase producing strains), *M. catarrhalis* (including β -lactamase producing strains), or *S. aureus* in patients 13 years of age or older.

3. MICROBIOLOGY

3.1 Introduction

Telithromycin, the first of the new ketolide class of antibacterial agents, is substantially different than the macrolides and azalides. It is differentiated from the MLS (macrolide/lincosamide/streptogramin) antibacterial agents by its more efficient multiple modes of action, its broad spectrum of activity against macrolide-, penicillin-, tetracycline, co-trimoxazole, and fluoroquinolone-resistant respiratory tract pathogens, and findings that it appears to be less efficient at selecting resistant isolates *in vitro* and *in vivo* than the macrolides or azalides. It differs from erythromycin A by the replacement of the neutral sugar, α -L-cladinose, at position 3 of the erythronolide ring with a keto group. Because of the lack of a 3- α -L-cladinose moiety, telithromycin retains activity against gram-positive bacteria expressing the inducible MLS_B mechanism of resistance, does not induce MLS_B resistance, and is highly stable in acidic environments. A C₁₁-C₁₂ carbamate residue addition to the erythronolide A ring is responsible for telithromycin's strong gram-positive *in vitro* activity. The imidazole-pyridinium ring extension to the carbamate side chain further enhances its *in vitro* activity, its pharmacokinetics and pharmacodynamics, its intracellular concentration, and its retention of *in vitro* activity against strains of gram-positive bacteria with an efflux mechanism of resistance to the macrolides. The superior activity of telithromycin over erythromycin A and other macrolides against gram-positive bacteria expressing *mef(A)* genome is apparently a function of the fact that the compound binds less efficiently to the efflux pump protein than do the macrolides and resultantly is not effectively eliminated from the bacterial cell. Telithromycin's additional mechanism of action over macrolides such as erythromycin, is a function of the C₁₁-C₁₂ carbamate alkylaryl side chain.

Figure 3-1. Telithromycin



The antibacterial spectrum of activity of telithromycin encompasses gram-positive cocci and bacilli, gram-negative cocci such as *Moraxella catarrhalis*, and a number of gram-negative bacilli including many frequently isolated respiratory tract pathogens such as *Haemophilus influenzae*, *Bordetella pertussis* and *B. parapertussis*. In addition its activity extends to intracellular and atypical pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia (Chlamydia) pneumoniae* as well as some anaerobic bacteria, including many oropharyngeal species. Telithromycin is typically inactive against members of the Enterobacteriaceae, *Pseudomonas aeruginosa*,

Acinetobacter baumannii/haemolyticus, and other non-fermentative gram-negative bacilli; e.g., *Stenotrophomonas maltophilia* and *Burkholderia cepacia*.

Data supporting the microbiologic efficacy of telithromycin against the common bacterial pathogens associated with community acquired respiratory tract infections will serve to support the request for clinical claims for telithromycin for treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis.

3.2 Mechanisms of Action

As with the macrolides and azalides, telithromycin prevents bacterial protein synthesis by binding to specific sites on the bacterial ribosome and interfering with elongation of nascent polypeptide chains. These compounds also interfere with a second bacterial cellular process, formation of the 50S ribosomal subunit.

3.2.1 Dual interaction of telithromycin with domains V and II

Interaction with domain V

The interaction with domain V of the 23S rRNA (at the peptidyl transferase loop) is comparable for 14- and 15-membered-ring macrolides, azithromycin, and telithromycin. A specific nucleotide, A2058, is pivotal for the binding of macrolide, lincosamide, and streptogramin B antibacterial agents to this site in domain V. The erythronolide A ring of telithromycin docks to the same domain V site of the 23S rRNA.

Interaction with domain II

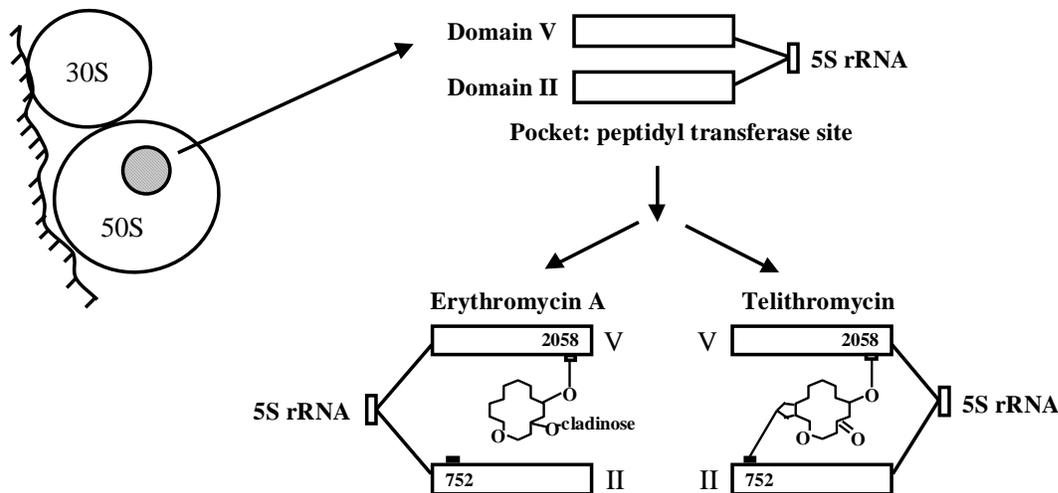
Telithromycin binds strongly in the A752 hairpin region of domain II of 23S rRNA, primarily due to the C₁₁-C₁₂ carbamate side chain on the erythronolide A ring. In contrast, erythromycin A, clarithromycin, and azithromycin do not interact strongly with domain II.

Consequences of the dual interaction of telithromycin with domains II and V

In an erythromycin A-susceptible strain of *S. pneumoniae*, the macrolides and telithromycin are able to bind to the A2058 residue of domain V. Because telithromycin also binds strongly to the A752 residue in the pocket of domain II, it exhibits a much higher overall binding affinity than the macrolides.

In strains of *S. pneumoniae* expressing the *erm*(B) genome, the A2058 site is methylated, significantly reducing the binding efficiency of the macrolides, resulting in resistance to erythromycin A and other 14- and 15-membered ring macrolides including clarithromycin and azithromycin. By contrast, the methylation of A2058 does not result in resistance to telithromycin because, by virtue of its additional strong binding at A752 of domain II, it retains affinity for the active pocket site.

Figure 3-2. Telithromycin mechanism of action



3.2.2 Inhibition of 30S and 50S ribosomal subunit formation by telithromycin

The macrolides and ketolides have a second target for inhibition of protein synthesis among susceptible bacteria, interference with the assembly of nascent 50S ribosomal subunits following binding to a specific receptor on the 50S precursor particle [9]. Incomplete particles are then subject to degradation by bacterial ribonucleases, leading to gradual depletion of functional ribosomes. This inhibition of assembly of the 50S ribosomal subunit is a lethal event for bacterial cells due to ribonuclease digestion of the ribosomal RNAs. When concentrations of drug are reached that essentially halt protein synthesis, telithromycin also reduces formation of the 30S ribosomal subunits, an additional mechanism for lethal disruption of ribosomal subunit formation.

3.3 Telithromycin's affinity for bacterial ribosomes

Telithromycin binds approximately 10 times more tightly than erythromycin A to MLS_B-susceptible ribosomes of *S. pneumoniae* and 20-fold more tightly to *Staphylococcus aureus* ribosomes. Similarly, telithromycin binds 6-fold more tightly to pneumococcal ribosomes than clarithromycin, as reflected in the lower MIC values of telithromycin. The presence of an A2058G mutation in domain V of the 23S rRNA essentially eliminates binding of erythromycin A, clarithromycin, and azithromycin to bacterial ribosomes. Telithromycin binds less efficiently following this mutation, but remains active against such strains whereas the macrolides do not. In summary, dual interaction with the bacterial ribosomes along with disruption of ribosomal subunit formation account for the markedly enhanced activity of telithromycin against both macrolide-susceptible and MLS_B-based macrolide-resistant organisms.

3.4 Decreased affinity for *mef(A)* efflux pump protein

Although, like the macrolides, telithromycin induces the expression of *mef(A)* with resultant production of an efflux protein that effectively eliminates the macrolides from the bacterial cell,

telithromycin binds less efficiently to the protein than do the macrolides and is, therefore, eliminated from the bacterial cell to a significantly lesser degree. Additionally the enhanced binding of telithromycin over the macrolides to the bacterial 23s rRNA further limits the availability of the drug to the efflux pump proteins. Consequently telithromycin retains activity against strains of *S. pneumoniae*, *S. pyogenes*, and other gram-positive organisms resistant to the macrolides based on an efflux mechanism.

3.5 Concentration-dependent bactericidal activity of telithromycin versus time-dependent activity for erythromycin and clarithromycin

In murine models of infection, AUC/MIC is the major PK/PD parameter determining the efficacy of both telithromycin and azithromycin. In a recent study, the neutropenic murine thigh-infection model was employed to determine whether there are differences between the 2 compounds in the pattern of bacterial killing against strains of *Streptococcus pneumoniae*. The 2 drugs were shown to differ markedly in their in vivo killing characteristics. Telithromycin exhibits concentration-dependent killing whereas azithromycin exhibits time-dependent killing. The maximum extent of killing over 6 hours was significantly greater with telithromycin than with azithromycin. The concentration-dependent killing of telithromycin was shown to extend from erythromycin A susceptible strains to organisms resistant to erythromycin A both because of efflux (expression of *erm(A)* genome) and methylation at the A2058 moiety of domain V of the 23S rRNA (expression of *erm(B)*).

3.6 *Streptococcus pneumoniae*

S. pneumoniae is the most common pathogen recovered in serious cases of bacterial community-acquired pneumonia and remains a significant contributor to both morbidity and mortality. It is also frequently associated with acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis and acute otitis media. The susceptibility of *S. pneumoniae* to penicillin G has fallen precipitously in recent years, as has susceptibility to erythromycin and other commonly prescribed macrolides (e.g., clarithromycin and azithromycin). These compounds are now active against <40% of penicillin-resistant isolates in many parts of the world (France, Spain, Southeast Asia, and Japan). In the PROTEKT US program <22% of the 2661 penicillin-resistant strains of pneumococci tested were susceptible to erythromycin, clarithromycin, or azithromycin. PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) is a highly-controlled international respiratory tract pathogen surveillance program that includes as integral components, the characterization on a molecular basis of the mechanisms of resistance to the macrolides and fluoroquinolones of strains of *S. pneumoniae* and the serotyping of *H. influenzae* and *S. pneumoniae* recovered from specific patient populations.

Macrolide (erythromycin A) resistance may result from a number of different mechanisms and is generally inducible. The 2 most common are target site modification, usually the result of di-methylation of a specific adenine residue (A2058—*Escherichia coli* numbering) on the 23S rRNA by an RNA methylase and efflux of the drug out of the bacterial cell. Methylation is thought to result in a conformational change in the ribosome leading to diminished binding of all macrolide, lincosamide, and streptogramin B antibacterials (MLS_B phenotype). The predominant methylase responsible for macrolide resistance among strains of *S. pneumoniae* is *erm(B)*. *Erm(A)* subclass *erm(TR)*, common in *S. pyogenes*, has also recently been reported among strains of *S. pneumoniae* [48]. Target site modification may also be the result of nucleotide substitutions in the 23S rRNA and

in genes that encode the L4 and L22 riboproteins. Mutations at positions 2058 or 2059 generate phenotypes that appear identical to those resulting from methylation, whereas mutations at other nucleotide positions (e.g., 2057, 2452, and 2611) have been shown to cause lower-level antibacterial resistance. Other phenotypes with mutations at various locations on the 23S rRNA have also been described [13].

Both among strains of *S. pneumoniae* and *S. pyogenes*, macrolide efflux is mediated by the product of the *mef(A)* gene. Isolates expressing *mef(A)* typically have moderately elevated macrolide MICs (e.g., *S. pneumoniae* erythromycin A MICs from 2 to 16 µg/mL and 1 to 8 µg/mL for *S. pyogenes*) while retaining susceptibility to clindamycin (M-phenotype). MICs of erythromycin A ≥ 128 µg/mL have, however, been reported. Expression of genome encoding both for methylase and for efflux in the same isolate has been described for *S. pneumoniae* as well as for *S. pyogenes* [6].

3.6.1 In vitro activity

Globally, increasing in vitro antimicrobial resistance among strains of *S. pneumoniae* to a variety of antibacterial agents is being experienced. Extremely high rates of nonsusceptibility to penicillin (76%), extended-spectrum cephalosporins (56%), azithromycin (95%), and co-trimoxazole (65%) among 276 recent pneumococcal isolates from Taiwan were recently reported [23]. Similarly, 32% of all invasive pneumococcal isolates in the metropolitan Atlanta area were shown to be macrolide-resistant in 1999 [18]. Likewise, in a large multicenter trial examining the in vitro activity of 32 antimicrobial agents against 1531 clinical isolates of *S. pneumoniae*, >25% were resistant to erythromycin and the other macrolides tested including clarithromycin and azithromycin. Against this large sample of pathogens, telithromycin was more active than linezolid, gatifloxacin, and moxifloxacin, 3 recently developed antimicrobial agents [14]. The MIC₅₀/MIC₉₀ for the 4 compounds were 0.015/0.12, 1.0/2.0, 0.25/0.25, and 0.12/0.12 µg/mL respectively.

Because oral cephalosporins are very frequently prescribed for empiric treatment of community-acquired respiratory tract infections, the finding that 15% of all clinical isolates of *S. pneumoniae* in the PROTEKT 2000/2001 study exhibited MICs above the NCCLS susceptible breakpoint of 4 µg/mL for cefuroxime axetil is of considerable import. Also of concern, resistance rates were even higher (27.3%) in the PROTEKT 1999/2000 worldwide surveillance study. The clinical significance of such resistance is increasingly being appreciated. Recent studies have demonstrated that among patients with bacteremic pneumococcal pneumonia, infection with penicillin-nonsusceptible pneumococci is associated with an increased risk of adverse outcome [34] and is an independent predictor of mortality [52] in populations with a high seroprevalence of human immunodeficiency virus. Similarly, in another recent review, 21 patients with bacteremic pneumococcal infections that failed to respond to therapy with macrolides were reported to subsequently respond to other antibiotics [31].

3.6.1.1 Macrolide-susceptible strains

In the combined PROTEKT database results for antimicrobial susceptibility testing of 16672 strains of pneumococci are presented. Telithromycin was more active than any of the macrolides tested against the 11384 erythromycin A-susceptible and erythromycin A-intermediate organisms; the MIC₅₀/MIC₉₀ for telithromycin, erythromycin A, clarithromycin, and azithromycin were 0.015/0.015, 0.06/0.12, 0.03/0.06, and 0.12/0.25 µg/mL, respectively.

Table 3-1. Comparative in vitro activities of antibiotics prescribed for RTIs caused by erythromycin-susceptible and -intermediate *S. pneumoniae* (11384 isolates) - PROTEKT

Antimicrobial agent	MIC (µg/mL)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	0.015	0.015	≤0.002 – 1	NA
Erythromycin A	0.06	0.12	≤0.03 – 0.5	99.7
Clarithromycin	0.03	0.06	≤0.015 – 4	99.9
Azithromycin	0.12	0.25	≤0.03 – 8	99.6
Clindamycin	0.25	0.25	≤0.03 – 8	99.7
Penicillin	0.06	1	≤0.008 – 8	73.0
Levofloxacin	1	1	≤0.12 – 32	99.3
Trimethoprim-sulfamethoxazole	0.25/4.75	8/152	≤0.12/2.28 – ≥32/608	75.5

^a Based on NCCLS interpretive criteria. NA: not applicable

The MIC₅₀ for telithromycin among isolates susceptible or intermediate to erythromycin A that were recovered from outpatients was 1 dilution lower (0.008 µg/mL) than that observed for the population as a whole.

3.6.1.2 Macrolide-resistant strains

Telithromycin was also significantly more active than the macrolides tested against erythromycin A-resistant strains of *S. pneumoniae*, for which cross-resistance to azithromycin and clarithromycin was essentially uniform. The MIC₅₀/MIC₉₀ for telithromycin, erythromycin A, clarithromycin, and azithromycin were 0.12/1.0, 16/≥128, 8/≥64, 16/≥128 µg/mL, respectively. At the proposed susceptibility breakpoint for *S. pneumoniae* of ≤1.0 µg/mL, 99.2% of all macrolide-resistant pneumococci were susceptible to telithromycin, making it the most active of all compounds tested, including the fluoroquinolone levofloxacin (MIC₅₀/MIC₉₀: 1.0/1.0 µg/mL; 98.1% susceptible).

Table 3-2. Comparative in vitro activities of antibiotics prescribed for RTIs caused by macrolide-resistant *S. pneumoniae* (5288 isolates) - PROTEKT

Antimicrobial agent	MIC (µg/mL)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	0.12	1	0.008 – 8 ^b	NA
Erythromycin A	16	≥128	1 – ≥128	0
Clarithromycin	8	≥64	0.03 – ≥64	0.2
Azithromycin	16	≥128	0.06 – ≥128	0.2
Clindamycin	0.25	8	≤0.03 – 8	57.0
Penicillin	2	4	≤0.008 – 8	16.9
Levofloxacin	1	1	0.12 – 32	98.1
Trimethoprim-sulfamethoxazole	4/76	8/152	≤0.12/2.28 – ≥32/608	22.7

^a Based on NCCLS interpretive criteria. NA: not applicable

^b The MIC for 1 isolate was originally reported as 16 µg/mL but upon duplicate repeat testing was found to be 8 µg/mL

3.6.1.3 MLS_B mechanism

In the combined PROTEKT database, of the 657 isolates confirmed to be resistant to macrolides based on methylation of 23S rRNA, 99.5% were susceptible to ≤1.0 µg/mL of telithromycin. Based on

molecular analysis of isolates recovered in the PROTEKT US program, 17.3% of all macrolide-resistant pneumococci were of the *erm(B)* genotype. Organisms resistant by this mechanism are typically cross-resistant to the macrolide, lincosamide, and streptogramin B classes of antibacterial agents (MLS_B). The MIC₅₀/MIC₉₀ for telithromycin, erythromycin A, clarithromycin, and azithromycin were 0.06/0.5, ≥128/≥128, ≥64/≥64, and ≥128/≥128 µg/mL, respectively.

Table 3-3. Comparative in vitro activities of antibiotics prescribed for RTIs caused by macrolide-resistant *S. pneumoniae* expressing *erm(B)* (657 isolates) - PROTEKT

Antimicrobial agent	MIC (µg/mL)			
	MIC ₅₀	MIC ₉₀	Range	%S ^a
Telithromycin	0.06	0.5	0.008 – 8	NA
Erythromycin A	≥128	≥128	1 – ≥128	0
Clarithromycin	≥64	≥64	1 – ≥64	0
Azithromycin	≥128	≥128	4 – ≥128	0
Clindamycin	8	8	0.06 – 8	2.3
Penicillin	2	4	≤0.008 – 8	22.2
Levofloxacin	1	1	0.5 – 32	96.7
Trimethoprim-sulfamethoxazole	4/76	16/304	≤0.12/2.28 – ≥32/608	25.0

^a Based on NCCLS interpretive criteria. NA: not applicable

The MIC₅₀ (0.03 µg/mL) for telithromycin among the 60 macrolide-resistant pneumococci expressing *erm(B)* genome that were recovered from blood was 1 doubling dilution lower than for the entire PROTEKT population.

3.6.1.4 Efflux mechanism

All 436 strains of *S. pneumoniae* resistant to erythromycin, clarithromycin, and azithromycin and expressing *mef(A)* in the combined PROTEKT database, were susceptible to ≤1.0 µg/mL of telithromycin. The MIC_{50/90} for telithromycin, erythromycin A, clarithromycin, and azithromycin against these pathogens were 0.12/0.5, 4/≥128, 4/≥64, and 8/≥128 µg/mL, respectively.

Table 3-4. Comparative in vitro activities of antibiotics prescribed for RTIs caused by macrolide-resistant *S. pneumoniae* expressing *mef(A)* (436 isolates) - PROTEKT

Antimicrobial agent	MIC (µg/mL)			
	MIC ₅₀	MIC ₉₀	Range	%S ^a
Telithromycin	0.12	0.5	0.008 – 1	NA
Erythromycin A	4	≥128	1 – ≥128	0
Clarithromycin	4	≥64	0.5 – ≥64	0
Azithromycin	8	≥128	1 – ≥128	0
Clindamycin	0.06	8	≤0.03 – 8	82.8
Penicillin	2	4	≤0.008 – 8	25.0
Levofloxacin	1	1	0.5 – 32	98.2
Trimethoprim-sulfamethoxazole	2/38	≥32/608	≤0.12/2.28 – ≥32/608	26.6

^a Based on NCCLS interpretive criteria. NA: not applicable

Based on molecular analysis of the isolates of *S. pneumoniae* recovered in the PROTEKT US program, 70.7% of all macrolide resistant pneumococci were of the *mef(A)* genotype.

3.6.1.5 Other mechanisms of macrolide resistance

Seventy-one of the macrolide-resistant strains of *S. pneumoniae* in the PROTEKT studies were shown to express both *erm(B)* and *mef(A)* genome. All of these isolates were susceptible to ≤ 1.0 $\mu\text{g/mL}$ of telithromycin ($\text{MIC}_{50} = 0.5$ $\mu\text{g/mL}$; $\text{MIC}_{90} = 0.5$ $\mu\text{g/mL}$). Both the MIC_{50} and the MIC_{90} for erythromycin A, clarithromycin, and azithromycin were greater than or equal to the /highest dilution tested for these compounds (128, 64, and 128 $\mu\text{g/mL}$, respectively).

Table 3-5. Comparative in vitro activities of antibiotics prescribed for RTIs caused by macrolide-resistant *S. pneumoniae* expressing both *mef(A)* and *erm(B)* (71 isolates) - PROTEKT

Antimicrobial agent	MIC ($\mu\text{g/mL}$)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	0.5	0.5	0.06 – 1	NA
Erythromycin A	≥ 128	≥ 128	8 – ≥ 128	0
Clarithromycin	≥ 64	≥ 64	4 – ≥ 64	0
Azithromycin	≥ 128	≥ 128	8 – ≥ 128	0
Clindamycin	8	8	0.06 – 8	2.8
Penicillin	4	4	0.06 – 8	2.8
Levofloxacin	1	1	0.5 – 8	98.6
Trimethoprim-sulfamethoxazole	8/152	16/304	0.25/4.75 – $\geq 32/608$	5.6
Tetracycline	≥ 32	≥ 32	8 – ≥ 32	0

^a Based on NCCLS interpretive criteria. NA: not applicable.

Again based on molecular analysis of the isolates of *S. pneumoniae* recovered in the PROTEKT US program, 299 (9.8%) of the macrolide-resistant pneumococci expressed both *erm(B)* and *mef(A)* genome. *Erm(TR)* genome was detected in 0.1% of the isolates in this study and for 63 strains (2.1%), no mechanism of macrolide resistance was identified.

3.6.1.6 Penicillin-resistant strains

Although resistance rates varied considerably among geographic regions, the overall high-level resistance rate to penicillin ($\text{MIC} > 1$ $\mu\text{g/mL}$) among strains of pneumococci tested in the PROTEKT program was 24.2%.

Penicillin G resistance rates were higher in the PROTEKT US study. Of the 10103 strains tested, 26.3% were fully resistant to penicillin. Of the 4027 isolates resistant to penicillin in the PROTEKT studies, resistance rates to the macrolides were $\geq 76.5\%$. By comparison, 99.1% of these pathogens were susceptible to ≤ 1 $\mu\text{g/mL}$ of telithromycin. The $\text{MIC}_{50/90}$ for these organisms to telithromycin, erythromycin A, clarithromycin, and azithromycin were 0.12/1.0, 8/ ≥ 128 , 8/ ≥ 64 , and 16/ ≥ 128 $\mu\text{g/mL}$, respectively.

Table 3-6. Comparative in vitro activities of antibiotics prescribed for RTIs caused by penicillin-resistant isolates of *S. pneumoniae* (4027 isolates) - PROTEKT

Antimicrobial agent	MIC (µg/mL)			
	MIC ₅₀	MIC ₉₀	Range	%S ^a
Telithromycin	0.12	1	0.004 – 8	NA
Erythromycin A	8	≥128	≤0.03 – ≥128	23.5
Clarithromycin	8	≥64	≤0.015 – ≥64	23.5
Azithromycin	16	≥128	≤0.03 – ≥128	23.4
Clindamycin	0.25	8	≤0.03 – 8	69.9
Penicillin	2	4	2 – 8	0
Levofloxacin	1	1	0.25 – 32	98.2
Trimethoprim-sulfamethoxazole	8/152	8/152	≤0.12/2.28 – ≥32/608	8.7

^a Based on NCCLS interpretive criteria. NA: not applicable

3.6.1.7 Fluoroquinolone-resistant strains

Of concern, evidence of emerging resistance to the fluoroquinolones was also noted in the PROTEKT studies; 154 pneumococcal isolates resistant to levofloxacin were detected. Of these isolates 81 were recovered as part of the PROTEKT US program. All of these pathogens were susceptible to ≤1 µg/mL of telithromycin (MIC₅₀ = 0.03 µg/mL; MIC₉₀ = 0.5 µg/mL). By comparison, the MIC_{50/90} for these strains for erythromycin A, clarithromycin, and azithromycin were 2/≥128, 1/≥64, and 4/≥128 µg/mL, respectively.

Table 3-7. Comparative in vitro activities of antibiotics prescribed for RTIs caused by levofloxacin-resistant *S. pneumoniae* (154 isolates) - PROTEKT

Antimicrobial agent	MIC (µg/mL)			
	MIC ₅₀	MIC ₉₀	Range	%S ^a
Telithromycin	0.03	0.5	0.004 – 1	NA
Erythromycin A	2	≥128	≤0.03 – ≥128	42.9
Clarithromycin	1	≥64	≤0.015 – ≥64	44.2
Azithromycin	4	≥128	≤0.03 – ≥128	42.9
Clindamycin	0.25	8	≤0.03 – 8	68.8
Penicillin	0.5	4	≤0.008 – 4	42.2
Levofloxacin	16	32	8 – 32	0
Trimethoprim-sulfamethoxazole	4/76	8/152	≤0.12/2.28 – ≥32/608	37.0

^a Based on NCCLS interpretive criteria. NA: not applicable

Similarly, the activity of telithromycin against 26 recent clinical isolates of fluoroquinolone-resistant pneumococci with known resistance mechanisms (efflux and topoisomerase II) was assessed by an agar dilution method following NCCLS guidelines [38]. Of these, 6 were intermediate in their susceptibility to penicillin and 7 were resistant. Eight isolates were resistant to clarithromycin due to expression of *mef* and/or *erm*. Ciprofloxacin, levofloxacin, and moxifloxacin MICs ranged from 8 to 64, 1 to 32, and 0.125 to 4 µg/mL respectively. By comparison, the telithromycin MIC₅₀ and MIC₉₀ values were 0.016 and 0.25 µg/mL. The telithromycin MIC was 2 µg/mL for a single isolate.

3.6.1.8 Multiply-resistant strains

In the PROTEKT program, 1500 strains of *S pneumoniae* concomitantly resistant to penicillin, the macrolides, trimethoprim-sulfamethoxazole, and tetracycline were recovered; 99.4% were susceptible to ≤ 1.0 $\mu\text{g/mL}$ of telithromycin ($\text{MIC}_{50} = 0.12$ $\mu\text{g/mL}$). Of these multiply-resistant isolates, 35 (12 from PROTEKT US) also demonstrated resistance to levofloxacin. All 35 were susceptible to ≤ 1 $\mu\text{g/mL}$ of telithromycin ($\text{MIC}_{50} = 0.06$ $\mu\text{g/mL}$).

Table 3-8. Comparative in vitro activities of antibiotics prescribed for RTIs caused by *S. pneumoniae* resistant to penicillin, macrolides, trimethoprim-sulfamethoxazole, and tetracycline (1500 isolates) - PROTEKT

Antimicrobial agent	MIC ($\mu\text{g/mL}$)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	0.12	1	0.008 – 8	NA
Erythromycin A	16	≥ 128	1 – ≥ 128	0
Clarithromycin	16	≥ 64	0.5 – ≥ 64	0
Azithromycin	16	≥ 128	1 – ≥ 128	0
Clindamycin	2	8	≤ 0.03 – 8	38.0
Penicillin	2	4	2 – 8	0
Levofloxacin	1	1	0.5 – 32	97.5
Trimethoprim-sulfamethoxazole	8/152	8/152	4/76 – ≥ 32 /608	0
Tetracycline	8	≥ 32	8 – ≥ 32	0

^a Based on NCCLS interpretive criteria. NA: not applicable

3.6.2 Bactericidal activity

The bactericidal activity of telithromycin against strains of *Streptococcus pneumoniae* with well-characterized mechanisms of resistance to erythromycin A and other macrolides has been investigated by the time kill-curve method.

3.6.2.1 Susceptible strains

Although results varied from strain to strain, in general telithromycin demonstrated rapid bactericidal activity against *S. pneumoniae* susceptible to erythromycin A and was more pronounced than that of either azithromycin or clarithromycin against these same strains. Telithromycin was completely bactericidal at 0.06 $\mu\text{g/mL}$ against 2 of 3 strains of macrolide-susceptible pneumococci after 4 hours incubation for 1 of the isolates and after 8 hours for the second. Similarly, bactericidal activity was demonstrable at 1 $\mu\text{g/mL}$ after 6 hours of incubation with the third strain tested.

3.6.2.2 Macrolide-resistant strains

Although inhibitory activity was uniformly demonstrable, the bactericidal activity of telithromycin against erythromycin A-resistant strains varied from strain to strain.

MLS_B mechanism

Telithromycin demonstrated rapid bactericidal activity against most strains of *S. pneumoniae* resistant to erythromycin due to methylation of the 23S rRNA (expression of *erm(B)* genome). Against 1 isolate, total bactericidal activity was observed after 4 hours at 0.06 µg/mL. Against a second strain, complete bactericidal activity was observed after 8 hours with 2µg/mL and after 12 hours with 0.5 µg/mL of telithromycin. Bactericidal activity was considerably weaker with a third strain tested; only bacteriostatic activity was noted at a concentration of 0.5 µg/mL. Neither azithromycin nor clarithromycin demonstrated activity against these strains demonstrating resistance based on a methylase mechanism.

Efflux mechanism

Although inhibitory for all strains tested, rapid bactericidal activity was inconsistently observed with telithromycin among strains of *S. pneumoniae* resistant to erythromycin A based on an efflux mechanism (expression of *mef(A)* genome). For 6 of the 10 strains tested, rapid regrowth was not observed with telithromycin and bactericidal activity was noted after 12 hours at a concentration of 0.125 µg/mL. With the remaining 4 strains, regrowth was recorded at concentrations <1 µg/mL for 2 stains and <0.5 µg/mL for the 2 others. After 12 hours, however, telithromycin was noted to be bactericidal at a concentration of 0.5 µg/mL against 9 of the 10 strains and at 4 µg/mL for the last isolate. The bactericidal activity of telithromycin was stronger than that of clarithromycin or azithromycin against strains resistant to erythromycin A based on this efflux mechanism.

Other mechanisms of macrolide resistance

Rapid bactericidal activity was demonstrable for some, but not all strains of *S. pneumoniae* resistant to the macrolides when both efflux (*mef(A)*) and ribosomal methylation (*erm(B)*) mechanisms were responsible. Telithromycin was rapidly bactericidal against a strain of *S. pneumoniae* resistant to erythromycin A based on a mutation in the genome encoding for the L4 ribosomal protein. Although inhibitory, telithromycin did not display rapid bactericidal activity against a laboratory-derived strain of *S. pneumoniae* resistant to erythromycin A resulting from a mutation in the genome encoding for the L22 riboprotein.

3.6.3 Murine models of infection

The *in vivo* therapeutic effect of telithromycin was compared to that of azithromycin, clarithromycin, and levofloxacin in a murine model of pneumonia induced with macrolide-susceptible and macrolide-resistant strains of *S. pneumoniae*. In the short-term after antibiotic administration, telithromycin demonstrated a superior therapeutic effect against pneumonia induced with both macrolide-susceptible and macrolide-resistant strains of *S. pneumoniae* than clarithromycin, azithromycin, and levofloxacin.

In another murine study, mice inoculated intratracheally with a macrolide-resistant strain of serotype 1 *S. pneumoniae* were treated orally with telithromycin. The investigators concluded that treatment of experimental pneumococcal pneumonia with telithromycin did not lead to emergence of resistance in this model with strains initially resistant to erythromycin.

3.7 *Haemophilus influenzae*

H. influenzae is the second most frequently isolated bacterial pathogen in outpatient respiratory tract infections. The prevalence of ampicillin resistance due to β -lactamase production among the nontypable strains responsible for community-acquired respiratory infections is very high. In some geographic areas, resistance rates as high as 58% to amoxicillin and 52% to trimethoprim-sulfamethoxazole have been reported [23]. Resistance to β -lactams due to modification of penicillin-binding proteins (β -lactamase-negative, ampicillin resistance [BLNAR]) represents a second, less commonly encountered, mechanism and β -lactamase-positive and amoxicillin-clavulanic acid-resistant isolates of *H. influenzae* (BLPACR) have also been reported [24].

Telithromycin demonstrates very good activity against clinical isolates of *H. influenzae*. Perceived differences in antimicrobial activity are, however, observed when performing antimicrobial susceptibility testing of strains of *H. influenzae* with various media. Haemophilus Test Medium (HTM) is recommended by the National Committee for Clinical Laboratory Standards [40], but its use results in higher MICs than those observed with other formulations of media.

Among 8064 recent clinical isolates tested in the PROTEKT studies following NCCLS guidelines, telithromycin was as active as azithromycin and more active than clarithromycin and erythromycin A. The MIC₅₀ and MIC₉₀ values for both telithromycin and azithromycin were 1 and 2 μ g/mL, whereas those for erythromycin A and clarithromycin were 4 and 8, and 8 and 16 μ g/mL, respectively. In concert with these in vitro findings, telithromycin was more effective than clarithromycin and comparable to azithromycin in a murine model of respiratory tract infection [42]. Epithelial lining fluid levels, typically 3 to 4 times the MIC₉₀ for this pathogen, and concentrations of telithromycin in alveolar macrophages at the site of infection are more than adequate for successful eradication of this pathogen from infected subjects. This has been clearly supported in clinical trials for the most serious community-acquired respiratory tract infection, pneumonia and in acute bacterial sinusitis in which clinical cure rates of 90.0% and 89.1% respectively among subjects infected with *H. influenzae* were achieved.

Table 3-9. Comparative in vitro activities of antibiotics prescribed for RTIs against *H. influenzae* (8064 isolates) - PROTEKT

Antimicrobial agent	MIC (μ g/mL)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	1	2	$\leq 0.002 - 32$	NA
Erythromycin A	4	8	$\leq 0.25 - \geq 128$	NA
Clarithromycin	8	16	$\leq 0.25 - 128$	79.7
Azithromycin	1	2	$\leq 0.06 - 32$	99.2
Cefuroxime	0.5	2	$\leq 0.12 - \geq 64$	98.3
Trimethoprim-sulfamethoxazole	0.06/1.14	4/76	$\leq 0.03/0.57 - \geq 32/608$	81.4
Ampicillin	0.5	8	$\leq 0.12 - 32$	78.6

^a Based on NCCLS interpretive criteria. NA: not applicable

3.7.1 In vitro activity against β -lactamase-producing strains

No significant differences in the activity of telithromycin were noted among the 1631 (20.2%) β -lactamase-positive and the 6433 β -lactamase negative strains of *H. influenzae* tested in the PROTEKT studies; 98.5% and 98.7% of strains were susceptible to ≤ 4 μ g/mL respectively.

Table 3-10. Comparative in vitro activities of antibiotics prescribed for RTIs against β -lactamase producing strains of *H. influenzae* (1631 isolates) - PROTEKT

Antimicrobial agent	MIC ($\mu\text{g/mL}$)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	2	4	0.008 – 16	NA
Erythromycin A	4	8	≤ 0.25 – 64	NA
Clarithromycin	8	16	≤ 0.25 – 128	73.8
Azithromycin	1	2	≤ 0.06 – 16	98.9
Cefuroxime	0.5	2	≤ 0.12 – 32	98.7
Trimethoprim-sulfamethoxazole	0.06/1.14	8/152	$\leq 0.03/0.57$ – 16/304	72.2
Ampicillin	8	32	2 – 32	0

^a Based on NCCLS interpretive criteria. NA: not applicable

3.8 *Moraxella catarrhalis*

3.8.1 In vitro activity

Over 90% of all isolates of *M. catarrhalis*, a common respiratory tract pathogen, produce β -lactamases that render them resistant to compounds such as amoxicillin.

3.8.2 In vitro activity against β -lactamase-producing strains

In the first full year of the PROTEKT studies, 94.7% of the 1071 strains of *M. catarrhalis* tested were resistant to ampicillin due to β -lactamase production. Telithromycin and azithromycin (MIC₅₀ = 0.06 $\mu\text{g/mL}$) were both more active than erythromycin A and clarithromycin (MIC₅₀ = 0.25 $\mu\text{g/mL}$) against these very recent clinical isolates.

Table 3-11. Comparative in vitro activities of antibiotics prescribed for RTIs against β -lactamase-producing strains of *M. catarrhalis* (1071 isolates) - PROTEKT 2000

Antimicrobial agent	MIC ($\mu\text{g/mL}$)		
	MIC ₅₀	MIC ₉₀	Range
Telithromycin	0.06	0.12	0.008 – 0.5
Erythromycin A	0.25	0.25	≤ 0.25 – 1
Clarithromycin	0.25	0.25	≤ 0.25 – 0.5
Azithromycin	0.06	0.06	≤ 0.06 – 0.25
Cefuroxime	1	2	0.25 – 8
Trimethoprim-sulfamethoxazole	0.25/4.56	0.5/9.5	$\leq 0.03/0.57$ – 4/76
Ampicillin	8	16	≤ 0.12 – ≥ 32

3.9 Atypical pathogens

3.9.1 *Mycoplasma pneumoniae*

M. pneumoniae, the most common cause of “atypical” pneumonia, is refractory to therapy with β -lactam antibiotics because of its lack of a cell wall. Telithromycin is highly active against this pathogen. A comparative in vitro study was performed examining the activities of telithromycin and several other antimicrobial agents against human mycoplasmas. All 25 isolates of *M. pneumoniae* tested were susceptible to ≤ 0.015 $\mu\text{g/mL}$ of telithromycin whereas MICs of levofloxacin ranged from 0.5 to 1 $\mu\text{g/mL}$ [5].

Table 3-12. Comparative in vitro activities of telithromycin and other antibiotics against *M. pneumoniae* (25 isolates)

Antimicrobial agent	MIC ($\mu\text{g/mL}$)		
	Range	50%	90%
Telithromycin	≤ 0.015	≤ 0.015	≤ 0.015
Erythromycin A	≤ 0.015	≤ 0.015	≤ 0.015
Clarithromycin	≤ 0.015	≤ 0.015	≤ 0.015
Dirithromycin	$\leq 0.015 - 0.06$	≤ 0.015	0.06
Azithromycin	≤ 0.015	≤ 0.015	≤ 0.015
Levofloxacin	0.5 – 1	0.5	1
Ofloxacin	1	1	1
Doxycycline	0.06 – 0.25	0.12	0.25

Similarly, the susceptibilities of mycoplasmas to 8 new antimicrobial agents were assessed by an agar dilution technique [26]. Strains of *M. pneumoniae* were uniformly resistant to linezolid whereas the macrolides, telithromycin and quinupristin-dalfopristin were highly active. An erythromycin-resistant strain was found to be cross-resistant to azithromycin, clarithromycin, and dirithromycin but susceptible to quinupristin-dalfopristin and telithromycin, the most active compound examined in the study. Both the MIC₅₀ and MIC₉₀ of telithromycin against this most common cause of atypical pneumonia were lower than for all other agents tested, including the fluoroquinolones.

Table 3-13. Comparative in vitro susceptibilities of *M. pneumoniae* to telithromycin and other selected antibiotics

Antimicrobial agent (number of strains)	MIC (µg/mL)		
	Range	50%	90%
Gatifloxacin (41)	0.25 – 1.0	0.25	0.5
Levofloxacin (41)	0.5 – 2.0	1.0	2.0
Moxifloxacin (35)	0.12	0.12	0.12
Linezolid (24)	>64	>64	>64
Tetracycline (30)	0.5 – 2.0	0.5	1.0
Minocycline (30)	0.25 – 1.0	0.5	1.0
Dirithromycin (45)	0.12 – 0.5	0.25	0.25
Quinupristin-dalfopristin (48)	0.004 – 0.06	0.015	0.03
Azithromycin (45)	0.008 – 0.12	0.015	0.03
Clarithromycin (45)	0.015 – 0.06	0.03	0.03
Erythromycin (45)	0.03 – 0.12	0.06	0.06
Telithromycin (47)	0.008 – 0.06	0.008	0.008

3.10 Intracellular pathogens

3.10.1 *Chlamydophila pneumoniae*

C. pneumoniae, an obligate intracellular bacterium, is frequently associated with community-acquired respiratory tract infection. Due to its intracellular nature and its primitive cell wall, it is generally refractory to therapy with β -lactam class antimicrobials. In addition, because of the technical difficulties in the laboratory diagnosis of infection with this pathogen, its prevalence as a cause of infection is underestimated. Telithromycin is highly active against *C. pneumoniae*. In a study determining the activity of several antimicrobials against 19 strains of *C. pneumoniae*, telithromycin was shown to be more active than the macrolides tested [22].

Table 3-14. Comparative in vitro activities of telithromycin and macrolides against *C. pneumoniae* (19 isolates)

Antimicrobial agent	MIC (µg/mL)		MBC ^a (µg/mL)
	MIC ₅₀	MIC ₉₀	MIC ₉₀
Telithromycin	0.0625	0.25	0.25
Roxithromycin	0.25	0.5	0.5
Erythromycin	0.125	0.25	0.25
Azithromycin	0.125	0.25	0.25

^aMBC: minimum bactericidal concentration.

A study reinforcing the above findings [21] investigated the MIC, minimum bactericidal concentration (MBC), and time-dependent killing of *C. pneumoniae*. In addition, the effect of a subinhibitory concentration of 0.5 times the MIC after a pre-exposure of 10 times the MIC over 12 hours was assessed. Telithromycin was shown to have bactericidal activity against *C. pneumoniae* and demonstrated a significant sub-MIC effect on this intracellular pathogen.

3.10.2 *Legionella pneumophila*

L. pneumophila, a bacterial pathogen that survives and multiplies within alveolar macrophages, is a serious cause of community-acquired pneumonia. Because of its intracellular nature and production of β -lactamases, it is refractory to treatment with β -lactam class antimicrobial agents. Telithromycin has been shown to be highly active against this pathogen both in vitro and in animal models of infection.

In an in vitro study that examined the susceptibilities of 13 antimicrobial agents against 30 strains of *Legionella* spp, telithromycin was shown to be more active than erythromycin A [45]. Similarly, the activity of telithromycin against intracellular *Legionella pneumophila* was found to be greater than that of erythromycin A and its antibacterial effects were shown to be both concentration and time dependent [4]. In vitro data from the international surveillance study PROTEKT demonstrated that telithromycin was more active than the macrolides tested (erythromycin A, clarithromycin, and azithromycin), trimethoprim-sulfamethoxazole, and tetracycline and as active as levofloxacin against 26 recent clinical isolates. The MIC₉₀ for telithromycin was 0.015 μ g/mL as compared to 0.06 μ g/mL for azithromycin and 0.25 μ g/mL for erythromycin A and clarithromycin, levels achieved in serum for only a short period of time after oral administration of azithromycin and erythromycin A.

Table 3-15. MIC distributions for antibiotics with activity against *L. pneumophila* - PROTEKT 2000

MIC (μ g/mL)	No. (%) of strains at each MIC for specified antibiotic						
	TEL	ERY A	CLA	AZI	LVF	COT	TET
<i>L. pneumophila</i>							
≤ 0.004	7 (26.9)	-	-	-	-	-	-
0.008	12 (46.2)	-	-	-	23 (88.5)	-	-
0.015	7 (26.9)	-	-	-	3 (11.5)	-	-
0.06	-	-	-	25 (96.2)	-	-	-
0.12	-	-	-	1 (3.8)	-	2 (7.7)	-
0.25	-	25 (96.2)	26 (100)	-	-	14 (53.8)	-
0.5	-	1 (3.8)	-	-	-	10 (38.5)	-
≥ 32	-	-	-	-	-	-	26 (100)
ND	-	-	-	-	-	-	-
Total	26	26	26	26	26	26	26

TEL: telithromycin, ERY A: erythromycin A, CLA: clarithromycin, AZI: azithromycin, LVF: levofloxacin, COT: co-trimoxazole, TET: tetracycline. -: No isolates at this MIC.

Telithromycin has been shown to be effective against *L. pneumophila* in vitro, in infected macrophages, and in a guinea pig model of Legionnaire's disease [15]. The impact of increasing concentrations of telithromycin on rapid bacterial clearance of legionellae from the lungs of experimentally infected guinea pigs has also been assessed. Animals were infected intraperitoneally with *L. pneumophila* serogroup 1. At 48 hours postinfection guinea pigs were treated twice, at 10-hour intervals, with 30, 50, 75, and 100 mg/kg of telithromycin. A group of 8 infected control animals received only 0.5% methylcellulose. All of the untreated control animals died after 84.4 ± 13.5 hours, whereas 100% of the telithromycin-treated guinea pigs survived ($p < 0.001$).

3.11 Other pathogens

3.11.1 *Staphylococcus aureus*

Although more often associated with skin and soft tissue infections, *S. aureus* is also an important cause of community acquired pneumonia resulting either from aspiration or from hematogenous spread. In both situations, pulmonary infection can lead to local complications (e.g., abscesses and pleural empyema). The disease often strikes within a few days after the onset of influenza. In addition, *S. aureus* is reportedly responsible for up to 18% of cases of acute bacterial rhinosinusitis. Of major concern are increasing reports of oxacillin-resistant *S. aureus* infections in the outpatient setting, the etiologic agents of which often remain susceptible to the macrolides and clindamycin.

Against strains of *S. aureus* fully susceptible to erythromycin A, telithromycin is 2 to 4 times more active than clarithromycin, with MIC₅₀ values ranging from 0.04 to 0.12 µg/mL. Against erythromycin A-resistant isolates, telithromycin displays good activity (MIC₅₀ range from 0.06 to 0.5 µg/mL) when resistance is based on an MLS_B inducible (IR) mechanism, whereas azithromycin, clarithromycin and other 14- or 15-membered-ring macrolides are inactive against such strains. Against MLS_B constitutively erythromycin A -resistant (CR) isolates, telithromycin and the 14- and 15-membered-ring macrolides are uniformly inactive.

Against 2676 recent clinical isolates of *S. aureus* in the PROTEKT studies, telithromycin was considerably more active than the macrolides tested. The MIC₅₀ for telithromycin was 0.06 µg/mL whereas that for erythromycin A, clarithromycin, and azithromycin were 0.25, 0.25, and 1.0 µg/mL, respectively.

Table 3-16. Comparative in vitro activities of antibiotics prescribed for RTIs caused by *S. aureus* (2676 Isolates) - PROTEKT

Antimicrobial agent	MIC (µg/mL)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	0.06	≥64	0.008 – ≥64	NA
Erythromycin A	0.25	≥128	≤0.03 – ≥128	64.3
Clarithromycin	0.25	≥64	0.25 – ≥64	64.8
Azithromycin	1	≥128	0.06 – ≥128	64.6
Clindamycin	0.12	≥8	≤0.03 – ≥8	80.4
Trimethoprim-sulfamethoxazole	0.12/2.28	0.12/2.28	≤0.12/2.28 – ≥32/608	95.6
Penicillin	≥8	≥8	≤0.008 – ≥8	14.2
Oxacillin	0.06	2	0.03 – ≥8	90.8
Levofloxacin	0.5	8	≤0.5 – ≥64	79.0
Tetracycline	0.5	≥32	≤0.12 – ≥32	82.2

^a Based on NCCLS interpretive criteria. NA: not applicable

Similarly, against erythromycin A susceptible strains, the MIC₅₀ and MIC₉₀ for telithromycin, erythromycin A, clarithromycin, and azithromycin were 0.06 and 0.06, 0.25 and 0.5, 0.12 and 0.25, and 0.5 and 1.0 µg/mL, respectively. Approximately 44% of the 935 isolates resistant to the macrolides tested were susceptible to ≤ 1.0 of telithromycin. Although only 17.4% of the 247 isolates of oxacillin-resistant *S. aureus* were susceptible to telithromycin (MIC = 0.25 µg/mL), 100% of these strains were resistant to >2 µg/mL of levofloxacin.

3.11.2 *Streptococcus pyogenes* and other β -hemolytic streptococci

Although more frequently associated with pharyngitis, pyoderma, and invasive infections of skin and soft tissues, *Streptococcus pyogenes* is also a cause of community acquired pneumonia, often associated with preceding viral infections such as influenza, measles, or varicella, or with chronic pulmonary disease. In addition, *S. pyogenes* is responsible for approximately 2% of all cases of acute bacterial maxillary sinusitis. Although uniformly susceptible to penicillin, resistance to members of the macrolide class of antibiotics and to clindamycin among strains of group A β -hemolytic streptococci has been increasingly reported in recent years [37], limiting the use of compounds such as erythromycin, clarithromycin, and azithromycin for therapeutic purposes in patients intolerant of β -lactams. *S. pyogenes* may demonstrate resistance to erythromycin A and other macrolides by one of several mechanisms. Most frequently, macrolide resistance is mediated by the *mef(A)* gene, rendering isolates resistant to 14- and 15-membered-ring macrolides but susceptible to 16-membered-ring macrolides and to clindamycin. Strains expressing *erm(A)* subclass *erm(TR)* are typically inducibly resistant to 14- and 15-membered ring macrolides but remain susceptible to 16-membered ring macrolides, the ketolides including telithromycin, and to clindamycin. In addition, strains expressing the *erm(B)* gene have also been described which demonstrate resistance to all macrolides and to the lincosamides, including clindamycin.

Telithromycin displays very good in vitro activity against β -hemolytic streptococci (Lancefield groups A, B, C, F and G). In the several studies performed, telithromycin was consistently more active than clarithromycin with MIC₅₀ values ranging from ≤ 0.008 to $0.06 \mu\text{g/mL}$ and MIC₉₀ values between 0.015 and $0.12 \mu\text{g/mL}$ for macrolide-susceptible isolates.

Telithromycin was more active than any of the macrolides tested against the 3918 strains of *S. pyogenes* recovered in the PROTEKT US study. The MIC_{50/90} for all isolates with telithromycin, erythromycin A, clarithromycin, and azithromycin were $0.03/0.03$, $0.06/0.12$, $0.06/0.06$, and $0.25/0.25 \mu\text{g/mL}$, respectively.

Table 3-17. Comparative in vitro activities of antibiotics prescribed for RTIs caused by *S. pyogenes* (3918 isolates) - PROTEKT US

Antimicrobial agent	MIC ($\mu\text{g/mL}$)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	0.03	0.03	$\leq 0.015 - \geq 16$	NA
Erythromycin A	≤ 0.06	0.12	$\leq 0.06 - \geq 16$	94.5
Clarithromycin	0.06	0.06	$\leq 0.03 - \geq 16$	94.7
Azithromycin	0.25	0.25	$\leq 0.03 - \geq 16$	94.5
Clindamycin	≤ 0.25	≤ 0.25	$\leq 0.25 - 2$	99.5
Penicillin	≤ 0.06	≤ 0.06	$\leq 0.06 - 0.12$	100
Levofloxacin	0.5	1	$\leq 0.12 - \geq 16$	99.9

^a Based on NCCLS interpretive criteria. NA: not applicable

Of import, against erythromycin A-resistant isolates, the MIC_{50/90} for telithromycin, erythromycin A, clarithromycin, and azithromycin were $0.25/1.0$, $\geq 16/\geq 16$, $8/\geq 16$, and $\geq 16/\geq 16 \mu\text{g/mL}$.

Table 3-18. Comparative in vitro activities of antibiotics prescribed for RTIs caused by macrolide-resistant *S. pyogenes* (213 isolates) - PROTEKT US

Antimicrobial agent	MIC (µg/mL)			%S ^a
	MIC ₅₀	MIC ₉₀	Range	
Telithromycin	0.25	1	≤0.015 – ≥16	NA
Erythromycin A	≥16	≥16	1 – ≥16	0
Clarithromycin	8	≥16	≤0.03 – ≥16	3.8
Azithromycin	≥16	≥16	0.06 – ≥16	3.3
Clindamycin	≤0.25	≤0.25	≤0.25 – 2	92.0
Penicillin	≤0.06	≤0.06	≤0.06 – 0.12	100
Levofloxacin	0.5	1	0.25 – 2	100

^a Based on NCCLS interpretive criteria. NA: not applicable

Of 143 macrolide-resistant strains of *S. pyogenes* in the PROTEKT Worldwide 1999/2000 program, 46.1 % expressed *mef*(A), 30.8% *erm*(B), and 23.1% *erm*(A) subclass *erm*(TR). The telithromycin MIC₅₀/MIC₉₀ for isolates with these specific mechanisms of resistance to erythromycin A were 8/64, 0.25/0.5, and 0.015/0.03 µg/mL respectively, underscoring the fact that telithromycin demonstrates good in vitro activity against Group A β-hemolytic streptococci resistant to the macrolides by 2 of the 3 commonly recognized mechanisms. Over 97% of all *S. pyogenes* in the PROTEKT US study were susceptible to ≤ 0.12 µg/mL of telithromycin.

3.11.3 Anaerobic bacteria

Oropharyngeal anaerobes sometimes play a contributory role in respiratory tract infections such as aspiration pneumonia and bacterial sinusitis. Telithromycin demonstrates good activity against many of these organisms, particularly the *Prevotella* spp and the peptostreptococci, but exhibits minimal activity against the protective gastrointestinal anaerobes including members of the *Bacteroides fragilis* group.

Table 3-19. Telithromycin: activity against anaerobes

	Number of isolates	Number of studies	Range of MIC ₅₀ values (µg/mL)
<i>Bacteroides fragilis</i>	244	3	4.0
<i>Bacteroides</i> species	114	3	0.25 – 4.0
<i>Prevotella</i> spp	753	5	0.008 – 0.5
<i>Porphyromonas</i> spp	188	2	0.008 – 0.06
<i>Fusobacterium</i> spp	261	2	2.0 – >64
<i>Actinomyces</i> spp	20	2	≤0.015
<i>Peptostreptococcus</i> spp	232	3	0.004 – 0.06
<i>Propionibacterium</i> spp	66	2	0.008 – 0.01
<i>Clostridium</i> spp	140	5	0.03 – >64
<i>Clostridium difficile</i>	169	7	0.06 – 1.0
Other gram-positive bacteria	11	2	≤0.001

3.12 Selection of Resistance

A thorough evaluation of the potential for selection of telithromycin-resistant strains of bacteria was conducted, including comparative in vitro, animal model, and in vivo clinical studies. As summarized below, the potential appears to be lower with telithromycin than that for other compounds in the MLS family of antibiotics.

3.12.1 Decreased propensity for in vitro selection of antibiotic resistant mutants in serial passage experiments

In a study examining 22 erythromycin-resistant mutants derived in vitro from 5 susceptible parent strains of *S. pneumoniae* by serial passage in the presence of subinhibitory concentrations of macrolides (azithromycin, clarithromycin, erythromycin, and roxithromycin), telithromycin, or clindamycin, resulting mechanisms of resistance were compared [8]. In 6 mutants, point mutations were detected in the L22 gene. The only mutant selected by telithromycin (for which the MIC increased from 0.008 to 0.25 µg/mL) contained a combination of 3 mutations in the L22 gene. L22 mutations were combined with an L4 mutation in 1 strain and with a 23S rRNA mutation in another strain. Nine other strains selected by various macrolides had A2058G (n = 1), A2058U (n = 2), A2059G (n = 1), C2610U (n = 1), and C2611U (n = 4) mutations (*Escherichia coli* numbering) in domain V of the 23S rRNA. One mutant with a single base deletion (A752), selected by clarithromycin and resistant to all macrolides tested (MIC >32 µg/mL), had an elevated MIC for telithromycin (4 µg/mL). Macrolides demonstrated different capacities to select for resistance and each mutation resulted in a specific MLS resistance profile. Of the 16 mutants with identified mechanisms of resistance, 4 were selected by azithromycin, 3 each by clarithromycin, roxithromycin, and clindamycin and 2 by erythromycin, whereas only 1 mutant was selected by the ketolide, telithromycin.

3.12.2 Diminished impact on the host usual flora versus other antimicrobial agents

Normal microbiota act as barriers against colonization with potentially pathogenic microorganisms and against overgrowth with opportunistic microorganisms already present. Administration of antibiotics, either therapeutically or as prophylaxis, disturbs the normal ecological balance between the host and the usual microbiota. By using antimicrobial agents that do not disturb this microbial equilibrium, the risk of emergence and spread of resistant strains between patients and dissemination of resistance determinants between microorganisms is minimized [47]. In addition, a large number of studies have demonstrated that the viridans group streptococci can serve as a reservoir of macrolide resistance and transfer such resistance to *S. pneumoniae* and *S. pyogenes* [7].

It has been theorized that compounds with a long elimination half-life with subinhibitory serum and epithelial lining fluid concentrations over a protracted period of time post-treatment may have an impact on emergence of resistance. In a prospective, open-label, randomized trial, 4 macrolides and the azalide azithromycin were studied for their propensity to promote resistance among the usual oral flora of children with respiratory tract infections [25]. One week after therapy was completed, up to 90% of children harbored macrolide-resistant organisms among their oral flora.

In a placebo-controlled study examining MLS resistance among commensal throat flora before and after clarithromycin therapy, it was determined that organisms demonstrating resistance to MLS class

antimicrobials could often already be detected in patients prior to initiation of therapy [49]. This rate significantly rose after treatment. Of particular concern was the finding that all of the *erm(B)* positive streptococci expressed the conjugative transposon Tn916. This suggests that a significant proportion of all MLS-resistant viridans group streptococci is capable of transferring MLS resistance genes to pathogenic flora.

In a study performed in children with acute otitis media, the effects of large doses of amoxicillin-clavulanate or azithromycin on nasopharyngeal carriage of *S. pneumoniae*, *H. influenzae*, viridans group streptococci, and *S. aureus* were assessed [19]. Results indicated that a significant decrease in nasopharyngeal colonization with *S. pneumoniae* and *H. influenzae* was observed in the amoxicillin-clavulanate group only. Of import, however, was the finding that an increased rate of isolation of viridans group streptococci was observed in both treatment groups and that these species demonstrated a level of resistance greater than that among pneumococci.

The effect of telithromycin on the normal oropharyngeal and intestinal microbiota was studied in healthy volunteers and compared with that of clarithromycin [16]. No overgrowth with yeasts or *Clostridium difficile* occurred with either compound. Increases in MICs for intestinal *Bacteroides* spp were observed with both antibiotics and persisted for 2 weeks after discontinuation of treatment. In addition, a significant emergence of highly clarithromycin-resistant viridans group streptococci, intestinal enterococci, and Enterobacteriaceae was detected in the clarithromycin group. The investigators concluded that the ecological profile of telithromycin seemed to be more favorable than that of clarithromycin in terms of resistance development in the normal microflora.

Similarly, the effects of 7 days of treatment with oral telithromycin on the intestinal, skin, and oropharyngeal microflora of healthy volunteers were compared to those of amoxicillin-clavulanate [35]. Stool yeast counts increased significantly in all patients, regardless of therapy. *Clostridium difficile* toxin, the etiologic agent of antibiotic-associated diarrhea and potentially fatal pseudomembranous colitis, was detected in the stools of a subset of patients treated with amoxicillin-clavulanate and was associated with digestive disorders in some subjects. In the oropharynx, amoxicillin-clavulanate significantly decreased the numbers of viridans group streptococci. Strains of these species resistant to both antibiotics were significantly more frequent after amoxicillin-clavulanate than with telithromycin. The authors concluded that the impact of telithromycin was less important than that of amoxicillin-clavulanate on oropharyngeal microbiota and that, unlike amoxicillin-clavulanate, telithromycin did not lead to colonization with *Clostridium difficile*.

Based on these and other similar findings, telithromycin appears to have less impact on the protective usual flora of treated subjects than many other antibacterials used to treat community-acquired respiratory tract infections, and does not appear to result in overgrowth with important pathogens such as *C. difficile*.

3.13 Microbiology summary

- Telithromycin is the first of a novel new class of antimicrobial agents, the ketolides, with a unique chemical structure designed to display activity against all of the common community-acquired respiratory tract pathogens
- Telithromycin exhibits a novel mechanism of action, inhibiting protein synthesis by binding to 2 sites on the 23S rRNA of bacterial ribosomes and interfering with formation of the 50S ribosomal subunits

- Telithromycin exhibits excellent, yet focused activity against the entire spectrum of community-encountered respiratory tract bacterial pathogens
- Telithromycin demonstrates enhanced activity against *S. pneumoniae* and *S. pyogenes* compared to that of currently available macrolides with in vitro activity comparable to that of azithromycin against strains of *H. influenzae*
- Telithromycin displays potent activity against strains of *S. pneumoniae* susceptible to the macrolides and the β -lactams, exhibiting strong concentration-dependent bactericidal activity against this pathogen
- Telithromycin retains activity against penicillin-resistant isolates of *S. pneumoniae* as well as macrolide-resistant isolates expressing an efflux and/or MLS_B mechanism of resistance or possessing a mutation in the gene encoding for the L4 ribosomal protein
- Telithromycin exhibits in vitro activity against *S. pneumoniae* isolates resistant to the fluoroquinolones, trimethoprim-sulfamethoxazole, and tetracyclines
- Telithromycin selects mutants of *S. pneumoniae* at a very low frequency
- Telithromycin is active in vitro against *S. aureus* (including some macrolide-resistant strains), and is highly active against *M. catarrhalis*
- Telithromycin is extremely active against the atypical/intracellular pathogens *Mycoplasma pneumoniae*, *Chlamydophila (Chlamydia) pneumoniae*, and *Legionella pneumophila* increasingly appreciated as causative of community-acquired pneumonia
- Telithromycin is highly concentrated in polymorphonuclear leukocytes and macrophages/monocytes resulting in balanced intracellular and extracellular levels

3.14 Microbiology conclusions

Telithromycin, the first of the new ketolide class of antibacterial agents, exhibits a novel mechanism of action that endows it with a highly focused spectrum of activity against outpatient respiratory tract pathogens. It displays especially strong activity against *S. pneumoniae*, including strains resistant to penicillin G and/or the macrolides, while demonstrating a low propensity to select for antibiotic-resistant mutants.

4. NONCLINICAL TOXICOLOGY, PHARMACOLOGY AND PHARMACOKINETICS

4.1 Safety profile in preclinical studies

The toxicity profile of telithromycin has been investigated in the adult rat, dog and monkey after repeated oral dosing of up to 6 months, 3 months and 1 month, respectively. Most of these studies included measures of toxicokinetics, and the reversibility of the changes was assessed after 1- and 6-month dosing in rats, and after 3-month dosing in dogs. In addition, reproductive toxicity studies were carried out in rats and rabbits, and telithromycin was tested for genotoxicity in a standard battery of tests.

Telithromycin has also been subjected to a range of tests designed to evaluate its potential general pharmacological effects on body systems. In particular, based on the structural similarity of telithromycin to compounds of the macrolide family, a comprehensive assessment of its effects on cardiac repolarization has been made in safety pharmacology.

Effects typical of macrolide antibiotics were observed, as reported, for example, for erythromycin, azithromycin, and clarithromycin. The liver was identified as the target organ in all tested species, microscopic changes compatible with phospholipidosis were observed in rats and dogs and safety pharmacology studies demonstrated delayed cardiac repolarization.

Reproductive toxicity studies did not show any evidence of direct teratogenic effects. Slight reduction of fertility indices was seen at parental toxic doses in rats.

Telithromycin was not genotoxic in a standard battery of tests.

4.1.1 Effects on the liver

In the toxicity studies in rats, dogs, and monkeys, elevations of liver enzymes associated, in some rat studies, with histological correlates of liver necrosis were noted at high doses. These effects were dose-related, and reversible during the recovery periods.

An *in vitro* study with human liver microsomes showed telithromycin to undergo slightly less covalent binding to microsomal proteins than clarithromycin or azithromycin. The potential for telithromycin to form nitrosoalkane complexes with the hepatic enzyme system cytochrome P450 was assessed and showed no nitrosoalkane complex was formed.

In addition, tissue distribution studies in rats showed no accumulation of telithromycin in the liver.

The No-Observed Adverse Effect Level (NOAEL) for the liver in both rat and dog studies was 50 mg/kg/day, whatever the duration of the study. Relative to exposure levels achieved in adult humans, these NOAELs gave ratios of 1.1 and 9.5 for rat and dog, respectively, based on free fractions of drug. Based on literature data, comparative ratios for clarithromycin are 0.5 and 1.6, respectively [1, 2, 10, 11, 27].

The NOAEL of 60 mg/kg/day in the 1-month monkey study corresponded to an exposure 2.3 times that in man at the therapeutic dose, again based on levels of free drug in adult humans.

4.1.2 Phospholipidosis-associated change

Telithromycin-induced phospholipidosis was seen in rat and dog toxicity studies, as a dose- and time-dependent phenomenon across studies. In the rat studies, tissues affected were the lungs, liver, mesenteric lymph nodes, jejunum/ileum, spleen and thymus. In the dog studies, additional tissues were affected, to include mainly the kidneys, gallbladder and gastrointestinal tract. Phospholipidosis was not associated with any degenerative changes except in the lungs of rats and the kidneys of dogs, where degenerative changes were only seen at the highest dose (exposure ratios of 9-fold or higher) or longest duration of administration (6 months in rats).

All phospholipidosis-associated changes were completely reversible, except for a few tissues at the highest dose levels for which it was only partially reversible within the period examined (4 or 12 weeks).

The NOAEL for phospholipidosis was 50 mg/kg/day in the 1- and 3-month oral toxicity studies in rats and dogs, and 20 mg/kg/day in the 6-month oral toxicity study in rats. Comparisons of exposures at these NOAELs to those achieved in the clinic at the therapeutic dose, and expressed in terms of free drug, gave ratios of 1.1 and 9.5 in rats and dogs, respectively, in the 1- and 3- month studies, and 0.16 in rats in the 6-month study.

Phospholipidosis has been commonly reported to be induced by macrolide antibiotics such as erythromycin and azithromycin. Azithromycin, in particular, induced phospholipidosis in rats and dogs in a similar if not larger range of tissues and at relatively low doses. This is compatible with the tissue retention properties of azithromycin which can be detected in organs for 9 days or more following cessation of treatment. By comparison, telithromycin is eliminated after approximately 48 hours and does not accumulate in tissues.

4.1.3 Effects on cardiac repolarization

Cardiovascular effects of telithromycin have been investigated in the rat and dog, as well as in relevant in vitro procedures. In addition, observations on blood pressure, heart rate, and ECG were included in the repeated-dose toxicity studies in the dog.

The principal effects of telithromycin on the cardiovascular system consisted of increases in heart rate and QTc duration at high doses in the dog (maximum QT_F increase of 11 ms after 15-minute intravenous infusion at 15 mg/kg, compared to 10 ms with clarithromycin at doses giving the same concentration). These effects correlated in vitro with increases in the action potential duration of stimulated rabbit Purkinje fibers and interactions with ion channels, including I_{kr} current in Chinese hamster ovary cells (IC₅₀ value for HERG channel inhibition of 42.5 μM, compared to 54.5 μM with clarithromycin) and I_{kr} current in human atrial myocytes.

In conclusion, in vivo and in vitro data on telithromycin were consistent in that these effects were seen at concentrations of free drug of approximately 5 to 8 μg/mL and above, levels approximately 7 to 12 times the mean C_{max} reached in the clinic at therapeutic dose.

4.1.4 Reproductive toxicity studies

Reproductive toxicity studies were carried out in the rat and rabbit, in order to assess the effects of telithromycin on fertility, embryofetal development and pre-post natal development. Most of these studies included measures of toxicokinetics, together with determinations of fetal and milk levels of telithromycin in the pre-post natal development study in rats.

Telithromycin induced maternal toxicity at the high doses in both rats and rabbits; consequent delayed fetal growth and maturation was observed in both species, with a small number of minor malformations at maternally toxic doses. No evidence of a direct teratogenic effect was observed. In the fertility study, fertility indices were slightly reduced at parental toxic doses, but histological examination of testes at these dose levels in the 1-, 3-, and 6-month repeated-dose studies in the rat did not show any adverse effects. In the pre-post natal study in rats, the high and maternally toxic dose reduced intrauterine growth with subsequent decreases in weight and survival index of pups at birth. Subsequent exposure via consumption of milk from dams treated orally up to 200 mg/kg/day had no effect on pup development or fertility.

4.1.5 Genotoxicity studies

Telithromycin was not genotoxic in a battery of tests - gene mutation in bacteria in vitro, gene mutation at the TK locus in L5178Y cells in vitro, clastogenic activity in human lymphocytes in vitro and the in vivo micronucleus test after oral dosing in mice.

4.2 Animal pharmacokinetics

The pharmacokinetics of telithromycin have been investigated in the mouse, rat, dog, and monkey, the species used for pharmacology and toxicology studies.

Telithromycin was rapidly absorbed after oral administration in mice, dogs, and rats, with bioavailabilities in the range of 36 to 54%. Volumes of distribution were large. Half-lives after intravenous administration were in the range of 1.2 to 2.3 hours.

Radioactivity was widely distributed in the rat after oral and intravenous administration, although levels in the central nervous system were low, indicating poor passage through the blood-brain barrier. Levels of radioactivity in tissue decreased in parallel to plasma levels with almost complete elimination of radioactivity by 24 hours after dosing.

In vivo metabolism studies showed that the main circulating metabolites in man were also seen in rats, dogs, and monkeys, in plasma or in urine.

Fecal elimination of radioactivity predominated in rats and dogs, as in humans. Studies in the rat confirmed biliary excretion and indicated a moderate enterohepatic circulation as well as the involvement of direct secretion of telithromycin into the gut lumen.

At concentrations of approximately 1 µg/mL, binding to serum proteins was approximately 90%, 60%, 45%, 50%, and 70% in mouse, rat, dog, monkey and man, respectively.

In conclusion, the safety profile of telithromycin demonstrated in preclinical studies is similar to that of marketed macrolides.

5. CLINICAL PHARMACOKINETICS

The clinical pharmacology of telithromycin has been investigated in an extensive program involving 1089 subjects in 46 studies (1015 treated with telithromycin). The key features of these studies are given in *Appendix 1, Clinical pharmacology studies of telithromycin*. Five studies investigated tissue and fluid penetration; 18 studies were interaction studies (2 food, 16 drug); and 12 studies involved special populations (with a total of 109 elderly subjects ≥ 65 years of age; 18 adolescents with RTIs; 78 subjects with renal impairment, 25 subjects with hepatic impairment, and 24 subjects with diagnosed cardiovascular disease). Whereas pharmacokinetics was investigated primarily in Phase I studies, pharmacokinetics will also be presented for 220 Phase III subjects with CAP (data from Study 3000).

The clinical pharmacokinetics of telithromycin has primarily been investigated in young and elderly healthy subjects at oral doses of 50 to 3200 mg, and at intravenous doses of 120 to 2000 mg (infused over 1.5 to 2.5 hours). Most of the studies in special populations, tissue penetration studies, and drug interaction studies were conducted using the oral therapeutic dose of 800 mg telithromycin once daily.

Of the 46 studies, 8 studies were conducted after the first Advisory Committee presentation. These 8 studies, marked with an asterisk in *Appendix 1*, were submitted to the FDA in Amendment 2 of 24 July 2002, and their results have been incorporated into this briefing document.

5.1 Absorption, distribution, metabolism, and elimination

5.1.1 Absorption and bioavailability

The absorption of telithromycin in humans is estimated to be almost complete (90%). Prior to entering the systemic circulation, telithromycin undergoes first-pass metabolism mainly by the liver and to some extent by the intestine. The absolute bioavailability of an 800-mg oral dose of telithromycin was 57% in both young and elderly subjects (Study 1044).

A crossover food-interaction study was performed with a single oral 800-mg dose of telithromycin after an overnight fast and immediately after a standard high-fat breakfast (Study 1003). The rate and extent of telithromycin absorption were not modified by food, indicating that telithromycin may be administered with or between meals.

5.1.2 Distribution

Protein binding

Telithromycin was 60 to 70% bound to serum proteins in healthy young subjects, elderly subjects, and subjects with hepatic impairment. Albumin was the major serum fraction responsible for binding. This moderate level of binding, and the absence of significant saturation at therapeutic levels, means that clinically relevant interactions by protein-binding displacement of telithromycin are unlikely.

Tissue distribution

Tissue distribution was confirmed in various biological tissues after multiple oral dosing, as summarized in the following table.

Table 5-1. Concentrations of telithromycin in respiratory tissues, fluids and white blood cells after oral dosing with telithromycin (800 mg)

Tissue	Subjects	Mean concentration (µg/mL)				
		2 h	6 h	12h	24h	48h
Epithelial lining fluid	Patients	14.9	–	3.27	0.84	–
Alveolar macrophages	Patients	69	–	318	162	–
Bronchial tissue ^a	Patients	3.88	–	1.41	0.78	–
Tonsils ^a	Tonsillitis	3.95 ^b	–	0.88	0.72	–
Saliva	Healthy	2.81	1.01	0.41 ^c	0.09	0.036
White blood cells	(Day 5) Healthy ^d	64.6	72.1	39.4	14.1	–
	(Day 10) Healthy ^d	83	60.9	40.6	20.9	8.9

^a Concentrations in µg/g; ^b 3h, ^c 10h, ^d 600 mg once a day.

LOQ: Below the lower limit of quantification; dash indicates no data collected.

Source data: Epithelial lining fluid, alveolar macrophages, bronchial tissue from Study 1043; tonsil tissue data from Study 1028; saliva data from Study 1014; all white blood cell data from Study 1002.

The concentrations of telithromycin observed in tissues are high compared with the MIC values for telithromycin against the main pathogens encountered in RTIs. High concentrations in epithelial lining fluid (ELF) and alveolar macrophages persisted for the 24-hour dosing interval.

The volume of distribution of telithromycin obtained after intravenous dosing was 2.9 L/kg (Study 1044).

5.1.3 Metabolites of telithromycin

In plasma, the main circulating compound after administration of an 800-mg radiolabeled dose was telithromycin, representing 56.7% of the total AUC of radioactivity (Study 1009). The main metabolite, RU 76363, represented 12.6% of the AUC of telithromycin. Three other plasma metabolites were quantified, each representing 3% or less of the AUC of telithromycin. None of the metabolites contributes appreciably to the antibiotic activity of telithromycin.

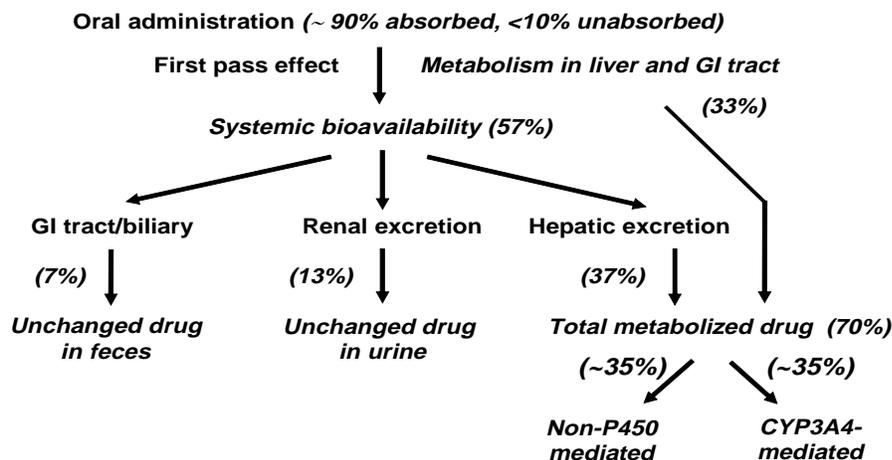
5.1.4 Pathways of elimination

Elimination pathways of telithromycin in humans have been investigated in a series of studies, from which the following conclusions can be drawn:

- After oral administration, approximately 90% of the dose is absorbed.
- Prior to entering the systemic circulation, telithromycin undergoes a first-pass effect (33% of dose). This effect is due to presystemic metabolism by the liver and the intestine.
- The 57% of dose reaching the systemic circulation as unchanged drug is eliminated by multiple pathways as follows:
 - 7% is excreted unchanged in feces by biliary and/or intestinal secretion.

- 13% is excreted unchanged in urine.
- 37% is metabolized by the liver.

Figure 5-1. Overall schematic of elimination pathways



Thus, approximately 70% of the dose undergoes metabolism (33% presystemic and 37% systemic). About half the overall metabolism is mediated by CYP3A4 and about half is non-CYP3A4 dependent. The multiple elimination pathways of telithromycin limit the risk of increased exposure when a single pathway is impaired, as indicated by the results of the renal effect studies (1016, 1062), the hepatic effect studies (1015, 1060), and the ketoconazole interaction study (1045). Impairment of multiple pathways was investigated in Study 1063, where renally impaired elderly subjects were given ketoconazole. Results are given in *Section 5.4, Pharmacokinetics in populations of special interest*.

5.2 Pharmacokinetic characteristics of telithromycin 800 mg (single and multiple dose)

The pharmacokinetics of single and multiple once-daily dosing for 7 days with telithromycin was assessed in young healthy subjects (18 to 29 years) in a crossover study (Study 1008). The mean pharmacokinetic parameters for the 800-mg doses of telithromycin (the therapeutic dose) in this study are summarized in the following table.

Table 5-2. Pharmacokinetic parameters of telithromycin in young healthy subjects after single dose and multiple oral daily dosing with telithromycin 800 mg

Parameter	Mean (CV%)			
	SD N = 18		MD ₇ N = 18	
Plasma				
C _{max} (µg/mL)	1.90	(42)	2.27	(31)
t _{max} (h)	1.0 ^a	[0.5-4.0] ^b	1.0 ^a	[0.5-3.0] ^b
C _{24h} (µg/mL)	0.030	(45)	0.070	(72)
AUC _(0-24h) (µg.h/mL)	8.25	(31)	12.5	(43)
t _{1/2,λ1} (h) ^c	2.43	(41)	2.87	(50)
t _{1/2,λz} (h) ^c	7.16	(19)	9.81	(20)
Ae ₍₀₋₂₄₎ /dose (%)	12.7	(33)	17.7	(27)
CL _{R(0-24)} (L/h)	12.3	(17)	12.5	(34)

SD = single dose, MD₇ = Day 7 of multiple dose (once daily for 7 days).

^a Median; ^b [min-max]; ^c Elimination half-lives calculated using a compartmental model.

The maximum concentration (C_{max}) after the first dose was similar to the value seen after 7 days of dosing. AUC and C_{24h} increased upon multiple dosing, and steady state (based on C_{24h}) was achieved by the second or third dose. Plasma concentrations of telithromycin showed a biphasic decrease over time. The terminal elimination half-life of telithromycin is about 10 hours after multiple dosing.

These pharmacokinetic characteristics are consistent with those seen in patients with RTIs.

There are no pharmacokinetic differences between men and women (Studies 1031, 1042, 1005, 1030, 3000).

5.3 Pharmacokinetics in elderly and adolescents

5.3.1 Elderly subjects, with and without CAP

The pharmacokinetics of telithromycin after multiple oral dosing with telithromycin 800 mg has been investigated in elderly healthy subjects and elderly subjects with CAP, and the results are summarized in the table below.

Table 5-3. Comparison of pharmacokinetics between elderly and young subjects after multiple oral dosing with telithromycin (800 mg qd)

Parameter	Mean (CV%)			
	Healthy subjects ^a		Subjects with CAP ^b	
	Elderly (N=14)	Young (N=12)	Elderly (N=20)	“Young” (N=142)
Age (years)	73.6 (11) ^c	21.3 (15)	69.8 (5.1)	39.0 (34)
C _{max} (µg/mL)	3.6 (40)	1.8 (62)	3.5 (63)	2.8 (50)
AUC _(0-24h) (µg.h/mL)	17.2 (32)	8.5 (31)	25.9 (70)	18.1 (63)

^a Treatment for 10 days, Study 1005; ^b Treatment for 7 to 10 days, Study 3000; ^c N=16

The pharmacokinetics of telithromycin was documented in elderly healthy subjects after single and repeated oral administration of the therapeutic dosage regimen (Study 1005). There is an overall

modest increase of 1.4- to 2-fold in C_{max} in elderly subjects (≥ 65 years) compared with younger subjects. The pharmacokinetics in elderly subjects with CAP (≥ 65 years) compared with “young subjects” (< 65 years) indicate that there is a modest 1.3-fold increase in C_{max} and a 1.4-fold increase in AUC in elderly subjects at the therapeutic dose of telithromycin (800 mg qd).

5.3.2 Adolescent subjects

A multiple-dose (800 mg qd) pharmacokinetic study (Study 1054) was conducted in adolescent subjects (age range 12-17 years) with bacterial RTIs. Results confirmed that the pharmacokinetics of telithromycin in these subjects was similar to that in healthy adults (Study 1008).

Table 5-4. Mean pharmacokinetic parameters (CV%) in adolescent subjects with bacterial RTIs vs. healthy adults

Parameter	Adolescent subjects Study 1054, n=18	Healthy adults Study 1008, n=18
Age	14.8 (10)	21.3 (14)
C_{max}	2.25 (34)	2.27 (31)
AUC _(0-24h)	13.1 (33)	12.5 (43)

Source: Study 1054; Study 1008

5.4 Pharmacokinetics in populations of special interest

Several studies were conducted to define the pharmacokinetic profile in populations of special interest. Emphasis has been placed on the following:

- Subjects with mild, moderate, and severe hepatic impairment
- Subjects with mild, moderate, and severe renal impairment
- Healthy subjects receiving ketoconazole to block the CYP3A4 pathway
- Subjects with impairment of multiple elimination pathways.

5.4.1 Subjects with hepatic impairment

Single dose

The pharmacokinetics of a single oral dose of 800 mg of telithromycin was examined in subjects with hepatic impairment (median Child Pugh score of 9, range 5 to 12) who were demographically matched to healthy control subjects (Study 1015). C_{max} and AUC were similar between subjects with hepatic impairment and healthy control subjects. This was true regardless of the Child Pugh status; hence data have been presented as mean values for all degrees of hepatic impairment. The metabolic clearance of telithromycin was decreased, but this was partially compensated for by a 1.5-fold increase in renal clearance, resulting in no change in exposure.

Table 5-5. Comparison of pharmacokinetics between subjects with hepatic impairment and healthy subjects after a single oral dose of 800 mg telithromycin

Parameter	Mean (CV%)	
	Subjects with hepatic impairment (N=12)	Healthy subjects (N=12)
C _{max} (µg/mL)	1.99 (52)	2.32 (43)
t _{max} (h)	0.75 ^a	1.0 ^a
C _{24h} (µg/mL)	0.088 (61)	0.039 (39)
AUC(0-∞) (µg·h/mL)	11.1 (38)	10.10 (30)
t _{1/2,λ1} (h)	2.60 (53)	2.00 (25)
t _{1/2,λz} (h)	14.16 (14)	10.33 (27)
CL _R (L/h)	17.3 (43)	10.78 (16)

^a Median value

Multiple dose

In a multiple-dose study (Study 1060), the steady-state pharmacokinetics of telithromycin was determined following 800-mg doses administered once daily for 7 days in 13 subjects with hepatic impairment (actual Child-Pugh scores of 5 to 11, median score of 7) who were demographically matched to 13 healthy controls.

Table 5-6. Steady-state telithromycin pharmacokinetics in subjects with hepatic impairment and in healthy subjects

Parameter	Mean (CV%)	
	Subjects with hepatic impairment (N=13)	Healthy subjects (N=13)
800 mg once daily		
C _{max} (µg/mL)	1.80 (23)	1.92 (30)
t _{max} (h) ^a	2.0 [1.5–6.0]	3.0 [0.5–6.0]
AUC(0–24) (µg·h/mL)	12.43 (20)	13.26 (27)
t _{1/2,λz} (h)	11.9 (21)	11.0 (20)
fu (%) ^b	24.5 (26)	21.0 (22)
Ae (0-24)/ dose (%)	22.6 (49)	19.2 (27)
CL _R (L/h)	14.8 (45)	11.7 (15)
R _{ac} ^c	1.43 (43)	1.53 (16)

^a Median [min–max].

^b fu (unbound fraction) = (fu C_{max} + fu C_{12h})/2.

^c R_{ac} (accumulation ratio) = AUC_(0–24h) Day 7 / AUC_(0–24h) Day 1.

Source data: Study 1060

Mean C_{max}, AUC, and t_{1/2} values were comparable for subjects with hepatic impairment and healthy control subjects. This was true regardless of the Child Pugh status, hence data have been presented as means for all degrees of hepatic impairment. Subjects with hepatic impairment showed a mean renal clearance that was 27% greater than that in healthy subjects. This was consistent with the increase in renal clearance of telithromycin observed in the single-dose study, indicating that this pathway is a compensatory route of elimination when hepatic function is impaired.

5.4.2 Subjects with renal impairment

The steady-state pharmacokinetics of telithromycin was determined in renally impaired subjects administered as a repeated dose of telithromycin (Study 1062). In this open-label, balanced, incomplete block, crossover study, multiple 400-, 600-, and 800-mg doses of telithromycin daily for 5 days were evaluated in 3 strata of subjects with renal impairment: *mild*, CL_{CR} 50 to 80 mL/min; *moderate*, CL_{CR} 30–49 mL/min; and *severe*, CL_{CR} <30 mL/min. In addition, healthy control subjects (CL_{CR}>80 mL/min) were treated with telithromycin 800 mg once daily for 5 days.

Pharmacokinetic results for the 800-mg dose, which is the clinically relevant dose, are summarized in the following table.

Table 5-7. Steady-state pharmacokinetics of telithromycin after dosing with 800 mg qd in subjects with various degrees of renal impairment

CL _{CR} (mL/min)	N	Mean (CV%)			
		AUC(0–24) _{ss} (µg.h/mL)	C _{max,ss} (µg/mL)	Fu (%)	CLR (L/h)
>80	9	12.4 (48.1)	2.1 (39.2)	50.9 (7)	12.7 (28.4)
50 – 80	8	16.0 (21.8)	2.6 (13.4)	48.5 (6)	7.3 (31.0)
30 – 49	8	14.8 (40.7)	2.2 (48.2)	46.9 (12)	4.1 (30.7)
<30	8	23.6 (29.2)	3.0 (39.5)	41.6 (17)	2.1 (40.6)

Fu = unbound fraction.

Source data: Study 1062

There were no significant differences in C_{max,ss} and AUC(0–24)_{ss} between healthy subjects and subjects with mild to moderate renal impairment. There was a 1.4-fold increase in C_{max,ss} and a 1.9-fold increase in AUC(0–24)_{ss} in the severe renally impaired group (CL_{CR} <30 mL/min) compared with healthy subjects. The small changes in unbound fraction between the various renal groups are unlikely to have any clinically significant effect on the pharmacokinetics of telithromycin.

5.4.3 Subjects receiving ketoconazole

Steady-state pharmacokinetics of telithromycin was determined in subjects where the CYP3A4 pathway was completely blocked. This was achieved by using an open-label, randomized, crossover design where healthy subjects were administered multiple doses of telithromycin 800 mg alone, then telithromycin 800 mg + ketoconazole 400 mg qd. Pharmacokinetic results are shown in the table below.

Table 5-8. Steady-state telithromycin pharmacokinetics in healthy subjects with and without ketoconazole

Parameter	Mean (CV%)	
	Ketoconazole N=11	Ketoconazole + telithromycin N=11
C _{max,ss} (µg/mL)	2.02 (37.9)	3.13 (35.8)
AUC(0–24) _{ss} (µg.h/mL)	14.43 (38.7)	28.6 (31.0)
t _{1/2,ss} (h)	11.24 (26.4)	12.58 (27.5)

Source data: Study 1045.

The table above indicates that after administration of a known potent inhibitor of the CYP3A4

pathway, the increase in telithromycin exposures is modest. This is a result of telithromycin not being exclusively eliminated by this pathway, as shown earlier.

5.4.4 Subjects ≥ 60 years of age with impairment of multiple elimination pathways

As indicated in *Section 5.1.4, Pathways of elimination*, increased exposure due to impairment of a single pathway is limited. Study 1063, designed in agreement with the Biopharmaceutics Division of the FDA, was carried out to further characterize telithromycin exposure in subjects where more than one pathway was impaired. This study was performed in subjects 60 years of age and older, who had mild to moderate impaired renal function and, in addition, who were administered ketoconazole to block their CYP3A4 metabolic capacity.

The following treatments were administered to these subjects:

- Ketoconazole (400 mg once daily) along with telithromycin (800 once daily) for 5 days
- Ketoconazole (400 mg once daily) along with clarithromycin (500 twice daily) for 5 days
- Ketoconazole alone (400 mg once daily) for 5 days.

Clarithromycin exposure was chosen as the comparator because of its elimination profile being similar to that of telithromycin and because it is a frequently prescribed antibiotic where clinical safety has been established. Subjects administered ketoconazole 400 mg and telithromycin 800 mg once daily for 5 days (see table below) exhibited exposure to telithromycin comparable to that seen in healthy individuals administered telithromycin along with ketoconazole (see *Section 5.4.3, Subjects receiving ketoconazole*). The exposure of telithromycin in these subjects was within the range observed in subjects with RTIs in Phase III trials.

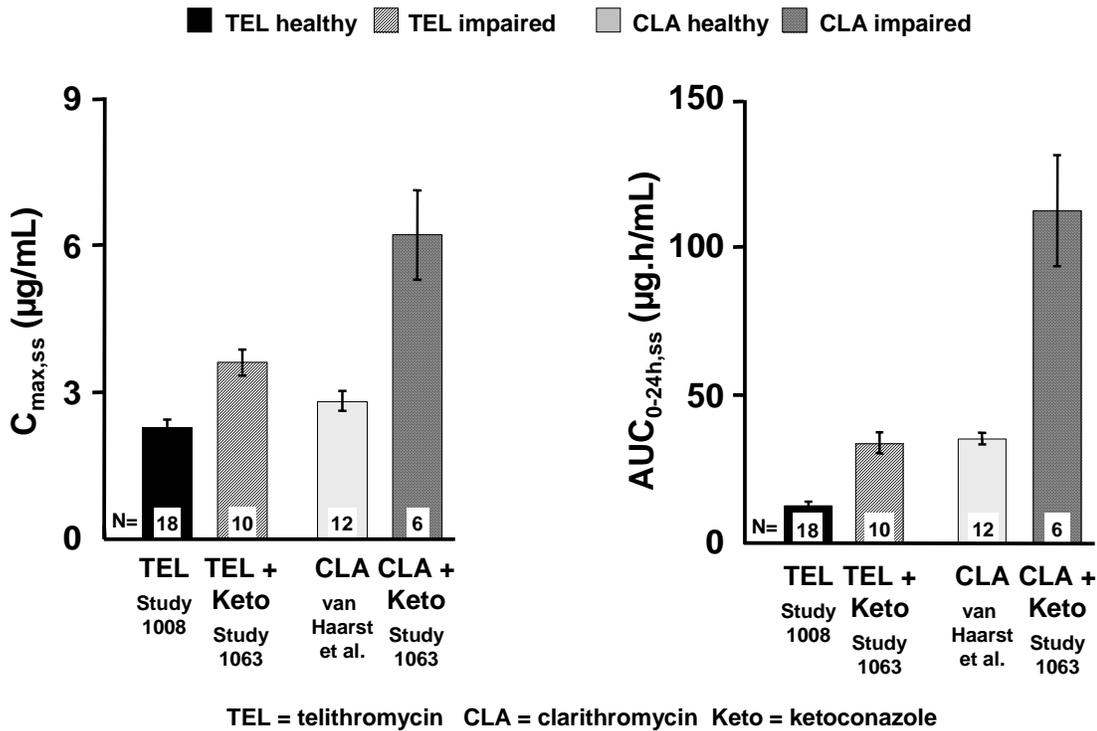
Table 5-9. Steady-state exposure of telithromycin (800 mg) and clarithromycin (500 mg bid) in subjects ≥ 60 years of age with multiple impairment (CL_{CR} 30-80 mL/min)

	Mean data (CV%)	
	Telithromycin	Clarithromycin
	N=10	N=6
Age (years)	74	69
CL_{CR} (mL/min)	49.5 (24.6)	56.8 (28.3)
$C_{max,ss}$ (μ g/mL)	3.6 (22)	6.2 (36)
AUC ₍₀₋₂₄₎ (μ g.h/mL)	33.4 (31)	112.2 (41)
CL_R (L/h)	6.1 (30)	6.4 (48)

Source: Study 1063

The exposure data for the clarithromycin subjects in this population is also shown in the table above. In order to put these levels into perspective, the figure below shows the data for telithromycin and clarithromycin obtained in the multiple impaired subjects (Study 1063) compared to healthy volunteer data reported for the two drugs. The reference data for telithromycin comes from Study 1008 which has been shown in Table 5-2, and the reference data for clarithromycin is from van Haarst et al., 1998 [53].

Figure 5-2. Telithromycin (TEL) and clarithromycin (CLA) exposure in subjects with multiple impairment, compared to respective healthy controls obtained from reference data



Telithromycin and clarithromycin show comparable exposures in this population with multiple impairment. The graph shows that the increase in C_{max} and AUC for telithromycin is 1.6-fold and 2.7-fold, respectively, compared to 2.2-fold and 3.3-fold, respectively, for clarithromycin.

Although the intention of Study 1063 was to recruit subjects with CL_{CR} in the range of 30-80 mL/min, 2 subjects were enrolled with $CL_{CR} < 30$ mL/min, and both were in the telithromycin + ketoconazole group. The telithromycin exposure in these 2 individuals indicated a C_{max} of 5.4 and 8.8 $\mu\text{g/mL}$ and an AUC (0-24) of 51.7 and 61.6 $\mu\text{g}\cdot\text{h/mL}$. In these subjects the AUC and C_{max} were higher than in those subjects with $CL_{CR} > 30$ mL/min. A dose reduction by 50% is recommended when CL_{CR} is < 30 mL/min.

In this study ECGs were obtained at the same time as plasma concentrations. The mean ECG data on Day -1 (drug-free baseline) and Day 5 (steady state on respective therapies) are shown for heart rate (HR) and QT intervals in the table below. It is important to note that there were differences in the baseline HR on Day -1 between the treatment groups ketoconazole alone, ketoconazole and telithromycin, and ketoconazole and clarithromycin, mean HR being 74.4, 56.2, and 67.3 bpm, respectively. There were corresponding different baseline QT intervals of 373, 413, and 386 ms, respectively, among the treatment groups. These baseline differences are likely due to small sample size.

Table 5-10. Mean (SD) values from 10 ECGs obtained on Day -1 (drug-free day) and Day 5 (on therapy)

Treatment group/ No. of subjects	Study day	HR (bpm)	QT (ms)	QTcB (ms)	QTcF (ms)	QTcN (ms)
Ketoconazole (n=11)	Day -1	74.4 (10.7)	373.2 (33.7)	412.4 (17.8)	398.6 (21.3)	399.2 (21.1)
	Day 5	73.1 (10.2)	371.6 (32.6)	407.0 (20.0)	394.7 (22.0)	395.1 (21.8)
Telithromycin and ketoconazole (n=12)	Day -1	56.2 (8.5)	412.9 (21.9)	396.9 (19.2)	401.9 (13.8)	401.6 (14.0)
	Day 5	63.7 (9.6)	401.6 (23.5)	410.4 (17.0)	407.2 (11.8)	407.4 (11.9)
Clarithromycin and ketoconazole ^a (n=7)	Day -1	67.3 (11.0)	385.8 (19.2)	406.1 (25.1)	399.0 (17.5)	399.2 (17.7)
	Day 5	72.0 (10.9)	384.6 (20.2)	419.0 (22.7)	407.0 (16.7)	407.5 (17.1)

^a Two subjects in the clarithromycin and ketoconazole group did not have any Day 5 measurements; these 2 subjects were excluded from the Day -1 calculation. One subject did not reach steady state due to a dosing issue; however, ECG data for this subject is included in the descriptive statistics.

HR: heart rate in beats per min; QT: uncorrected QT interval; QTcB: QT interval corrected for heart rate by Bazett formula; QTcF: QTcF interval corrected for heart rate by Fridericia formula; QTcN: QT interval corrected for heart rate by formula with an exponent derived from QT and RR interval data obtained from drug-free periods of study population.

In the telithromycin group, there were no male subjects with QTc (Bazett) (QT corrected for heart rate by the Bazett formula) >450 ms and no female subjects with values >470 ms. In addition, no treatment groups had an absolute QTc (Bazett) value >500 ms in any of the 10 ECGs obtained on Day 5.

5.5 Drug interactions

As shown in *Section 5.1.4, Pathways of elimination*, telithromycin has multiple pathways of elimination, hence its ability for increased exposure due to inhibition of metabolic pathways by drug interaction is limited. In this drug-interaction section we will outline data to support this.

Several specific metabolic drug interaction studies were performed in humans to assess the following:

- The effect of CYP3A4 inhibitors (itraconazole, ketoconazole, grapefruit juice), the CYP3A4 inducer rifampin, and gastric pH modulators (ranitidine, Maalox[®]) on the pharmacokinetics of telithromycin.
- The effect of telithromycin on the pharmacokinetics of CYP3A4 substrates (cisapride, midazolam, simvastatin), CYP2D6 substrates (paroxetine, metoprolol), and other CYP450 substrates (theophylline, warfarin, digoxin, sotalol, and the oral contraceptive ethinyl estradiol).

5.5.1 Pharmacokinetic parameters of telithromycin in presence of co-administered drug

CYP3A4 inhibitors

- **Itraconazole, ketoconazole:** Telithromycin AUC_{(0-24)ss} increased ~1.5-fold following itraconazole co-administration and 2-fold following ketoconazole co-administration, while C_{max,ss} increased 1.2- and 1.5-fold, respectively. This modest increase in AUC and C_{max,ss}, even with a potent inhibitor of CYP3A4 such as ketoconazole, is consistent with the multiple elimination pathways of telithromycin and the high (57%) absolute bioavailability of telithromycin.

- **Grapefruit juice:** The pharmacokinetics of telithromycin was not affected when telithromycin was co-administered with a single dose of grapefruit juice.

CYP3A4 inducer

- **Rifampin:** The interaction of single and multiple doses of telithromycin 800 mg with rifampin 600 mg was assessed in a crossover study conducted in 12 healthy young men (Study 1058). During concomitant administration of rifampin and telithromycin in repeated doses, C_{max} and AUC of telithromycin were decreased 79% and 86%, respectively.

Gastric pH modulators

- **Ranitidine, Maalox®:** Co-administration of intra-gastric pH-altering agents did not alter the pharmacokinetics of telithromycin (Study 1020).

5.5.2 Pharmacokinetic parameters of co-administered drug in presence of telithromycin

CYP3A4 substrates

- **Cisapride:** An increase in cisapride exposure was seen on co-administration with telithromycin, as demonstrated by increases in 2.0-fold in C_{max} at steady state and 2.4-fold in AUC (Study 1041). Cisapride is known to be mostly eliminated via the CYP3A4 pathway, and the same type of interaction has been reported with clarithromycin (increase of 2.7-fold for C_{max} and 3.2 fold for AUC [53]).
- **Midazolam:** Midazolam is a recommended model substrate that is used to evaluate the inhibition potential for the CYP3A4 pathway. Concomitant administration of telithromycin with intravenous or oral midazolam resulted in 2- or 6-fold increases, respectively, in the AUC of midazolam due to inhibition of CYP3A4-dependent metabolism of midazolam (Study 1056). This level of interaction is similar to that of clarithromycin, and significantly less than that observed with ketoconazole. The table below compares this interaction at clinically relevant doses between telithromycin, clarithromycin, and ketoconazole for orally administered midazolam.

Table 5-11. Fold increase of midazolam exposure

Inhibitor	N	C _{max}	AUC
Telithromycin ^a	12	2.6	6.1
Clarithromycin ^b	16	3	7
Ketoconazole ^a	9	5	16

^a 6 mg dose of midazolam; ^b 4 mg dose of midazolam

Source: Telithromycin data from Study 1056; clarithromycin data from Gorski et al., 1998 [20]; ketoconazole data from Tsunoda et al., 1999 [51]

- **Simvastatin:** An increase in simvastatin exposure was seen when co-administered with telithromycin (Study 1048). While the elimination half-life of simvastatin was not changed, telithromycin increased the bioavailability of simvastatin. C_{max} and AUC values for simvastatin were increased 5.3-fold and 8.9-fold, respectively, while values for simvastatin acid increased 15- and 12-fold, respectively. For statins such as pravastatin and fluvastatin, an interaction is not expected due to non-involvement of the CYP3A4 pathway in their elimination. For atorvastatin (Lipitor®) a lesser interaction is expected due to decreased involvement of CYP3A4 in its elimination.

Simvastatin is a CYP 3A4 substrate and is sensitive to blockage of this enzyme. This is due to a high intestinal first-pass metabolism of this drug. Other mild CYP3A4 inhibitors also have an effect on the exposures of simvastatin. The data from a new study (Study 1067) using clarithromycin (see table below) has not yet been fully evaluated by the FDA. A few examples of this effect are shown below.

Table 5-12. Fold increase due to CYP3A4 inhibition

Inhibitor	N	Simvastatin		Simvastatin acid	
		C _{max}	AUC	C _{max}	AUC
Telithromycin	30	5.3	8.9	15	12
Clarithromycin ^a	12	9.8	8.9	17.9	21.2
Grapefruit juice	10	9	16	7	7
Itraconazole	10	10	10	17	19

Source: Telithromycin, Study 1048; grapefruit juice, Lilja et al., 1998 [29]; itraconazole, Neuvonen et al., 1998 [41]

^a Clarithromycin, Study 1067, data finalized, final report not yet available.

The data from a new recently completed study (Study 1065) has not yet been fully evaluated by the FDA. This study indicates that the magnitude of interaction between telithromycin and simvastatin can be reduced by more than 50% when the two are administered 12 hours apart, as shown in the table below.

Table 5-13. Effect of telithromycin on CYP3A4 inhibitor simvastatin

Parameter	Fold increase in simvastatin exposure ^a (90% confidence interval)		
	Telithromycin 800 mg qd concomitant N=14	Telithromycin 800 mg qd 12 hours apart N=14	
Simvastatin	C _{max}	7.7 (6.3-9.5)	3.4 (2.8-4.2)
	AUC	8.4 (5.9-11.9)	3.8 (2.8-5.1)
Simvastatin acid	C _{max}	10.0 (8.3-12.1)	3.2 (2.6-3.8)
	AUC	9.4 (7.4-11.9)	4.3 (3.3-5.4)

^a After 40 mg single dose of simvastatin; Study 1065, data finalized, final report not yet available.

In summary, it can be seen that the effect on all CYP3A4 substrates is similar between telithromycin and clarithromycin. Telithromycin has the added advantage that its duration of administration for certain RTIs is less compared with macrolides and, as shown earlier, its multiple elimination pathways.

CYP2D6 substrates

- **Paroxetine:** Co-administration of telithromycin with paroxetine did not alter the pharmacokinetics of paroxetine (Study 1022).
- **Metoprolol:** Co-administration of telithromycin slightly increased the bioavailability of metoprolol (1.4-fold increase for both C_{max} and AUC) without affecting elimination, suggesting a minor first-pass effect from CYP2D6 inhibition (Study 1061).

Other drugs

- **Theophylline:** AUC_{(0-12)ss} and C_{max,ss} values of theophylline both increased by approximately 1.2-fold after co-administration of telithromycin (Study 1011).

- **Warfarin:** There was no pharmacokinetic or pharmacodynamic interaction between telithromycin and racemic warfarin (Study 1012).
- **Digoxin:** The AUC of digoxin increased by 1.4-fold, the C_{max} increased by 1.7-fold, and the trough plasma concentrations by 1.2-fold on co-administration with telithromycin (Study 1013). However, trough plasma concentrations of digoxin (when equilibrium between plasma and tissue concentrations are achieved) remained within the recommended therapeutic range for all subjects, and there were no signs of digoxin toxicity. The precautions usually associated with digoxin therapy should be considered (e.g., monitoring of digoxin side effects).
- **Sotalol:** In the presence of telithromycin, AUC and C_{max} values for sotalol were decreased by 20% and 34%, respectively, after a single 160-mg dose of sotalol (Study 1057). This interaction is due to a decrease in sotalol absorption in the presence of telithromycin.
- **Oral contraceptives:** A multiple-dose study of the interaction between telithromycin and a low-dose triphasic oral contraceptive showed that telithromycin did not affect anti-ovulatory action (Study 1042).

Based on the studies cited above, the drug interaction potential of telithromycin can be summarized as follows:

- The increase in telithromycin exposure due to impairment of metabolic pathways for drug interaction is minimal. This is primarily due to its multiple pathways of elimination.
- The potential for telithromycin to inhibit the CYP3A4 pathway is similar to that seen with clarithromycin and less than that seen with known potent inhibitors.
- Telithromycin is administered for shorter treatment durations for certain RTIs compared to macrolides, and is given once daily, indicating that there will be less potential for exposure increase and hence drug interactions.

6. EFFICACY BY INDICATION

6.1 Scope of the clinical program

6.1.1 Indications

The target indications for telithromycin are community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), and acute sinusitis (AS).

6.1.2 Studies performed

Fourteen Phase III studies were conducted in the US, Europe, South America, Australia, and South Africa to support the claim for the 3 target indications. In addition, 2 studies in CAP (Studies 2105 and 3107) were conducted in Japan. Efficacy data from the Japanese studies were not fully integrated in the NDA, and in agreement with the FDA, only data from subjects with resistant *S. pneumoniae* isolates are used to support the claim. Hence, in the presentation of efficacy data for CAP, a distinction is made between “Western studies” (conducted in the US, Europe, South America, Australia, and South Africa) and the Japanese studies. In addition, a large trial in CAP, AECB, and acute sinusitis subjects (Study 3014) was conducted in the US with minimal exclusion criteria and performed in the usual care settings. This study is presented separately because of differences in study design and efficacy outcomes.

Across the 3 indications, 9 active-controlled studies are used to support the claims. In addition, there are 5 uncontrolled studies (4 open-label Western studies in CAP and 1 double-blind comparative study of 2 durations of treatment with telithromycin in acute sinusitis), that are also used to support the claim for the appropriate indication.

The study design and dosing regimen of the 17 Phase II and III studies (14 Western Phase III studies, 2 Japanese Phase II and III studies, and Study 3014) used to support the claim are summarized in the table below.

Table 6-1. Phase II and III studies submitted to NDA 21-144

Indication/ Study No.	Study Design	Treatment Regimen		
Community-acquired pneumonia				
3000	Open label	7 to 10 d	TEL	800 mg qd
3001	Double-blind	10 d	TEL	800 mg qd
		10 d	AMX	1000 mg tid
3006	Double-blind	10 d	TEL	800 mg qd
		10 d	CLA	500 mg bid
3009	Double-blind	7 to 10 d	TEL	800 mg qd
		7 to 10 d	TVA	200 mg qd
3009OL	Open label	7 to 10 d	TEL	800 mg qd
3010	Open label	7 d	TEL	800 mg qd
3012	Open label	7 d	TEL	800 mg qd
4003	Double-blind	5 d	TEL	800 mg qd
		7 d	TEL	800 mg qd
		10 d	CLA	500 mg bid
2105 (Japan)	Double-blind	7 d	TEL	600 mg qd
		7 d	TEL	800 mg qd
3107 (Japan)	Double-blind	7 d	TEL	600 mg qd
		7 d	LVF	100 mg tid
Acute exacerbation of chronic bronchitis				
3003	Double-blind	5 d	TEL	800 mg qd
		10 d	AMC	500 mg/125 mg tid
3007	Double-blind	5 d	TEL	800 mg qd
		10 d	CXM	500 mg bid
3013	Double-blind	5 d	TEL	800 mg qd
		10 d	CLA	500 mg bid
Acute sinusitis				
3002	Double-blind	5 d	TEL	800 mg qd
		10 d	TEL	800 mg qd
3005	Double-blind	5 d	TEL	800 mg qd
		10 d	TEL	800 mg qd
		10 d	AMC	500 mg/125 mg tid
3011	Double-blind	5 d	TEL	800 mg qd
		10 d	CXM	250 mg bid
Large Trial in a Usual Care Setting				
3014	Open-label	5 d in AS	TEL	800 mg qd ^a
		7 to 10 d in CAP/AECB	TEL	800 mg qd ^a
		7 to 10 d in all indications	AMC	875 mg/125 mg tid ^b

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

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

^b In subjects with known severe renal impairment, the dose was reduced to 500 mg amoxicillin (500/125 mg tablet) bid if creatinine clearance was between 10 and 30 mL/min, and to 500 mg qd if creatinine clearance was <10 mL/min.

6.1.3 Number of subjects randomized and treated in the Phase III program

A total of 5817 subjects (≥13 years of age) were randomized (or assigned, as in open-label studies 3000, 3009OL, 3010, and 3012) to telithromycin (4078 subjects) or comparator drugs (1739 subjects)

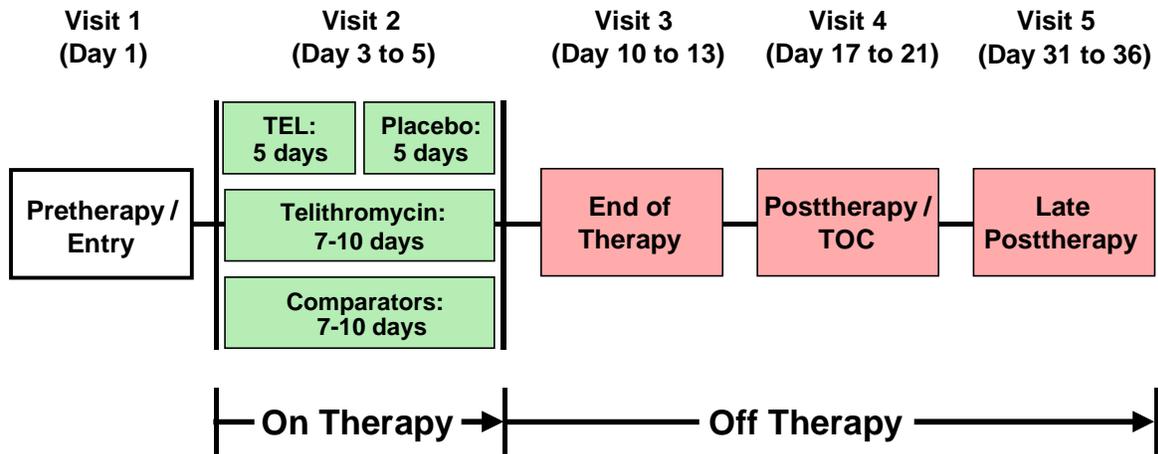
in the Phase III clinical program (Western studies): 4070 were treated with telithromycin and 1735 with a comparator antibiotic. Twelve subjects were randomized but did not receive treatment.

The number of subjects in the safety evaluable population is given in *Section 7.1, Extent of exposure*.

6.2 Study design

The overall design for all Western studies in the clinical development of telithromycin is presented below.

Figure 6-1. General study design for Western Phase III studies



In the Japanese studies, the main efficacy outcome measure was assessed at the end of treatment (7 days) to comply with Japanese guidelines for evaluating the efficacy of anti-infectives. However, a second efficacy outcome was evaluated 7 days after the end of treatment, corresponding to a time window of 14 to 28 days after commencing treatment, which is in the time window used for test of cure (TOC) evaluation in Western studies (Days 17 to 21).

6.2.1 Schedule of efficacy assessments

In all studies, clinical signs and symptoms of infection were assessed at each study visit.

6.2.2 Dosing

6.2.2.1 Telithromycin

In all the Western Phase III studies, telithromycin was administered as an oral dose of 800 mg once daily. The duration of treatment in each indication was as follows:

- CAP: 5 or 7 days (Study 4003), 7 days only (Studies 3010 and 3012), 7 to 10 days (Studies 3000, 3009, and 3009OL), or 10 days (Studies 3001 and 3006)
- AECB: 5 days (Studies 3003, 3007, and 3013)
- Acute sinusitis: 5 days only (Study 3011), or 5 or 10 days (Studies 3002 and 3005)

When the telithromycin dosing regimen called for fewer days of active medication than in the comparative treatment group, a regimen of placebo treatment continued until the maximum number of days of treatment (10 days) was achieved in order to maintain the blind (see the figure at the beginning of *Section 6.2, Study design*).

6.2.2.2 Active comparators

Comparator dosing regimens (all given orally) were as follows:

- In the controlled CAP studies, comparator regimens were amoxicillin 1000 mg tid for 10 days (Study 3001), clarithromycin 500 mg bid for 10 days (Studies 3006 and 4003), trovafloxacin 200 mg once daily for 7 to 10 days (Study 3009), and levofloxacin 100 mg tid for 7 days (Japanese Study 3107). There was no active comparator in the Japanese Study 2105, which compared 2 doses of telithromycin (600 and 800 mg) in a randomized, double-blind design.
- In the AECB studies, comparator regimens were coadministration of amoxicillin-clavulanic acid at 500/125 mg tid for 10 days (Study 3003), cefuroxime axetil 500 mg bid for 10 days (Study 3007), and clarithromycin 500 mg bid for 10 days (Study 3013).
- In acute sinusitis Study 3005, coadministration of amoxicillin-clavulanic acid at 500/125 mg tid for 10 days was used as the comparator. There was no active comparator in Study 3002, which compared 2 durations of treatment with telithromycin (5 days and 10 days) in a randomized, double-blind design. In Study 3011, cefuroxime axetil 250 mg bid for 10 days was used as the comparator.

6.2.3 Standardization of processes

Processes used for clinical evaluation (time windows for assessment of outcome [Western and Japanese studies], study variables, categorization of clinical outcome) and bacteriological evaluation (isolation of causative pathogens, susceptibility testing, serotyping, genotyping, categorization of bacteriological outcome, and diagnosis and evaluation of outcome due to atypical and intracellular organisms) were standardized across all studies. These processes are described in *Appendix 2, Standardization of processes for Phase III studies*.

6.3 Statistical methods

6.3.1 Definition and analysis of study populations

6.3.1.1 Analysis populations

Analyses were based on clinical and bacteriological outcome data assessed at post-therapy/TOC and late post-therapy in the individual studies. These analyses were performed for 4 populations:

Table 6-2. Analysis populations

Population	Definition
mITT	All randomized subjects, as treated, with a confirmed diagnosis of infection who received at least 1 dose of study medication. A confirmed diagnosis was defined by clinical signs and symptoms and X-ray findings as defined in the protocols.
PPc	All mITT subjects except those with major protocol violations and/or indeterminate responses. ^a
bmITT	All mITT subjects with a pathogen at pretherapy/entry considered by the investigator to be responsible for the infection.
PPb	All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.

Population definitions: mITT = modified intent-to-treat; PPc = clinically evaluable per protocol; bmITT = bacteriologically evaluable modified intent-to-treat; PPb = bacteriologically evaluable per protocol.

^a See Section 6.3.1.2, *Evaluability criteria*

Note that the definition of the mITT is different from the classic definition of intent-to-treat (ITT, i.e., all randomized subjects). The aim of analyzing mITT instead of ITT for analysis was to exclude subjects with a clear misdiagnosis and to provide a more clinically consistent approach to establish statistical and clinical equivalence between telithromycin and the active comparators under study.

6.3.1.2 Evaluability criteria

Subjects were excluded from the PPc population if they had one or more major protocol violations or had indeterminate responses and were therefore included only in the mITT/bmITT analyses.

The major protocol violation criteria were as follows:

- wrong entry diagnosis
- signs and symptoms insufficient to meet clinical criteria
- insufficient treatment duration - fewer than 5 consecutive days of treatment except if the subject was considered a failure during the first 5 days where 2 days of treatment were required; less than a 70% compliance rate overall unless the subject was considered a failure before the last dose on Day 7
- treatment unblinded before post-therapy/TOC
- treatment discontinued a posteriori because of laboratory exclusion criteria at pretherapy/entry.

Indeterminate response criteria were as follows:

- missing appropriate post-treatment information or inability to determine outcome at post-therapy/TOC: for subjects with a missing post-therapy/TOC assessment, clinical failure or unsatisfactory bacteriological response before the planned assessment was carried forward to post-therapy/TOC
- if the late post-therapy assessment was missing, failure before the planned assessment was carried forward to late post-therapy
- in circumstances where it was not possible to give a binary cure or failure response, the clinical and bacteriological responses were considered indeterminate and these subjects were excluded from the per-protocol analysis.

In the mITT and bmITT by-subject analyses, subjects with indeterminate response were classified as failures.

6.3.2 Efficacy analyses

6.3.2.1 Primary efficacy analysis

The primary efficacy analysis was to determine equivalence between telithromycin and active comparators, using a two-tailed 95% confidence interval approach (1992 FDA Points to Consider) for the clinical outcome at post-therapy/TOC in the PPc population. Estimates of cure rates with confidence intervals were prepared for the open-label studies.

6.3.2.2 Secondary efficacy analyses

The following analyses were secondary and supportive to the primary endpoint:

- clinical outcome at post-therapy/TOC in the mITT population,
- clinical outcome at late post-therapy in the PPc and mITT populations, and
- bacteriological outcome at post-therapy/TOC and late post-therapy in the PPb and bmITT populations.

6.3.2.3 Analysis methods and equivalence criteria

The two-sided 95% confidence interval was calculated as follows:

$$\text{lower bound} = (P_h - P_c) - 1.96 \times S - \frac{1}{2} \left(\frac{1}{N_h} + \frac{1}{N_c} \right)$$

$$\text{upper bound} = (P_h - P_c) + 1.96 \times S + \frac{1}{2} \left(\frac{1}{N_h} + \frac{1}{N_c} \right)$$

where S is the standard deviation for the treatment difference = $\sqrt{\frac{P_h(1-P_h)}{N_h} + \frac{P_c(1-P_c)}{N_c}}$, N_h and N_c are the numbers of subjects for telithromycin and comparator, respectively, and P_h and P_c are the observed response rates.

The 2 treatments were considered equivalent if the lower limit of the confidence interval was greater than or equal to -15% and the upper limit contained zero, for efficacy rates of 80% to 90%, for the better of the 2 study medications. A lower limit greater than or equal to -10% would have been required if the efficacy rate was above 90%.

In studies with 3 treatment arms (Studies 3005 and 4003), a closed comparison test was performed, comparing 10 days of telithromycin treatment with 10 days of comparator and 5 days of telithromycin with 10 days of comparator if equivalence was demonstrated in the first comparison.

6.4 Clinical studies

The number of subjects in telithromycin-treated populations is summarized below.

Table 6-3. Number of telithromycin-treated subjects in Phase III populations by indication

Indication	Population					
	Randomized	Treated	mITT	PPc	bmITT	PPb
CAP (Western studies)	2365	2365	2289	1925	1061	653
AECB	618	615	612	480	172	136
Acute sinusitis	1095	1090	980	731	345	253
Total	4078	4070	3881	3136	1578	1042

Population definitions: mITT = modified intent-to-treat; PPc = clinically evaluable per protocol; bmITT = bacteriologically evaluable modified intent-to-treat; PPb = bacteriologically evaluable per protocol.

6.4.1 Community-acquired pneumonia

The clinical and bacteriological effectiveness of 800 mg telithromycin administered orally once daily for 5 to 10 days in the treatment of community-acquired pneumonia (CAP) in adults was evaluated in 4 double-blind, randomized, comparative studies (Studies 3001, 3006, 3009, and 4003) and in 4 uncontrolled studies (Studies 3000, 3009OL, 3010, and 3012). In addition, 2 double-blind studies were conducted in Japan (Studies 2105 and Study 3107). For the Japanese studies, only data concerning resistant *S. pneumoniae* isolates are reported in this briefing document. The studies conducted in CAP are summarized in the table below.

Table 6-4. CAP: Studies conducted

Study No.	Study design	Treatment regimen			No. in mITT
Western studies					
3001	Double-blind	TEL	800 mg qd	10 d	199
		AMX	1000 mg tid	10 d	205
3006	Double-blind	TEL	800 mg qd	10 d	204
		CLA	500 mg bid	10 d	212
3009	Double-blind	TEL	800 mg qd	7 - 10 d	100
		TVA	200 mg qd	7 - 10 d	104
4003	Double-blind	TEL	800 mg qd	5 d	187
		TEL	800 mg qd	7 d	191
		CLA	500 mg bid	10 d	181
3000	Open label	TEL	800 mg qd	7 - 10 d	240
3009OL	Open label	TEL	800 mg qd	7 - 10 d	212
3010	Open label	TEL	800 mg qd	7 d	418
3012	Open label	TEL	800 mg qd	7 d	538
All CAP (Western studies)				TEL Comparators	2289 702
Japanese studies					
2105	Double-blind	TEL	600 mg qd	7 d	46
		TEL	800 mg qd	7 d	50
3107	Double-blind	TEL	600 mg qd	7 d	126
		LVF	100 mg tid	7 d	111
All CAP (Japanese studies)				TEL Comparators	222 111

TEL = telithromycin, AMX = amoxicillin; CLA = clarithromycin; TVA = trovafloxacin, CLA = clarithromycin, LVF = levofloxacin

6.4.1.1 Controlled studies

In Study 3001, amoxicillin 1000 mg tid was chosen as the comparator because, in countries with high prevalence of penicillin G-resistant *S. pneumoniae*, an accepted treatment standard is to increase the dose of the β -lactam antibiotics in order to achieve plasma drug concentrations above the MIC of strains with decreased susceptibility to penicillin G. Recent studies have demonstrated that amoxicillin is safe and effective at this dosage [50].

The aim of Study 3006 was to provide clinical and bacteriological efficacy data for a broad population of outpatients with CAP, including subjects with common and atypical pathogens, with clarithromycin 500 mg bid as the active comparator.

In Study 3009, trovafloxacin 200 mg once daily was chosen as the comparator because it is active against common as well as intracellular and atypical pathogens, and has excellent activity against *S. pneumoniae* resistant to penicillin G and the macrolides (erythromycin A). Trovafloxacin was approved in the US at this dosage for the treatment of CAP. Study 3009 was stopped prematurely after the FDA restricted trovafloxacin to inpatient use for severe infections as a result of safety concerns that arose during postmarketing surveillance.

Study 4003 was a double-blind, active-controlled study performed in adult subjects with CAP. The study was primarily performed to demonstrate equivalence in clinical efficacy at TOC comparing 5 or 7 days of telithromycin with 10 days of clarithromycin.

The Japanese Study 2105 compared 2 different doses of telithromycin (600 mg and 800 mg) and Study 3107 used levofloxacin as the comparator. Drug exposure with 600 mg in Japanese subjects is similar to the 800 mg dose used in Western subjects. Therefore, 600 mg per day was the dose chosen for Japanese subjects.

6.4.1.2 Uncontrolled studies

Studies 3000, 3009OL, 3010, and 3012 were open-label, multicenter, uncontrolled noncomparative studies performed to increase the clinical experience in subjects with *S. pneumoniae* resistant to penicillin G and/or erythromycin A (the macrolides). In Studies 3010 and 3012, the treatment duration was limited to 7 days in order to increase the experience with a reduced treatment duration in this indication.

Inclusion criteria used to enrich for *S. pneumoniae*

In selected studies the inclusion criteria were modified to increase the likelihood of recruiting subjects with *S. pneumoniae* infections (“enriched” studies). In Studies 3001, 3009OL, 3010, and 3012 inclusion criteria were customized to select a population that was more likely to have pneumococcal pneumonia, with at least one of the following: fever, chills, pleuritic chest pain, WBC >10,000/mm³, or a Gram stain showing gram-positive diplococci. In addition, in Study 3009OL, all subjects had to have consolidation on their chest X-ray at pretherapy/entry.

6.4.1.3 Exclusion criteria related to severity at entry

In the Western studies, subjects requiring intravenous treatment according to American Thoracic Society or British Thoracic Society criteria (see *Appendix 3. Key inclusion/exclusion criteria*) were excluded. In the Japanese studies, cases were excluded if 3 or more of the following symptoms were

present: body temperature $\geq 38.6^{\circ}\text{C}$ (101.2°F); white blood cell count $\geq 20,000/\text{mm}^3$; chest X-ray score ≥ 6 points; C-reactive protein ≥ 20 mg/dL.

6.4.1.4 Duration of treatment

The treatment duration was 10 days in Studies 3006 and 3001. Treatment duration was 7 to 10 days in Studies 3000, 3009, 3009OL. Studies 3010, 3012 and 4003 had a treatment duration of 7 days (Study 4003 also had a 5 day treatment arm).

6.4.1.5 Subject disposition and demographics

The subject disposition within each population (Western studies) is shown below.

Table 6-5. CAP (Western studies): Subject disposition

Population	Telithromycin	Comparators	Total
Randomized	2365	729	3094
Treated	2365	728	3093
mITT	2289	702	2991
PPc	1925	540	2465
bmITT	1061	244	1305
PPb	653	144	797

The key demographic characteristics are summarized in the table below.

Table 6-6. CAP (Western studies): Key demographic characteristics - mITT population

Characteristic	All CAP studies	
	Telithromycin	Comparators
Total Treated	2289	702
Sex		
Male	1290 (56.4)	357 (50.9)
Female	999 (43.6)	345 (49.1)
Age		
Mean (years)	44.8	45.6
13 to 18 years	52 (2.3)	21 (3.0)
>18 to <65 years	1904 (83.2)	557 (79.3)
≥ 65 years	333 (14.5)	124 (17.7)
Race		
White	1561 (68.2)	544 (77.5)
Black	538 (23.5)	123 (17.5)
Asian	33 (1.4)	8 (1.1)
Other	156 (6.8)	26 (3.7)
Smoker	696 (36.4)	209 (40.1)

Key pretherapy/entry characteristics for the mITT population are summarized in the table below.

Table 6-7. CAP (Western studies): Key pretherapy/entry characteristics - mITT population

	All CAP	
	Telithromycin	Comparators
Total Treated	2289	702
Fever >39°C	948 (41.4)	294 (41.9)
WBC >10 ³ /mm ³	1084 (47.4)	344 (49.0)
X-ray findings		
Bilateral	425 (18.6)	52 (7.6)
Multiple lobes	315 (13.8)	65 (9.5)
Documented pneumococcal bacteremia	98 (4.3)	24 (3.4)
Severity, moderate ^a	1542 (67.4)	501 (71.4)
Fine score		
Class I	1164 (50.8)	331 (47.2)
Class II	770 (33.6)	228 (32.5)
Class ≥III	355 (15.5)	143 (20.3)

^a As assessed by the investigator.

The CAP population studied is large (2289 telithromycin, 702 comparators) and overall the baseline characteristics were balanced between the treatment groups. Although the studies targeted mostly outpatients with CAP eligible for treatment with oral antibiotics, they included a large number of subjects with comorbidity risks. The experience obtained with telithromycin in these subjects is substantial in the most vulnerable outpatients: subjects ≥65 years of age (333 subjects), with Fine score ≥III (355 subjects), or with bilateral pneumonia (425 subjects).

6.4.1.6 Clinical outcome (Western studies)

The primary efficacy analysis in CAP (Western studies) was the analysis of clinical outcome at post-therapy/TOC (Days 17 to 24) in the per protocol population of subjects (PPc). Clinical outcomes at post-therapy/TOC for the PPc and mITT populations are summarized in the table below.

Table 6-8. CAP (Western studies): Clinical cure rate by study for telithromycin and comparator(s) at post-therapy/TOC

	Telithromycin			Comparator			95% CI ^a
	N	n	(%)	N	n	(%)	
PPc population							
Study 3001	149	141 (94.6)		152	137 (90.1)		[-2.1; 11.1]
Study 3006	162	143 (88.3)		156	138 (88.5)		[-7.9; 7.5]
Study 3009	80	72 (90.0)		86	81 (94.2)		[-13.6; 5.2]
Study 4003							
TEL 5 d	159	142 (89.3)		146	134 (91.8)		[-9.7; 4.7]
TEL 7 d	161	143 (88.8)		146	134 (91.8)		[-10.2; 4.3]
Study 3000	197	183 (92.9)					
Study 3009OL	187	175 (93.6)					
Study 3010	357	332 (93.0)					
Study 3012	473	424 (89.6)					
All CAP studies	1925	1755 (91.2)		540	490 (90.7)		[-2.4; 3.3]
mITT population							
Study 3001	199	171 (85.9)		205	161 (78.5)		[-0.5; 15.3]
Study 3006	204	161 (78.9)		212	171 (80.7)		[-9.9; 6.5]
Study 3009	100	82 (82.0)		104	89 (85.6)		[-14.7; 7.5]
Study 4003							
TEL 5 d	187	154 (82.4)		181	147 (81.2)		[-7.3; 9.6]
TEL 7 d	191	157 (82.2)		181	147 (81.2)		[-7.4; 9.4]
Study 3000	240	191 (79.6)					
Study 3009OL	212	182 (85.8)					
Study 3010	418	357 (85.4)					
Study 3012	538	447 (83.1)					
All CAP studies	2289	1902 (83.1)		702	568 (80.9)		

^a 95% confidence interval of the difference in cure rates between the treatment groups.

Rates in the PPc population based on pooled data from the All CAP studies were similar for the telithromycin and comparator treatment regimens. Overall, a total of 1755/1925 (91.2%) subjects in the telithromycin group were designated as clinically cured at post-therapy/TOC. The results of clinical efficacy obtained in the mITT population confirmed the results obtained in the PPc population.

In Study 3009 vs. trovafloxacin, both treatments gave high cure rates, exceeding 90%. This study was stopped before the planned sample size was reached, when the FDA restricted the use of trovafloxacin because of postmarketing safety concerns, but the results also support the efficacy of telithromycin in this indication.

6.4.1.7 Clinical cure rate by pathogen (Western studies)

The clinical cure rate at post-therapy/TOC for the PPb population in Western studies are presented below for select common causative pathogens. The overall eradication rate was high with cure rates for the telithromycin-treated subjects of 94.3% in *S. pneumoniae*, 90.0% in *H. influenzae*, 88.0% *M. catarrhalis*, and 81.8% in *S. aureus*. Atypical and intracellular pathogens are discussed in Section 6.4.1.11, *Clinical outcome among subjects infected with atypical and intracellular pathogens*.

Table 6-9. CAP (Western studies): Clinical cure rates by pathogen in telithromycin-treated subjects - PPb population

Causative pathogen	Clinical cure					
	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
<i>S. pneumoniae</i>	318	300	(94.3)	70	63	(90.0)
<i>H. influenzae</i>	229	206	(90.0)	44	42	(95.5)
<i>M. catarrhalis</i>	50	44	(88.0)	9	7	(77.8)
<i>S. aureus</i>	44	36	(81.8)	6	6	(100)
Other	190	168	(88.4)	55	48	(87.3)
Total (all pathogens)	831	754	(90.7)	184	166	(90.2)

Other = includes organisms recovered in culture from sputum meeting the definition of adequate and identified by the investigator as causative, but which may or may not be generally recognized as pathogenic in subjects with this type of infection.

N = subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry. n = subjects in the PPb population whose causative pathogen was eradicated or who were assessed as clinical cure.

6.4.1.7.1 *S. pneumoniae* isolates resistant to penicillin G and/or macrolides (Western studies and Japanese Studies 2105 and 3107)

Data obtained in the Western studies and in the Japanese studies (Studies 2105 and 3107) are first presented separately, and are then integrated. Only the data obtained from the Japanese studies at post-therapy/TOC with *S. pneumoniae* isolates resistant to penicillin G and/or macrolides (600 and 800 mg) are pooled with the corresponding data from the Western studies.

Table 6-10. CAP (All studies): Clinical cure rates at post-therapy/TOC for *S. pneumoniae* resistant isolates^a from single and mixed pathogen infections in telithromycin-treated subjects - PPb population

Causative pathogen	All Western ^b			All Japanese ^c			All CAP studies ^d		
	N	n	(%)	N	n	(%)	N	n	(%)
All <i>S. pneumoniae</i>	318	300	(94.3)	30	28	(93.3)	348	328	(94.3)
PRSP	19	16	(84.2)	8	8	(100)	27	24	(88.9)
ERSP	29	25	(86.2)	21	19	(90.5)	50	44	(88.0)
PRSP and ERSP	11	8	(72.7)	8	8	(100)	19	16	(84.2)
PRSP only	8	8	(100)	0	0		8	8	(100)
ERSP only	18	17	(94.4)	13	11	(84.6)	31	28	(90.3)

N = number of subjects; n = number clinically cured; PRSP = penicillin G-resistant (MIC \geq 2.0 μ g/mL); ERSP = erythromycin A- (macrolide-) resistant (MIC \geq 1.0 μ g/mL).

^a Subjects with *S. pneumoniae* isolates resistant to both penicillin G and the macrolides (erythromycin A) are displayed in both the PRSP and ERSP categories.

^b Includes controlled CAP Studies 3001 (vs. amoxicillin), 3006 (vs. clarithromycin), and 3009 (vs. trovafloxacin); uncontrolled CAP Studies 3000, 3009OL, 3010.

^c Includes the 2 Japanese studies (2105 and 3107).

^d Includes all Western CAP studies and the 2 Japanese studies

For all patients infected with *S. pneumoniae*, as well as for the subsets of subjects with penicillin G- and/or macrolide-resistant (erythromycin A) pneumococci, the clinical cure rates were comparable. The efficacy of telithromycin in subjects with *S. pneumoniae* resistant to macrolides has been confirmed at >85% in a substantial cohort of subjects (50 subjects).

The efficacy rates are consistent among those subjects with single pathogen infections confirm the high efficacy of telithromycin with cure rates above 90%.

Table 6-11. CAP (All studies): Clinical cure rates at post-therapy/TOC for *S. pneumoniae* resistant isolates^a from single pathogen infections among telithromycin-treated subjects - PPb population/All CAP Studies

Causative pathogen	All CAP ^b Studies		
	N	n	(%)
All <i>S. pneumoniae</i>	243	229	(94.6)
PRSP	16	15	(93.8)
ERSP	32	29	(90.6)
PRSP and ERSP	10	9	(90.0)
PRSP only	6	6	(100)
ERSP only	22	20	(90.9)

N = number of subjects; n = number clinically cured; PRSP = penicillin G-resistant (MIC ≥ 2.0 $\mu\text{g/mL}$); ERSP = erythromycin A- (macrolide-) resistant (MIC ≥ 1.0 $\mu\text{g/mL}$).

^a Subjects with *S. pneumoniae* isolates resistant to both penicillin G and/or the macrolides (erythromycin A) are displayed in both the PRSP and ERSP categories.

^b Includes all Western CAP studies and the Japanese studies (2105 and 3107).

There were 6 treatment failures among subjects with macrolide-resistant (erythromycin A) *S. pneumoniae* out of 50 cases isolated. Only 1 of these 6 subjects had a documented *S. pneumoniae* on a second culture (Subject 3009OL/0369/105 whose HIV status was questionable). The other 5 subjects either had the *S. pneumoniae* eradicated or the status was unknown because a second blood culture was not performed. Short summaries for each of these cases are presented below.

Single pathogen infection

- Subject 3009OL/0369/105: This subject was a 37-year-old female, Fine score II, with consolidation on the pretherapy/entry chest X-ray, she presented with CAP caused by *S. pneumoniae* isolated from blood and respiratory specimens (telithromycin MIC, 0.12 $\mu\text{g/mL}$; penicillin G MIC, 2 $\mu\text{g/mL}$; erythromycin A MIC, 4 $\mu\text{g/mL}$; genotype *mef*[A]). The HIV status of this South African subject is unknown (the prevalence of HIV infection is high in this population). The subject received telithromycin for 4 days and was then treated with intravenous antibiotics of penicillin G (1.2 million units every 6 hours) and cefoxitin (1 gram every 8 hours) because her clinical status was described as unchanged by the investigator. A blood culture was performed on Day 4, before the change in antibiotics, that showed a *S. pneumoniae* susceptible to telithromycin (MIC of 0.5 $\mu\text{g/mL}$). The clinical outcome after subsequent antimicrobial treatment was cure.
- Subject 2105/15/15-1: This subject was a 68-year-old male; he presented with pneumonia caused by *S. pneumoniae* isolated from the sputum (telithromycin MIC: 0.5 mg/mL; penicillin G MIC: 0.06 mg/mL; erythromycin A MIC >512 mg/mL; genotype *erm*[B]). After clinical symptoms and C-reactive protein had normalized initially, this subject was classified as a failure 1 week after the end of treatment because the investigator prescribed an additional antibiotic (clarithromycin, 200 mg bid, 6 days), to prevent relapse, based on his clinical judgment.
- Subject 3107/042/104: This subject was a 69-year-old male, with bronchiectasis, anemia and Hepatitis C virus carriage; he presented with mild pneumonia caused by *S. pneumoniae* isolated from the sputum (telithromycin MIC, 0.008 mg/mL; penicillin G MIC, 0.06 mg/mL; erythromycin A MIC, 16 mg/mL; genotype *erm*[B]). On Day 3, temperature and sputum purulence had decreased but chest X-ray findings were unchanged, and the WBC count remained elevated. On

Day 7, the subject's temperature was 36.3°C, and his chest X-ray had improved, but a new antibiotic (amoxicillin-clavulanic acid) was prescribed because of remaining opacities on the X-ray and high CRP. The initial pathogen was not re-isolated and no new pathogens were cultured. The clinical outcome at test of cure was categorized as failure because an additional antimicrobial agent was prescribed, despite the fact that the clinical signs had improved.

Mixed pathogen infections

- Subject 3000/605/1091: This subject was a 78-year-old female, Fine score III, with consolidation on the pretherapy/entry chest X-ray; she presented with pneumonia caused by *S. pneumoniae* isolated in blood (telithromycin MIC, 0.03 µg/mL; penicillin G MIC, 2 µg/mL; erythromycin A MIC, 32 µg/mL; genotype *erm*[B]). The *S. pneumoniae* was associated with 2 other causative pathogens isolated from respiratory specimens, *H. influenzae* (telithromycin MIC, 1 µg/mL) and *M. catarrhalis* (telithromycin MIC was not performed, pathogen was susceptible by disk diffusion). After initial improvement, the subject was treated with intravenous antibiotics for a recurrence of symptoms (dyspnea and fever) associated with a diagnosis by the investigator of urinary tract infection due to *S. aureus*. The subject's clinical status at TOC was improved and the blood culture was negative but the *S. pneumoniae* was presumed to be persistent because of the additional antibiotics required for treatment of the secondary urinary tract infection.
- Subject 3001/1002/027: This subject was a 71-year-old female, Fine score IV, with lobar consolidation on the pretherapy/entry chest X-ray and a history of COPD; she presented with pneumonia caused by *S. pneumoniae* isolated in sputum, (telithromycin MIC, 0.03 µg/mL; penicillin G MIC, 2 µg/mL; erythromycin A MIC, 32 µg/mL; genotype *erm*[B]). The *S. pneumoniae* was associated with 2 other causative pathogens isolated from sputum, *H. influenzae* (telithromycin MIC, 1 µg/mL) and *S. aureus* (telithromycin MIC, 0.12 µg/mL). This subject had low blood pressure at entry (95/70 mm Hg), and after worsening of the symptoms on Day 2, died on Day 4 from a severe multiorgan failure considered not related to the study medication by the investigator. The exclusion criteria used were based on the American Thoracic Society and the British Thoracic Society criteria for severity of CAP (systolic blood pressure ≤ 90 mm Hg is considered as shock) as well as the judgement of the investigator. *A posteriori* this subject should have received intravenous treatment at entry, given the low blood pressure, age, and CAP.
- Subject 3012/1041/003: This subject was a 78-year-old female, Fine score II, with preexisting bilateral multiple lobe COPD unrelated to infection, bilateral single lobe atelectasis, and left single lobe infiltrate, diabetes mellitus, and a past history of smoking; she presented with moderate CAP caused by *S. pneumoniae* isolated from sputum (telithromycin MIC, 0.12 µg/mL; penicillin G MIC, 0.03 µg/mL; erythromycin A MIC, 8 µg/mL; genotype *mef*[A]). The *S. pneumoniae* was associated with *M. catarrhalis* (MIC was not performed). At the on-therapy and end-of-therapy visits it was impossible to obtain sputum specimens for culture. On Day 16, the subject was hospitalized for fever and worsening pneumonia. Chest X-ray showed lungs to be hyperexpanded compatible with preexisting condition of COPD unrelated to infection and an infiltrate in the left lung base and lingula, which was assessed as worse compared with pretherapy/entry. There was no sputum sample collected for culture during the hospitalization. Clinical outcome was failure and bacteriological outcome was presumed persistence for *S. pneumoniae* and *M. catarrhalis*. Subsequent antimicrobial treatment with levofloxacin was given. After completing the course of levofloxacin therapy, the clinical outcome was assessed as cure.

Efficacy according to genotype

Evaluation of clinical efficacy data by different mechanisms of resistance (as presented below)

demonstrated that telithromycin was efficacious, irrespective of the mechanism of resistance identified among the clinical isolates recovered from subjects: *erm*(B), *mef*(A), and both *erm*(B)/*mef*(A).

Table 6-12. CAP: Clinical cure rates by genotype among subjects with *S. pneumoniae* isolates resistant to erythromycin A from single and mixed pathogen infections - PPb population

Genotype	Clinical cure		
	N	n	(%)
Western studies			
<i>erm</i> (B)	13	11	(84.6)
<i>mef</i> (A)	13	11	(84.6)
<i>erm</i> (B)/ <i>mef</i> (A)	2	2	(100)
Negative for <i>erm</i> (B) and <i>mef</i> (A)	1	1	(100)
Japanese studies			
<i>erm</i> (B)	15	13	(86.7)
<i>mef</i> (A)	5	5	(100)
<i>erm</i> (B)/ <i>mef</i> (A)	1	1	(100)
All studies			
<i>erm</i> (B)	28	24	(85.7)
<i>mef</i> (A)	18	16	(88.9)
<i>erm</i> (B)/ <i>mef</i> (A)	3	3	(100)
Negative for <i>erm</i> (B) and <i>mef</i> (A)	1	1	(100)

N = subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry.

n = subjects in the PPb population whose causative pathogen was eradicated or who was clinically cured.

Note: Strains of *S. pneumoniae* expressing the *mef*(E) gene have been reclassified as *mef*(A) based on international scientific recommendation.

6.4.1.7.2 Efficacy according to level of resistance to erythromycin

The clinical cure rates at post-therapy/TOC according to erythromycin MIC values for *S. pneumoniae* in telithromycin-treated subjects are displayed below for the PPb population in all CAP studies.

Table 6-13. CAP (Western and Japanese studies): Bacteriological eradication and clinical cure rates at post-therapy/TOC for *S. pneumoniae* resistant to erythromycin A (≥ 1 $\mu\text{g/mL}$) according to erythromycin MIC in telithromycin-treated subjects - PPb population

MIC ($\mu\text{g/mL}$)	Bacteriological Eradication			Clinical Cure		
	N	n	(%)	N	n	(%)
2	1	1	(100)	1	1	(100)
4	5	4	(80.0)	5	4	(80.0)
8	10	9	(90.0)	10	9	(90.0)
16	4	4	(100)	4	4	(100)
32	4	2	(50.0)	4	2	(50.0)
128	1	1	(100)	1	1	(100)
256	13	11	(84.6)	13	12	(92.3)
≥ 512	12	12	(100)	12	11	(91.7)
Total	50	44	(88.0)	50	44	(88.0)

Telithromycin retains excellent efficacy against *S. pneumoniae* that are highly resistant to macrolides (erythromycin A).

6.4.1.7.3 Pneumococcal bacteremia (Western studies)

Pneumococcal bacteremia is associated with an increased risk of morbidity in community-acquired pneumonia. The following table presents data on *S. pneumoniae*, including macrolide- and/or penicillin-resistant pathogens, isolated from blood cultures in studies performed in Western countries (single and mixed pathogen infections). No blood cultures were obtained in the Japanese studies.

Table 6-14. CAP (Western studies): Clinical cure in subjects with pneumococcal bacteremia in telithromycin-treated subjects at post-therapy/TOC - PPb population

Causative pathogen	All CAP (Western Studies)	
	N	n
Blood culture positive		
All <i>S. pneumoniae</i> ^a	82	74
PRSP	7	5
ERSP	10	8
ERSP blood culture negative, urinary antigen <i>S. pneumoniae</i> positive ^b	4	4

N = number of subjects; n = number clinically cured; PRSP = penicillin G-resistant (MIC ≥2.0 µg/mL); ERSP = erythromycin A- (macrolide-) resistant (MIC ≥1.0 µg/mL).

^a Subjects with *S. pneumoniae* isolates resistant to both penicillin G and the macrolides (erythromycin A) are displayed in both the PRSP and ERSP categories.

^b Sputum positive, blood culture negative, urinary antigen Binax positive

There were 82 CAP subjects treated with telithromycin who had *S. pneumoniae* isolated from blood cultures and who were evaluable in the PPb population. The overall efficacy rate in these high risk subjects was high, 90.2%. Eight subjects were classified as clinical failures at post-therapy/TOC; none of these subjects died. Brief narratives for these subjects are in *Appendix 4. Narratives for subjects with S. pneumoniae isolated from the blood at entry who failed therapy with telithromycin.*

The overall clinical cure rates were comparable for all subjects infected with *S. pneumoniae*, for subjects with penicillin G-resistant *S. pneumoniae*, and for those with erythromycin A- (macrolide-) resistant *S. pneumoniae*.

Clinical cures were achieved in 5 of the 7 subjects who had bacteremia due to isolates resistant to penicillin G and in 8 of the 10 subjects with isolates resistant to the macrolides (erythromycin A). The 2 subjects who failed therapy with resistant pneumococcal bacteremia (Subjects 3000/605/1091 and 3009OL/0369/105) are described in *Appendix 5, Narratives for subjects with erythromycin and/or penicillin G-resistant S. pneumoniae isolated from the blood at entry who failed therapy with telithromycin.* Of note, 1 of the 2 subjects infected with ERSP who failed therapy had a secondary urinary infection due to *S. aureus*, but the ERSP was eradicated from the blood during therapy and was not reisolated. Therefore, 9/10 subjects with *S. pneumoniae* erythromycin resistance responded to telithromycin with eradication or presumed eradication during treatment.

Additionally, 4 subjects had ERSP strain isolated from the sputum and were positive for the presence of *S. pneumoniae* soluble urinary antigen, a marker for bacteremic disease, but negative for the organism in blood culture. The macrolide-resistant pneumococci were eradicated from the sputum of all 4 subjects and they were classified as clinically cured with telithromycin.

Thus, an 80% cure rate was observed among the 10 subjects with documented bacteremia due to macrolide-resistant strains of *S. pneumoniae*, and for 9 of these 10 subjects the organism was, in fact, eradicated from the blood. This represents strong evidence for the efficacy of telithromycin against strains of *S. pneumoniae* resistant to the macrolides.

6.4.1.8 Efficacy according to telithromycin MIC (Western studies)

The bacteriological eradication and clinical cure rates at post-therapy/TOC according to MIC values for *S. pneumoniae* in telithromycin-treated subjects are displayed below for the PPb population in all CAP studies performed in Western countries. High efficacy was obtained up to an MIC of 1 µg/mL which was the highest MIC observed in the subjects treated with telithromycin.

Table 6-15. CAP (Western studies): Bacteriological eradication and clinical cure rates at post-therapy/TOC for *S. pneumoniae* according to MIC in telithromycin-treated subjects - PPb population

MIC (µg/mL)	Bacteriological Eradication			Clinical Cure		
	N	n	(%)	N	n	(%)
<i>S. pneumoniae</i>						
0.004	4	4	(100)	4	4	(100)
0.008	125	123	(98.4)	125	121	(96.8)
0.016 ^a	113	109	(96.5)	113	106	(93.8)
0.03	23	21	(91.3)	23	21	(91.3)
0.06	6	6	(100)	6	6	(100)
0.12	6	4	(66.7)	6	4	(66.7)
0.25	1	1	(100)	1	1	(100)
0.5	3	3	(100)	3	3	(100)
1	5	5	(100)	5	5	(100)
N/A	32	29	(90.6)	32	29	(90.6)
Total	318	305	(95.9)	318	300	(94.5)

N = number of subjects; n = number bacteriologically eradicated or clinically cured.

^a Data for MIC values of 0.015 and 0.016 have been pooled

The table below provides the Western and Japanese ERSP and PRSP MIC data.

Table 6-16. CAP (Western and Japanese studies): Bacteriological eradication and clinical cure rates at post-therapy/TOC for resistant isolates of *S. pneumoniae* according to MIC in telithromycin-treated subjects - PPb population

MIC (µg/mL)	Bacteriological Eradication			Clinical Cure		
	N	n	(%)	N	n	(%)
<i>Penicillin G-resistant S. pneumoniae</i>						
0.008	3	3	(100)	3	3	(100)
0.016 ^a	2	2	(100)	2	2	(100)
0.03	8	6	(75.0)	8	6	(75.0)
0.06	4	4	(100)	4	4	(100)
0.12	6	5	(83.3)	6	5	(83.3)
0.25	1	1	(100)	1	1	(100)
0.5	2	2	(100)	2	2	(100)
1	1	1	(100)	1	1	(100)
Total	27	24	(88.9)	27	24	(88.9)
<i>Macrolide (erythromycin A)-resistant S. pneumoniae</i>						
0.016 ^a	2	2	(100)	2	2	(100)
0.03	13	10	(76.9)	13	11	(84.6)
0.06	10	9	(90.0)	10	10	(100)
0.12	13	11	(84.6)	13	10	(76.9)
0.25	3	3	(100)	3	3	(100)
0.5	4	4	(100)	4	3	(75.0)
1	5	5	(100)	5	5	(100)
Total	50	44	(88.0)	50	44	(88.0)

N = number of subjects; n = number bacteriologically eradicated or clinically cured.

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

In both Western and Japanese studies, high efficacy was obtained in penicillin G- and macrolide-resistant *S. pneumoniae* up to an MIC of 1 µg/mL (the highest MIC observed in the subjects treated with telithromycin). This confirmed the efficacy rates for all *S. pneumoniae* in Western studies.

6.4.1.9 *H. influenzae*

In general, excellent bacteriological eradication and clinical cure rates at post-therapy/TOC according to MIC values for *H. influenzae* in telithromycin-treated subjects are displayed below for the PPb population in all CAP studies performed in Western countries. High efficacy was observed up to an MIC of 8 µg/mL.

Table 6-17. CAP (Western studies): Bacteriological eradication and clinical cure rates at post-therapy/TOC for *H. influenzae* according to MIC in telithromycin-treated subjects - PPb population

MIC (µg/mL)	Bacteriological Eradication			Clinical Cure		
	N	n	(%)	N	n	(%)
<i>H. influenzae</i>						
0.002	1	1	(100)	1	1	(100)
0.12	1	1	(100)	1	1	(100)
0.25	3	3	(100)	3	3	(100)
0.5	5	3	(60.0)	5	4	(80.0)
1	47	41	(87.2)	47	40	(85.1)
2	96	86	(89.6)	96	88	(91.7)
4	40	35	(87.5)	40	36	(90.0)
8	11	11	(100)	11	11	(100)
N/A	25	23	(92.0)	25	22	(88.0)
Total	229	204	(89.1)	229	206	(90.0)

N = number of subjects; n = number bacteriologically eradicated or clinically cured.

Efficacy remained high up to an MIC of 8 with 11 out of 11 subjects clinically cured with bacterial eradication of the *H. influenzae*.

6.4.1.10 Other key RTI pathogens

Isolated even less frequently than *H. influenzae* from sputum specimens of patients with CAP, *M. catarrhalis* is still the third most often identified common bacterial pathogen in this disease. Most strains of this species recovered from patients in the US are β-lactamase positive and resistant to amoxicillin and other penicillins. Telithromycin demonstrated good clinical efficacy among subjects infected with *M. catarrhalis*, with 24/26 (92.3%) β-lactamase positive isolates clinically cured.

S. aureus can be responsible for severe nosocomial pneumonia requiring intravenous treatment, but is also isolated from subjects with pneumonia in the community setting. High clinical efficacy was observed in *S. aureus* isolates (36/44, 81.8%), with a 50% clinical cure rate in methicillin-resistant *S. aureus* isolates. Most of the *S. aureus* clinical isolates had MICs in the range of 0.06 to 0.25 µg/mL; 1 isolate had an MIC of 8 µg/mL, which was clinically cured.

6.4.1.11 Clinical outcome among subjects infected with atypical and intracellular pathogens

C. pneumoniae and *M. pneumoniae* are frequently responsible for mild to moderate pneumonia among outpatients. *L. pneumophila*, although less frequently isolated in outpatients, can more often be associated with severe complications (including death), particularly in cases of delayed treatment.

Telithromycin has demonstrated excellent in vitro activity and high intracellular penetration against the atypical and intracellular group of pathogens. The clinical efficacy of telithromycin based on stringent and specific diagnostic criteria recommended by the FDA is shown below for these 3 pathogens.

Table 6-18. CAP (Western studies): Clinical outcome at post-therapy/TOC in atypical and intracellular pathogen isolates in the PPc population using highly specific criteria

Pathogen	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
<i>Mycoplasma pneumoniae</i>	37	36	(97.3)	22	20	(90.9)
<i>Chlamydomphila pneumoniae</i>	36	34	(94.4)	19	18	(94.7)
<i>Legionella pneumophila</i>	13	13	(100)	3	2	(66.7)

N = number of subjects; n = number clinically cured.

Telithromycin has excellent clinical cure rates at post-therapy/TOC against *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*.

6.4.1.12 Efficacy in subgroups of special interest (Western studies)

Clinical outcomes in subgroups of special interest are summarized in the table below.

Table 6-19. CAP (Western studies): Clinical outcome for subsets of special interest in telithromycin-treated subjects at post-therapy/TOC - PPc population

Subgroup	Clinical outcome: Cure					
	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
Per protocol (overall)	1925	1755	(91.2)	540	490	(90.7)
Age (years)						
<65	1647	1512	(91.8)	444	407	(91.7)
≥65	278	243	(87.4)	96	83	(86.5)
X-ray findings						
Bilateral	369	335	(90.8)	40	37	(92.5)
Multiple lobes	270	240	(88.9)	46	38	(82.6)
Pneumococcal bacteremia ^a	82	74	(90.2)	19	15	(78.9)
Fine score						
Class I	957	880	(92.0)	252	239	(94.8)
Class II	671	608	(90.6)	178	158	(88.8)
Class ≥III	297	267	(89.9)	110	93	(84.5)

N = number of subjects, n = number clinically cured

^a PPb population: Two subjects (3000/101/1365 and 3006/012/0007) were excluded from the PPb population.

They were considered as failures due to a switch to another antibiotic because of an adverse event, in the PPc population of subjects with pneumococcal bacteremia.

Telithromycin is highly effective in the treatment of subjects who are at increased risk of morbidity and mortality. Clinical outcome was similar among subjects ≥65 years and <65 years of age and was similar to that for comparators. Clinical outcome in subjects with more severe disease was excellent and similar to comparators. The rates of clinical cure in subjects with Fine scores of I, II, or ≥III were similar. In subjects with documented pneumococcal bacteremia in the PPb population, the clinical cure rate was 90.2%.

6.4.1.13 Summary

- Telithromycin 800 mg/day for 7 to 10 days was highly effective in the treatment of outpatients with community-acquired pneumonia based on a large number of subjects (1755/1925 subjects, 91.2%). Excellent clinical activity was also demonstrated in subjects with the highest risk of morbidity and mortality, such as subjects ≥ 65 years of age (87.4%, 243/278), subjects with documented pneumococcal bacteremia (90.2%, 74/82), and subjects with Fine score \geq III (89.9%, 267/297).
- Telithromycin showed excellent efficacy against the key pathogens responsible for pneumonia in outpatients, including both common and atypical/intracellular pathogens:
 - *S. pneumoniae* (94.3% clinical cure [300/318]),
 - *H. influenzae* (90.0% [206/229]),
 - *M. catarrhalis* (88.0% [44/50]),
 - *S. aureus* (81.8% [36/44]),
 - *M. pneumoniae* (97.3% [36/37]),
 - *C. pneumoniae* (94.4% [34/36]), and
 - *L. pneumophila* (100% [13/13]).
- Telithromycin was also highly effective in treating subjects infected with resistant strains of *S. pneumoniae*:
 - For macrolide- (erythromycin A-) resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 44/50 (88.0%) isolates. For penicillin G-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 24/27 (88.9%) isolates.
 - When only single pathogen infections are considered, 29/32 (90.6%) of *S. pneumoniae* resistant to the macrolides (erythromycin A) were clinically cured, and 15/16 (93.8%) of *S. pneumoniae* resistant to penicillin G.
 - Highly active in ERSP bacteremia (8/10 subjects) and also in subjects with ERSP in sputum and a soluble urinary antigen as surrogate for bacteremia (Binax, 4/4).

Telithromycin given at a dose of 800 mg per day for 7 to 10 days provides a highly effective treatment for CAP in outpatients with a targeted spectrum of activity.

6.4.2 Acute exacerbation of chronic bronchitis

The clinical and bacteriological effectiveness of telithromycin 800 mg administered once daily for 5 days in the treatment of acute exacerbation of chronic bronchitis (AECB) in adults was evaluated in 3 international/multicenter, randomized, double-blind, active-controlled comparative studies.

Table 6-20. AECB: Studies conducted

Study No.	Study design	Treatment regimen			No. in mITT
3003	Double-blind	TEL	800 mg qd	5 d	160
		AMC	500 mg/ 125 mg tid	10 d	160
3007	Double-blind	TEL	800 mg qd	5 d	182
		CXM	500 mg bid	10 d	191
3013	Double-blind	TEL	800 mg qd	5 d	270
		CLA	500 mg bid	10 d	282
All AECB			TEL		612
			Comparators		633

TEL = telithromycin, AMC = amoxicillin-clavulanic acid (Augmentin[®]), CXM = cefuroxime axetil, CLA = clarithromycin

In the AECB studies, subjects were enrolled if they had at least 2 (Study 3007) or 3 (Studies 3003 and 3013) Anthonisen criteria (Anthonisen Type I and II) [3]. In Study 3003 all subjects were to have documented chronic obstructive pulmonary disease (COPD).

Table 6-21. AECB: Subject disposition

Population	Telithromycin	Comparators	Total
Randomized	618	636	1254
Treated	615	634	1249
mITT	612	633	1245
PPc	480	485	965
bmITT	172	167	339
PPb	136	134	270

Pretherapy/entry characteristics, including smoking status, clinical findings, characteristics of the current AECB episode, and medical history, were generally similar between treatment groups.

Table 6-22. AECB: Key demographic and pretherapy/entry characteristics for telithromycin-treated subjects - mITT population

Subgroup	All AECB			
	Telithromycin		Comparators	
Total Treated	612		633	
Sex				
Male	322	(52.6)	353	(55.8)
Female	290	(47.4)	280	(44.2)
Age				
Mean (years)	57.7		59.0	
13 to 18 years	1	(0.2)	1	(0.2)
>18 to <65 years	388	(63.4)	368	(58.1)
≥65 years	223	(36.4)	264	(41.7)
Race				
White	566	(92.5)	580	(91.6)
Black	32	(5.2)	39	(6.2)
Asian	5	(0.8)	6	(0.9)
Other	9	(1.5)	8	(1.3)
History of COPD ^a	437	(71.4)	452	(71.4)
FEV ₁ /FVC <60%	175	(28.6)	177	(28.0)

^a In Study 3003, subjects for whom the date of diagnosis of COPD was missing from the case report form were not included in the number of subjects with a known history of COPD. These excluded subjects did have documented obstruction in lung function tests.

6.4.2.1 Clinical outcome

The primary efficacy analysis in AECB was the analysis of clinical outcome at post-therapy/TOC (Days 17 to 21) in the per protocol population of subjects (PPc). Clinical outcome at post-therapy/TOC for the PPc and mITT populations are summarized below.

Table 6-23. AECB: Clinical cure rate by study for telithromycin and comparator(s) at/TOC

	Telithromycin			Comparators			95% CI ^a
	N	n	(%)	N	n	(%)	
PPc population							
Study 3003	115	99	(86.1)	112	92	(82.1)	[-6.4; 14.3]
Study 3007	140	121	(86.4)	142	118	(83.1)	[-5.8; 12.4]
Study 3013	225	193	(85.8)	231	206	(89.2)	[-9.9; 3.1]
All AECB	480	413	(86.0)	485	416	(85.8)	[-4.3; 4.9]
mITT population							
Study 3003	160	130	(81.3)	160	125	(78.1)	[-6.3; 12.6]
Study 3007	182	142	(78.0)	191	138	(72.3)	[-3.5; 15.1]
Study 3013	270	224	(83.0)	282	236	(83.7)	[-7.3; 5.9]
All AECB	612	496	(81.0)	633	499	(78.8)	[-2.4; 6.8]

N = number of subjects; n = number clinically cured

^a 95% confidence interval of the difference in cure rates between the treatment groups.

6.4.2.2 Clinical cure rate by pathogen

The bacteriological eradication (documented and presumed eradication) and clinical cure rates at post-therapy/TOC for the PPb population are summarized in the tables below for the targeted causative pathogens. Cure rates were slightly lower for all treatment groups (telithromycin and comparators) in this indication, where the outcome is more related to the underlying condition and overall severity of the episode of exacerbation.

Table 6-24. AECB: Clinical cure by pathogen – PPb population

Causative pathogen	Clinical cure					
	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
<i>S. pneumoniae</i>	27	22	(81.5)	19	15	(78.9)
<i>H. influenzae</i>	60	44	(73.3)	53	45	(84.9)
<i>M. catarrhalis</i>	29	27	(93.1)	34	29	(85.3)
Other	40	32	(80.0)	53	45	(84.9)
Total (all pathogens)	156	125	(80.1)	159	134	(84.3)

N = subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry; n = number clinically cured.

Other = includes organisms recovered in culture from sputum meeting the definition of adequate and identified by the investigator as causative, but which may or may not be generally recognized as pathogenic in subjects with this type of infection.

Subjects with a higher degree of bronchial obstruction are more likely to be colonized with *H. influenzae*, and the pathogens isolated in these subjects are more difficult to eradicate. The high prevalence of these organisms during quiescent periods may be related to impaired local clearance mechanisms. As a result, the decision to initiate antibiotics in this condition is driven by the subjects' clinical signs and symptoms.

Atypical and intracellular pathogens

Using highly specific criteria based on FDA recommendations, the clinical cure rate at post-therapy/TOC was 3/3 in the subjects with *M. pneumoniae* infection and 11/12 (91.7%) in subjects with *C. pneumoniae*.

6.4.2.3 Analysis of results in population subsets

Clinical and bacteriological outcomes in population subsets stratified by sex, age, race, and weight were similar to those observed in the overall per protocol population among subjects who received telithromycin for AECB.

Table 6-25. AECB: Clinical cure at post-therapy/TOC by demographic subgroup - PPc population

Subgroup	Clinical outcome: Cure					
	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
Per protocol (overall)	480	413	(86.0)	485	416	(85.8)
Age (years)						
<65	296	256	(86.5)	270	237	(87.8)
≥65	184	157	(85.3)	215	179	(83.3)
Risk factors for morbidity ^a						
At least 1	338	290	(85.8)	332	284	(85.5)
At least 2	171	142	(83.0)	181	152	(84.0)
FEV ₁ /FVC <60%	149	117	(78.5)	157	129	(82.2)

N = number of subjects, n = number clinically cured

^a Respiratory insufficiency, congestive heart failure, diabetes mellitus, alcoholism, renal disease, sickle-cell disease, liver disease, coronary artery disease, cancer (other than pulmonary), cerebrovascular disease (Studies 3003 and 3007); COPD, allergy to antibiotics, intravenous drug use, inhaled corticosteroid use (past 30 days) (Study 3007)

Clinical outcome was similar among subjects ≥65 years and <65 years of age and was similar to that for comparators. Subjects with more severe disease had excellent outcomes, similar to comparators. Clinical outcome in subjects with risk factors for morbidity was good (85.8%, at least 1 risk factor; 83.0%, at least 2 risk factors). As expected, the outcome in subjects with severe bronchial obstruction (FEV₁/FVC <60%) was slightly decreased, but remained high (78.5%, 117/149 subjects) and similar to comparators (82.2%, 129/157).

6.4.2.4 Summary

- Telithromycin 800 mg once daily for 5 days was shown to be equivalent in clinical efficacy to widely used treatments (cefuroxime axetil, clarithromycin, or amoxicillin-clavulanic acid, administered 2 to 3 times daily) given for 10 days. The efficacy of telithromycin was consistent across all subgroups of subjects, including those with increased risk for morbidity; e.g., subjects ≥65 years of age (85.3%), and subjects with severe bronchial obstruction, defined by FEV₁/FVC <60%, (78.5%).
- The clinical cure rates by pathogen were higher for common pathogens and atypicals:
 - *S. pneumoniae* (81.5% clinical cure [22/27]),
 - *H. influenzae* (73.3% [44/60]),
 - *M. catarrhalis* (93.1% [27/29]),
 - *C. pneumoniae* (91.7% [11/12]), and
 - *M. pneumoniae* (100% [3/3]).

Treatment with telithromycin 800 mg once daily for 5 days is effective in AECB due to *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, *C. pneumoniae*, and *M. pneumoniae*. Telithromycin is effective in outpatients at risk of complications (elderly subjects, subjects with significant obstruction). The short duration of treatment may increase patient compliance. This could in turn result in less potential the rate of antimicrobial resistance potentially associated with longer durations of treatment and missed doses at the end of treatment.

6.4.3 Acute sinusitis

Sinusitis is regarded as one of the most common health-care complaints in the United States affecting an estimated 35 million Americans each year [39]. The main pathogens of bacterial sinusitis are similar to those that cause community-acquired pneumonia and acute exacerbation of chronic bronchitis. In addition, the prevalence of resistance among pathogens causative of this syndrome parallels that seen with other respiratory diseases. Resistance to many antibiotics continues to evolve in the pathogens commonly found in acute sinusitis.

Among the 525 strains of *S. pneumoniae* recovered from sinus cultures in the PROTEKT program, 31.1% of all isolates were resistant to penicillin G (MIC ≥ 2 $\mu\text{g/mL}$), and 40.1% were resistant to the macrolides (erythromycin MIC >0.5 $\mu\text{g/mL}$). Seventy of the 525 (13.3%) of the sinus culture isolates were multiply drug resistant (penicillin, the macrolides, trimethoprim-sulfamethoxazole, and tetracycline). Considering the epidemiology of antimicrobial resistance and the elevated MICs for many antimicrobials (for example, the macrolides and β -lactams) against these commonly incriminated pathogens, it is unlikely that tissue concentrations sufficient to be efficacious would be achieved. Use of fluoroquinolones in this indication is commonly being questioned because their spectrum is not targeted to RTIs, they are active against gram-negative bacteria, and they select for resistance to fluoroquinolones. Therefore, a real medical need exists in this indication for a compound such as telithromycin.

The clinical and bacteriological effectiveness of 800 mg oral telithromycin administered once daily for 5 or 10 days in the treatment of acute sinusitis in adults was evaluated in 3 international/multicenter, randomized, double-blind, comparative studies (Studies 3002, 3005, and 3011).

The aim of Study 3002 was to investigate the clinical efficacy and bacteriological eradication rate in subjects with pathogens isolated at pretherapy/entry by sinus puncture. All subjects had sinus puncture at entry, and sinus X-ray findings were to show either total opacity or air fluid levels in all subjects.

The primary aim of Study 3005 was to provide clinical efficacy data obtained from a broad range of investigators of varying specialties that can be extrapolated to the overall population of subjects with acute sinusitis. Amoxicillin-clavulanic acid was chosen as the comparator as it is known to provide excellent coverage against the 3 main pathogens involved in acute sinusitis: *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

In addition to studying clinical efficacy, the aim of Study 3011 was to increase the experience with *S. pneumoniae* resistant to penicillin G and/or macrolides (erythromycin A) using telithromycin administered for 5 days. Bacterial documentation was obtained by sinus puncture at the US sites and by sinus endoscopy at all non-US sites.

Table 6-26. Acute sinusitis: Studies conducted

Study No.	Study design	Treatment regimen			No. in mITT
3002	Double-blind	TEL	800 mg qd	5 d	167
		TEL	800 mg qd	10 d	168
3005	Double-blind	TEL	800 mg qd	5 d	201
		TEL	800 mg qd	10 d	204
		AMC	500/125 mg tid	10 d	202
3011	Double-blind	TEL	800 mg qd	5 d	240
		CXM	250 mg bid	10 d	116
All AS studies		TEL		5 d	608
		TEL		10 d	372
		Comparators		10 d	318

TEL = telithromycin; AMC = amoxicillin-clavulanic acid (Augmentin[®]); CXM = cefuroxime axetil

Subject disposition in the 3 acute sinusitis studies is summarized in the table below.

Table 6-27. Acute sinusitis: Subject disposition

Population	Telithromycin		Comparator	Total
	5-day	10-day	10-day	
Randomized	667	428	374	1469
Treated	665	425	373	1463
mITT population	608	372	318	1298
PPc population	458	273	226	957
bmITT population	232	113	71	416
PPb population	177	76	57	310

A total of 161 subjects (1 from Study 3002, 142 from Study 3005, and 18 from Study 3011) were excluded from all population analyses of efficacy, except ITT. Of these 161 subjects, 61 were excluded for various reasons (mainly due to unconfirmed diagnosis on X-ray) and 100 subjects were excluded from Study 3005 (telithromycin 5-day group: 30 subjects; telithromycin 10-day group: 36 subjects; and amoxicillin-clavulanic acid 10-day group: 34 subjects) because of treatment with expired (1 subject) or suspected degraded (99 subjects) study medication.

The key demographic characteristics for subjects treated with telithromycin are summarized in the table below across all 3 studies.

Table 6-28. Acute sinusitis: Key demographic characteristics - mITT population

Subgroup	Telithromycin		Comparators	
	5-day	10-day	10-day	
Total	608	372	318	
Sex				
Male	275 (45.2)	167 (44.9)	118 (37.1)	
Female	333 (54.8)	205 (55.1)	200 (62.9)	
Age (years)				
Mean	39.2	40.3	40.1	
13 to 18	13 (2.1)	4 (1.1)	6 (1.9)	
>18 to <65	563 (92.6)	352 (94.6)	297 (93.4)	
≥65	32 (5.3)	16 (4.3)	15 (4.7)	
Race				
White	556 (91.4)	349 (93.8)	278 (87.4)	
Black	24 (3.9)	13 (3.5)	24 (7.5)	
Asian/Oriental	20 (3.3)	7 (1.9)	13 (4.1)	
Other	8 (1.3)	3 (0.8)	3 (0.9)	

Table 6-29. Acute sinusitis: Key pretherapy/entry characteristics - mITT population

Subgroup	Telithromycin		Comparators	
	5 days	10 days	10 days	
Total	608	372	318	
Sinus puncture at entry	325 (53.5)	188 (50.5)	78 (24.5)	
Sinus X-ray findings				
Total opacity	235 (38.7)	136 (36.6)	64 (20.1)	
Air fluid level	252 (41.4)	157 (42.2)	139 (43.7)	
Mucosal thickening only ^a	166 (27.3)	97 (26.1)	130 (40.9)	
Prior episode of allergic rhinitis in the past 30 days	93 (15.3)	25 (6.7)	56 (17.6)	
History of asthma	72 (11.8)	36 (9.7)	42 (13.2)	
Prior ENT-related surgery	118 (19.4)	48 (12.9)	55 (17.3)	

^a Level of mucosal thickening in Study 3005 was ≥6 mm. The level in Study 3011 was ≥10 mm. Only total opacity or air fluid level were to be present in Study 3002.

6.4.3.1 Clinical outcome

The primary efficacy analysis in acute sinusitis was the analysis of clinical outcome at post-therapy/TOC (Days 17 to 24) in the per protocol population of subjects (PPc). Clinical outcome at post-therapy/TOC is summarized in the table below.

Table 6-30. Acute sinusitis: Clinical cure rate by study at post-therapy/TOC

Study	Telithromycin						Comparators			95% CI
	5 days			10 days			10 days			
	N	n	(%)	N	n	(%)	N	n	(%)	
PPc population										
Study 3002	123	112	(91.1)	133	121	(91.0)	NA			[-7.7; 7.9] ^a
Study 3005	146	110	(75.3)	140	102	(72.9)	137	102	(74.5)	[-9.9; 11.7] ^b [-12.7; 9.5] ^c [-8.4; 13.3] ^a
Study 3011	189	161	(85.2)	NA			89	73	(82.0)	[-7.1; 13.4] ^b
All AS Studies	458	383	(83.6)	273	223	(81.7)	226	175	(77.4)	[-0.6; 12.9] ^b [-3.3; 11.8] ^c [-4.1; 7.9] ^a
mITT population										
Study 3002	167	138	(82.6)	168	147	(87.5)	NA			[-13.1; 3.3] ^a
Study 3005	201	140	(69.7)	204	140	(68.6)	202	138	(68.3)	[-8.2; 10.9] ^b [-9.2; 9.8] ^c [-8.5; 10.5] ^a
Study 3011	240	193	(80.4)	NA			116	84	(72.4)	[-2.2; 18.2] ^b
All AS Studies	608	471	(77.5)	372	287	(77.2)	318	222	(69.8)	[1.4; 13.9] ^b [0.4; 14.2] ^c [-5.3; 5.9] ^a

Comparators = amoxicillin-clavulanic acid (Study 3005); and cefuroxime axetil (Study 3011).

NA = not applicable. AS = acute sinusitis.

^a Pairwise comparison between 5-day and 10-day telithromycin regimen.

^b Pairwise comparison between 5-day telithromycin regimen and 10-day comparator regimen.

^c Pairwise comparison between 10-day telithromycin regimen and 10-day comparator regimen.

With 5 days of telithromycin treatment (PPc population), the clinical cure rate ranged between 75.3% and 91.1%. Furthermore, the clinical cure rates in 2 double-blind studies with 5 days of telithromycin were also equivalent to 10 days of therapy with cefuroxime axetil or amoxicillin-clavulanic acid, the comparators in Studies 3005 and 3011. Efficacy with 5 days of treatment with telithromycin was equivalent to 10 days of telithromycin. Clinical efficacy data obtained in the mITT population confirmed the results obtained in the PPc population.

6.4.3.2 Clinical cure rate by pathogen

The clinical cure rates at post-therapy/TOC for key pathogens in the 5-day and 10-day telithromycin treatment groups are presented below for the PPb population. Given the equivalence between the 5-day and 10-day treatments, the data are also pooled in the table below to allow comparison across treatment groups. Overall, the cure rate was high for all of the key pathogens evaluated for this indication.

Table 6-31. Acute sinusitis: Clinical cure rate by pathogen for telithromycin-treated subjects-PPb population

Causative pathogen	Clinical cure											
	Telithromycin ^a									Comparators		
	5-days			10-days			5 and 10-days			10-days		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
<i>S. pneumoniae</i>	61	55	(90.2)	30	27	(90.0)	91	82	(90.1)	16	14	(87.5)
<i>H. influenzae</i>	48	42	(87.5)	16	15	(93.8)	64	57	(89.1)	15	13	(86.7)
<i>M. catarrhalis</i>	14	13	(92.9)	4	3	(75.0)	18	16	(88.9)	7	7	(100)
<i>S. aureus</i>	19	18	(94.7)	4	4	(100)	23	22	(95.6)	4	3	(75.0)
<i>S. pyogenes</i>	2	2	(100)	3	3	(100)	5	5	(100)	0		
Other	81	62	(76.5)	42	38	(90.5)	123	100	(81.3)	29	20	(69.0)
Total (all pathogens)	225	192	(85.3)	99	90	(90.9)	324	282	(87.0)	71	57	(80.3)

N = subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry, n = number clinically cured
Other = includes organisms recovered in culture from sputum meeting the definition of adequate and identified by the investigator as causative, but which may or may not be generally recognized as pathogenic in subjects with this type of infection.

^a Telithromycin has more isolates because Study 3002 only had telithromycin treatments (5 vs. 10 days).

6.4.3.3 *S. pneumoniae* resistant to penicillin G and/or macrolides (erythromycin A)

The table below presents pooled data from subjects with *S. pneumoniae* resistant to penicillin G and erythromycin A.

Table 6-32. Acute sinusitis: Clinical efficacy for *S. pneumoniae* resistant isolates^a from single and mixed pathogen infections in telithromycin-treated subjects at post-therapy/TOC - PPb population

Causative pathogen	All AS Studies								
	5 days			10 days			5 and 10 days		
	N	n	(%)	N	n	(%)	N	n	(%)
All <i>S. pneumoniae</i>	61	55	(90.2)	30	27	(90.0)	91	82	(90.1)
PRSP	10	8	(80.0)	3	3	(100)	13	11	(84.6)
ERSP	14	12	(85.7)	7	6	(85.7)	21	18	(85.7)
PRSP and ERSP	8	6	(75.0)	3	3	(100)	11	9	(81.8)
PRSP only ^b	2	2	(100)	0	0		2	2	(100)
ERSP only ^b	6	6	(100)	4	3	(75.0)	10	9	(90.0)

N = number of subjects, n = number clinically cured, PRSP = penicillin G-resistant (MIC ≥ 2.0 $\mu\text{g/mL}$); ERSP = erythromycin A-resistant (MIC ≥ 1.0 $\mu\text{g/mL}$).

^a Subjects with *S. pneumoniae* isolates resistant to both penicillin G and the macrolides (erythromycin A) are displayed in both the PRSP and ERSP categories.

^b Excludes strains that are both PRSP and ERSP.

Telithromycin is highly effective against antibiotic-resistant *S. pneumoniae* isolates in the 5-day treatment arm:

- For penicillin G-resistant *S. pneumoniae*, the clinical outcome was cure in 8/10 (80.0%) subjects treated for 5 days. For macrolide- (erythromycin A-) resistant *S. pneumoniae* the clinical outcome was cure in 12/14 (85.7%) subjects treated for 5 days.

Excellent efficacy was likewise obtained against resistant *S. pneumoniae* isolates when the 5- and 10-day treatment arms were pooled:

- For penicillin G-resistant *S. pneumoniae*, the clinical outcome was cure in 11/13 (84.6%) subjects treated for either 5 or 10 days. For macrolide- (erythromycin A-) resistant *S. pneumoniae*, the clinical outcome was cure in 18/21 (85.7%) subjects treated for either 5 or 10 days.

6.4.3.4 Efficacy in subgroups of special interest

Clinical and bacteriological outcomes in population subsets by sex, age, race, and weight were similar to those observed in the overall per protocol population among subjects who received telithromycin for acute sinusitis.

Efficacy rates by study and for the total acute sinusitis indication for telithromycin-treated subjects are summarized in the table below according to entry characteristics.

Table 6-33. Acute sinusitis: Clinical cure rate (PPc) at post-therapy/TOC by selected pretherapy/entry characteristics and prognostic factors

Subgroup	Telithromycin			Comparators		
	5 days			10 days		
	N	n	(%)	N	n	(%)
Per protocol (overall)	458	383	(83.6)	226	175	(77.4)
Severity of infection (investigator assessment)						
Moderate	341	280	(82.1)	169	131	(77.5)
Severe	95	82	(86.3)	45	35	(77.8)
Sinus X-ray findings						
Total opacity	173	153	(88.4)	43	33	(76.7)
Mucosal thickening only ^a	90	65	(72.2)	74	53	(71.6)
Episodes of allergic rhinitis in previous 30 days	75	61	(81.3)	43	27	(62.8)

^a Level of mucosal thickening in Study 3005 was ≥ 6 mm. The level in Study 3011 was ≥ 10 mm. Only total opacity or air fluid level were to be present in Study 3002.

Subjects with mucosal thickening only tended to have lower cure rates. These subjects may have had acute bacterial exacerbations of chronic sinusitis and have been prone to relapse.

6.4.3.5 Summary

- Telithromycin 800 mg once daily for 5 days was shown to be equivalent in clinical efficacy to widely used treatments (cefuroxime axetil or amoxicillin-clavulanic acid, administered 2 to 3 times daily) given for 10 days. This may represent an advantage for increased patient compliance thereby reducing the rate of antibiotic resistance.
- The clinical cure rates by pathogen were high in telithromycin-treated subjects for key pathogens:
 - *S. pneumoniae* (90.1% clinical cure [82/91]),
 - *H. influenzae* (89.1% [57/64]),
 - *M. catarrhalis* (88.9% [16/18]), and
 - *S. aureus* (95.6% [22/23]).
- Telithromycin was highly effective against antibiotic-resistant *S. pneumoniae* isolates in both the 5- and 10-day treatment arms:

- Penicillin G-resistant *S. pneumoniae* (80.0% 5 days [8/10], 100% 10 days [3/3]),
- Macrolide- (erythromycin A-) resistant *S. pneumoniae* (85.7% 5 days [12/14], 85.7% 10 days [6/7]).

Telithromycin at 800 mg once daily for 5 days was equivalent to 10 days of treatment with a standard antibiotic treatment, and presents an attractive antibiotic treatment alternative.

6.5 Summary of effectiveness assessments in a large usual care setting trial

The overall objective of the large usual care setting trial (Study 3014) was to characterize the safety and effectiveness of telithromycin vs. amoxicillin-clavulanic acid when used for the treatment of community-acquired respiratory tract infections in a large population of subjects.

Safety was evaluated with respect to the occurrence of serious adverse events and adverse events of special interest (hepatic, cardiac, vasculitic, and visual). Adverse events of special interest were adjudicated by a blinded independent panel of external experts (Clinical Events Committee [CEC]). Events determined by the CEC to meet the predefined safety endpoints were used as the endpoints for the primary safety analysis.

In Study 3014, 24140 subjects with a clinical diagnosis of community-acquired pneumonia, acute exacerbation of chronic bronchitis, or acute sinusitis were enrolled and treated. When analyzed in terms of hospitalization, prescription of new antimicrobial medication for the primary infection or complication, and time lost from work, the effectiveness of telithromycin was comparable overall to that of AMC in all 3 indications.

- Occurrence of hospitalization (at Visit 2 - telithromycin, 129/11746 [1.10%]; AMC, 112/11535 [0.97%]; at Visit 3 - telithromycin, 90/11979 [0.75%]; AMC, 78/11762 [0.66%]).
- Prescription of a new antimicrobial medication for the primary infection or a complication of the primary infection (at Visit 2 - telithromycin, 1282/11757 [10.9%]; AMC, 1215/11538 [10.5%]; at Visit 3 - telithromycin, 819/11980 [6.8%]; AMC, 830/11760 [7.1%]). New antimicrobial medications prescribed for the primary infection or complications were similar in overall incidence, but there was a difference in the choice of antimicrobial. β -lactams were prescribed for more subjects in the telithromycin group, whereas macrolides and fluoroquinolones were prescribed for more subjects in the AMC group.
- Time lost from work (at Visit 2 - telithromycin, 1080/12277 [8.8%]; AMC, 1161/12146 [9.6%]; at Visit 3 - telithromycin, 259/12276 [2.1%]; AMC, 276/12147 [2.3%]).

Both treatments showed greater effectiveness (lower rates of hospitalization, prescription of new antimicrobial medication for the primary infection or complication, and time lost from work) in subjects <50 years of age than in subjects \geq 50 years of age, showing comparable effectiveness in each age category.

6.6 Summary of clinical efficacy

The efficacy of telithromycin has been established in 14 Phase III studies in 3 indications, CAP, AECB and acute sinusitis. Telithromycin given for a short treatment duration of 5 days in AECB and

acute sinusitis demonstrated equivalent efficacy to standard comparator treatments given for 10 days. This attribute should enhance patient compliance and will result in an overall reduction of antibiotic exposure. Community-acquired pneumonia was effectively treated with a 7 to 10 day telithromycin treatment regimen.

Efficacy was demonstrated in a broad category of outpatients, including the most vulnerable subjects, such as elderly, subjects with pneumococcal bacteremia, or subjects with a significant degree of bronchial obstruction.

The antibacterial spectrum of telithromycin is well focused on respiratory pathogens. Telithromycin proved to be highly active among outpatients infected with common pathogens such as *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (irrespective of β -lactamase production), and *S. aureus*. It also demonstrated a high degree of efficacy against the atypical and intracellular pathogens, *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*.

Clinical efficacy among subjects with infections caused by *S. pneumoniae* resistant to penicillin G and/or the macrolides (erythromycin A) was well demonstrated with 24 clinical cures among 27 CAP subjects for penicillin G-resistant strains and 44 clinical cures among 50 subjects with macrolide-resistant strains. Similarly, efficacy against resistant strains of *S. pneumoniae* was demonstrated among subjects with acute bacterial sinusitis.

7. SAFETY

This section presents the safety data obtained from the following sources: 16 integrated Phase III studies; Study 3014, a large study assessing the safety of telithromycin which was performed in a usual care setting; and postmarketing exposure of nearly 1 million prescriptions.

7.1 Extent of exposure

The Phase III safety-evaluable population included all subjects who received at least 1 dose of study treatment and had at least 1 safety assessment following randomization. The following table summarizes the Phase III safety-evaluable population.

Table 7-1. Safety-evaluable population in telithromycin Phase III clinical program

Number of Subjects						
Integrated Phase III Studies					Study 3014	
All studies		Controlled		Uncontrolled		
TEL	COMP	TEL	COMP	TEL	TEL	AMC
4472	2139	2702	2139	1770	12159	11978

TEL = telithromycin; COMP = pooled active comparators; AMC = amoxicillin-clavulanic acid

Telithromycin is now marketed in several countries for the treatment of respiratory tract infections (including Germany, France, Spain, Italy, Brazil and Mexico) since its initial launch in Germany in October 2001. Current exposures are estimated at nearly 1 million courses of therapy¹.

7.2 Phase III studies

7.2.1 Demographics of safety population in Phase III studies

The Phase III safety database contains data from 16 integrated Phase III studies,² including 11 controlled studies. Comparators used in these controlled studies included, amoxicillin, amoxicillin-clavulanic acid, cefuroxime, clarithromycin, levofloxacin, and trovafloxacin. A listing of these studies can be found in *Appendix 6, Phase II and III studies submitted to NDA 21-144*.

Demographic characteristics were comparable between the telithromycin and active comparator treatment groups. The demographic and baseline characteristics of the safety-evaluable population are summarized in the following 2 tables for all 16 integrated Phase III studies and the 11 controlled Phase III studies, respectively.

¹ Exposure numbers based on internal company sales data to retail and outpatient pharmacies.

² The 16 studies analyzed for safety include 2 studies in the indication on pharyngitis/tonsillitis. These studies are not included in the efficacy analyses as this indication is not being sought.

Table 7-2. Demographic characteristics for safety-evaluable population: telithromycin-treated subjects in all Phase III studies

Demographic variable		Number (%) of Telithromycin subjects/characteristics	
		All Phase III Studies	
		TEL 5 d N=1891	TEL 7 to 10 d N=2581
Sex	Male	913 (48.3)	1383 (53.6)
	Female	978 (51.7)	1198 (46.4)
Age (years)	13 to 18	58 (3.1)	55 (2.1)
	>18 to <65	1539 (81.4)	2196 (85.1)
	≥65	294 (15.5)	330 (12.8)
	Median (Range)	42.0 (13-92)	42.0 (13-99)

TEL = telithromycin

Table 7-3. Demographic characteristics for safety-evaluable population in controlled Phase III studies

Demographic variable		Number (%) of subjects/characteristics		
		Controlled Phase III Studies		
		TEL 5 d N=1725	TEL 7 to 10 d N=977	Comparator 7 to 10 d N=2139
Sex	Male	831 (48.2)	486 (49.7)	1031 (48.2)
	Female	894 (51.8)	491 (50.3)	1108 (51.8)
Age (years)	13 to 18	54 (3.1)	15 (1.5)	73 (3.4)
	>18 to <65	1379 (79.9)	826 (84.5)	1650 (77.1)
	≥65	292 (16.9)	136 (13.9)	416 (19.4)
	Median (Range)	43.0 (13-92)	42.0 (16-99)	44.0 (13-97)

TEL = telithromycin

7.2.2 Treatment duration in Phase III studies

Of the 6611 safety-evaluable subjects in 16 integrated Phase III studies, 4472 subjects received telithromycin and 2139 subjects received comparator drugs. Treatment duration with telithromycin ranged from 5 to 10 days, with data on duration being available in 4446 of the 4472 safety-evaluable subjects.

Table 7-4. Subjects exposed to telithromycin in Phase III studies and treatment duration

Indication	Treatment Regimen (Days)	Phase III studies	Controlled Phase III studies
		No. of Subjects	No. of Subjects
CAP	5	191	191
	7 to 10	2144	712
AECB	5	607	607
Acute sinusitis	5	661	495
	10	419	254
Tonsillitis/pharyngitis	5	424	424
Total treated for 5 days		1883	1717
Total treated for 7 to 10 days ^a		2563	966
Total number of subjects ^b		4446	2683

CAP = community-acquired pneumonia; AECB = acute exacerbation of chronic bronchitis

^a Includes those subjects treated for 10 days

^b Of the 2702 safety evaluable-subjects in controlled Phase III studies, 19 did not have data for treatment duration. Similarly for all studies, subjects with missing values for treatment duration were excluded.

7.2.3 Treatment-emergent adverse events in Phase III studies

For all Phase III studies, treatment emergent adverse events (TEAEs) included any on-treatment adverse event that was not present before treatment or was present before treatment and became more intense (increased in severity) or more frequent during the treatment period, as determined by the investigators. In addition, any on-treatment adverse event that was considered possibly related to study medication by the investigators, that led to permanent discontinuation of study medication, or that resulted in death, was considered treatment-emergent. Possibly related TEAEs are those events the investigators reported as “possibly related” to study medication and those on-treatment adverse events with missing causality.

For all Phase III Studies, the on-treatment period encompassed the period from the first day of study medication to 7 days after the last dose was taken.

With the exception of deaths, the presentation of the TEAEs in this section includes only data from the 11 randomized, controlled Phase III studies. Results of the 5 uncontrolled Phase III studies showed a comparable safety profile.

7.2.3.1 TEAEs in controlled Phase III studies

Of the 2702 subjects treated with telithromycin in the 11 controlled Phase III trials, 1348 subjects (49.9%) reported at least 1 TEAE as compared to 1035 of 2139 subjects (48.4%) treated with a comparator drug. Possibly related TEAEs were reported in 861 subjects (31.9%) treated with telithromycin compared with 606 subjects (28.3%) treated with a comparator drug.

The following table shows the MedDRA system organ classes (SOCs) for which all TEAEs and possibly related TEAEs were most commonly reported in the controlled Phase III studies. TEAEs of the gastrointestinal and nervous system disorders SOCs were the most common events reported. TEAEs of the eye disorders SOC were infrequent but appeared to be different between treatments, occurring in 41/2702 (1.5%) telithromycin-treated subjects and 15/2139 (0.7%) comparator-treated

subjects in the 16 integrated Phase III studies. This difference appeared to be caused by an increased rate of transient blurred vision as presented under TEAEs by decreasing frequency.

Table 7-5. System organ classes for which all and possibly related TEAEs were most commonly reported in controlled Phase III studies

MedDRA System organ class	Number (%) of subjects	
	Telithromycin N=2702	Comparator N=2139
All TEAEs^a		
Subjects with TEAEs	1348 (49.9)	1035 (48.4)
Gastrointestinal disorders	731 (27.1)	473 (22.1)
Nervous system disorders	318 (11.8)	263 (12.3)
Infections and infestations	276 (10.2)	243 (11.4)
Respiratory, thoracic and mediastinal disorders	167 (6.2)	145 (6.8)
Investigations ^b	105 (3.9)	92 (4.3)
Possibly related TEAEs^a		
Subjects with possibly related TEAEs	861 (31.9)	606 (28.3)
Gastrointestinal disorders	620 (22.9)	369 (17.3)
Nervous system disorders	178 (6.6)	169 (7.9)
Infections and infestations	67 (2.5)	73 (3.4)
Investigations ^b	56 (2.1)	53 (2.5)
Skin and subcutaneous tissue disorders	37 (1.4)	39 (1.8)

^a Based on the 5 most frequently affected SOCs in each treatment group.

^b The Investigations SOC includes asymptomatic laboratory abnormalities

TEAEs by decreasing frequency

TEAEs occurring in more than 2% of subjects and possibly related TEAEs occurring in more than 1% of subjects in either treatment group in the controlled Phase III studies are shown by decreasing frequency in the table below.

Table 7-6. All and possibly related TEAEs by decreasing frequency in controlled Phase III studies

Preferred term	Number (%) of subjects	
	Telithromycin N=2702	Comparator N=2139
All TEAEs^a		
Subjects with TEAEs	1348 (49.9)	1035 (48.4)
Diarrhea NOS	292 (10.8)	184 (8.6)
Nausea	213 (7.9)	99 (4.6)
Headache NOS	148 (5.5)	125 (5.8)
Dizziness (excl. vertigo)	99 (3.7)	57 (2.7)
Vomiting NOS	79 (2.9)	48 (2.2)
Loose stools	63 (2.3)	33 (1.5)
Dysgeusia	43 (1.6)	77 (3.6)
Possibly related TEAEs^a		
Subjects with possibly related TEAEs	861 (31.9)	606 (28.3)
Diarrhea NOS	270 (10.0)	171 (8.0)
Nausea	190 (7.0)	87 (4.1)
Headache NOS	54 (2.0)	53 (2.5)
Dizziness (excl. vertigo)	75 (2.8)	33 (1.5)
Vomiting NOS	64 (2.4)	30 (1.4)
Loose stools	58 (2.1)	30 (1.4)
Dyspepsia	36 (1.3)	21 (1.0)
Dysgeusia	40 (1.5)	76 (3.6)

^a Based on a frequency of all TEAEs of $\geq 2.0\%$ and possibly related TEAEs of $\geq 1.0\%$ in telithromycin or comparator treatment groups.

NOS = not otherwise specified

Diarrhea NOS was the most common individual TEAE in the telithromycin and comparator treatment groups in the controlled Phase III studies.

Blurred vision was reported more frequently with telithromycin (20/4472, 0.4%) than with the comparators (3/2139, 0.1%); of these 20 subjects, 15 had events considered possibly related to telithromycin by the investigator. These events were generally mild in intensity, with no possibly related severe reports received. They started most frequently within the first 2 days of treatment. Among the 15 telithromycin-treated subjects with possibly related blurred vision, 11 subjects were female (8 of whom were ≤ 36 years of age). No cases of blurred vision with telithromycin occurred in elderly (>65 years of age) or adolescent (<18 years of age) subjects in the 16 Phase III studies. All drug-related cases of blurred vision recovered fully. No specific pattern of medical history or concomitant medication was found in these subjects. Only 1 telithromycin-treated subject (Subject 3008/0209/005, a 30-year-old female in Study 3008) discontinued study medication due to mild blurred vision. The subject recovered without sequelae. No blurred vision events were reported as serious TEAEs in the integrated Phase III studies.

Two ophthalmologic clinical pharmacology studies were conducted to better characterize visual events and to investigate the mechanism. Ophthalmic examinations in these 2 studies included examination of the lens, cornea and fundi, visual acuity, anterior chamber angle, intraocular pressure, refraction, accommodation, color vision and visual fields (left and right). In single dose Study 1059, no blurred vision occurred with telithromycin 800 mg but following a single dose of 2400 mg, 3 times the

therapeutic dose, blurred vision was observed in 4/15 subjects under the age of 50. In Study 1064, blurred vision was reported in 12/24 subjects after a single suprathreshold dose of telithromycin 2400 mg. Results from these studies showed:

- Blurred vision was transient, and consistently described by subjects as a brief delay in focusing when adjusting from near to far vision. Onset of the event occurred within a few hours of dosing (median time to onset was 3 hours), with a duration of a few hours. All events resolved completely.
- Despite subjective descriptions of “blurred vision”, no changes in visual acuity were noted in subjects with blurred vision.
- There were no noted changes in the fundus, color vision, visual field or contrast sensitivity function, thereby excluding retinal toxicity as a cause for the blurred vision. The lack of significant changes in intraocular pressure or anterior chamber angle excluded angle closure glaucoma.
- A parasympathetic agonist effect (muscarinic) on the ciliary body can be hypothesized as a primary mechanism leading to the observed accommodation delay. Association with nausea, which was present in 9/16 of subjects with blurred vision at high dose in ophthalmologic Phase I studies, is consistent with this possible mechanism. In Phase I studies the higher incidence of blurred vision in subjects less than 50 years of age is also consistent with a primary mechanism affecting accommodation.

Based on the clinical descriptions and objective findings from these 2 studies, the mechanism for the reported blurred vision is most consistent with a transient effect on the ciliary body delaying relaxation of the lens and hence accommodation. Importantly, potentially more serious and irreversible causes, such as angle closure glaucoma and retinopathy, have been excluded.

TEAEs by intensity

The majority of subjects with TEAEs had events of mild or moderate intensity in both the telithromycin and comparator treatment groups in the controlled Phase III studies. The frequency of subjects with severe TEAEs was low across the treatment groups with no clinically meaningful differences noted between them. The most frequent severe TEAEs were gastrointestinal, occurring in 50/2702 telithromycin-treated subjects (2.4%) and 27/2139 comparator-treated subjects (1.6%).

Table 7-7. All and possibly related TEAEs by intensity in controlled Phase III studies

Intensity	Number (%) of subjects			
	All TEAEs		Possibly related TEAEs	
	Telithromycin N=2702	Comparator N=2139	Telithromycin N=2702	Comparator N=2139
Mild	979 (36.2)	758 (35.4)	623 (23.1)	435 (20.3)
Moderate	589 (21.8)	465 (21.7)	296 (11.0)	230 (10.8)
Severe	134 (5.0)	106 (5.0)	70 (2.6)	40 (1.9)

7.2.4 Deaths, Serious Adverse Events and Discontinuations due to TEAEs in Phase III studies

7.2.4.1 Deaths in Phase III studies

A total of 26 subjects died in the Phase III clinical program. The incidence of death was very low and comparable between telithromycin and comparator treatment groups. None of the deaths were considered related to study medication by the study investigator. As expected, most of the deaths occurred in CAP studies where subjects tend to have underlying conditions or illnesses associated with increased mortality. The observed incidence of death in CAP subjects in the Phase III studies is consistent with published death rates in patients treated for outpatient pneumonia [17].

The number (%) of deaths occurring on- or post-treatment in the Phase III studies is presented in the following table.

Table 7-8. Deaths (on-treatment and post-treatment) in Phase III studies

Indication	n/N (%) subjects	
	Telithromycin	Comparator
Subjects who died	17/4472 (0.4)	9/2139 (0.4)
Controlled Studies	7/2702 (0.3)	9/2139 (0.4)
CAP	5/916 (0.5)	5/723 (0.7)
AECB	2/609 (0.3)	3/626 (0.5)
Acute Sinusitis	0/750 (0.0)	0/366 (0.0)
Tonsillitis/Pharyngitis	0/427 (0.0)	1/424 (0.2)
Uncontrolled Studies	10/1770 (0.6)	NA
CAP	10/1437 (0.7)	NA

n = number of subjects who died, N = number of subjects in population; NA = not applicable

A listing of deaths and a brief narrative for each of the subjects who had a TEAE with an outcome of death is presented in *Appendix 7, Deaths in Phase III studies*.

7.2.4.2 Serious TEAEs in controlled Phase III studies

The frequency of serious TEAEs was comparable between treatment groups in the controlled Phase III studies (telithromycin: 59/2702, 2.2%; comparators: 61/2139, 2.9%). The incidence of possibly related serious TEAEs was low in each treatment group (telithromycin: 9/2702, 0.3%; comparators: 6/2139, 0.3%).

Overall rates of serious TEAEs were balanced between telithromycin and comparator-treated subjects. The most frequently reported serious events in both treatment groups were those requiring hospitalization (telithromycin: 42/2702, 1.6%; comparators: 49/2139, 2.3%) and those deemed medically important by the investigator (telithromycin: 23/2702, 0.9%; comparators: 22/2139, 1.0%).

The following table shows the SOCs for which all and possibly related serious TEAEs were most commonly reported in the controlled Phase III studies.

Table 7-9. System organ classes for which all and possibly related serious TEAEs were most commonly reported in controlled Phase III studies

MedDRA system organ class	Number (%) of subjects	
	Telithromycin (N=2702)	Comparator (N=2139)
Subjects with serious TEAEs^a	59 (2.2)	61 (2.9)
Infections and infestations	17 (0.6)	26 (1.2)
Respiratory, thoracic and mediastinal disorders	12 (0.4)	8 (0.4)
Vascular disorders	5 (0.2)	1 (0.0)
Renal and urinary disorders	4 (0.1)	3 (0.1)
Immune system disorders	4 (0.1)	1 (0.0)
Cardiac disorders	3 (0.1)	8 (0.4)
Gastrointestinal disorders	3 (0.1)	4 (0.2)
Psychiatric disorders	2 (0.1)	4 (0.2)
Subjects with possibly related serious TEAEs^b	9 (0.3)	6 (0.3)
Infections and infestations	3 (0.1)	1 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.0)
Gastrointestinal disorders	1 (0.0)	1 (0.0)
Hepatobiliary disorders	2 (0.1)	0 (0.0)
Immune system disorders	2 (0.1)	1 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.0)
Psychiatric disorders	0 (0.0)	1 (0.0)
Skin and subcutaneous tissue disorders	1 (0.0)	0 (0.0)

^a Based on the 5 most frequently affected SOCs in each treatment group.

^b All SOCs for which possibly related serious TEAEs were reported in controlled Phase III studies are shown.

Serious TEAEs in controlled Phase III studies, irrespective of causality, were reported most frequently for the infections and infestations SOC in both telithromycin and comparator treatment groups. Most serious events were respiratory in nature, likely representative of the underlying indications for treatment. Pneumonia aggravated was the most common individual serious TEAE in the comparator group (11/2139, 0.5%) and was reported more frequently than in telithromycin-treated subjects (2/2702, 0.1%). Acute exacerbation of chronic bronchitis NOS and pleural effusion were the most common serious TEAEs in telithromycin-treated subjects (both 3/2702, 0.1%) and were reported at similar rates in comparator-treated subjects (3/2139, 0.1% and 1/2139, <0.1%, respectively). There was 1 case of granulomatous hepatitis with eosinophilic infiltration on biopsy that resolved with an asymptomatic recurrence 9 months later without further telithromycin exposure suggesting a pre-existing and undiagnosed autoimmune disorder as a cause.

7.2.4.3 Discontinuations due to TEAEs in controlled Phase III studies

In the controlled Phase III studies, the overall rates of TEAEs leading to discontinuation of study medication were low and balanced between telithromycin (4.4%) and comparator (4.3%) groups. The frequency of all and possibly related TEAEs resulting in discontinuation of study medication is presented for controlled Phase III studies in the following table.

Table 7-10. All and possibly related TEAEs^a resulting in discontinuation of study medication in controlled Phase III studies

Preferred term	Number (%) of subjects	
	Telithromycin (N = 2702)	Comparator (N = 2139)
Subjects with TEAE resulting in discontinuation of study medication	119 (4.4)	92 (4.3)
Diarrhea NOS	23 (0.9)	13 (0.6)
Vomiting NOS	21 (0.8)	10 (0.5)
Nausea	19 (0.7)	10 (0.5)
Liver function tests NOS abnormal	5 (0.2)	5 (0.2)
Abdominal pain NOS	5 (0.2)	2 (0.1)
Dizziness (excl. vertigo)	5 (0.2)	1 (0.0)
Headache NOS	2 (0.1)	7 (0.3)
Rash NOS	2 (0.1)	5 (0.2)
Subjects with possibly related TEAE resulting in discontinuation of study medication	86 (3.2)	60 (2.8)
Diarrhea NOS	22 (0.8)	13 (0.6)
Vomiting NOS	21 (0.8)	7 (0.3)
Nausea	19 (0.7)	9 (0.4)
Liver function tests NOS abnormal	3 (0.1)	3 (0.1)
Abdominal pain NOS	5 (0.2)	2 (0.1)
Dizziness (excl. vertigo)	5 (0.2)	1 (0.0)
Headache NOS	2 (0.1)	5 (0.2)
Rash NOS	2 (0.1)	5 (0.2)

^a Based on a frequency of all TEAEs resulting in discontinuation of $\geq 0.2\%$ in telithromycin or comparator treatment groups in controlled Phase III studies.

Note: The numbers in each column are not additive because a subject may have had more than 1 adverse event that resulted in discontinuation of study medication.

NOS = not otherwise specified

The gastrointestinal events of diarrhea NOS, vomiting NOS and nausea were the most frequently reported TEAE leading to discontinuation in both telithromycin- and comparator-treated subjects.

7.2.5 Frequency of clinically-noteworthy laboratory values

The frequencies of clinically noteworthy abnormal laboratory values (CNALVs) for each analyte are presented for all 11 controlled Phase III studies, as well as according to CAP and non-CAP indication. The treatment groups compared for the controlled studies are telithromycin (5 to 10 days) versus comparator (7 to 10 days) for CAP and telithromycin (5 or 10 days) vs. comparator (10 days) for non-CAP.

Table 7-11. Clinically noteworthy laboratory analytes in controlled Phase III studies
n/N (%) subjects

Laboratory parameter	CAP studies		Non-CAP studies			All Studies	
	TEL (5 to 10 d)	Comp (7 to 10 d)	TEL (5 d)	TEL (10 d)	Comp (10 d)	All TEL	All COMP
Hemoglobin ↓	0/915 (0.0)	1/719 (0.1)	0/1520 (0.0)	0/254 (0.0)	0/1410 (0.0)	0/2689 (0.0)	1/2129 (0.0)
Platelets ↓	2/912 (0.2)	1/717 (0.1)	2/1515 (0.1)	0/254 (0.0)	1/1407 (0.1)	4/2681 (0.1)	2/2124 (0.1)
PT INR ↑	21/470 (4.5)	21/469 (4.5)	22/917 (2.4)	12/252 (4.8)	27/922 (2.9)	55/1639 (3.4)	48/1391 (3.5)
Leukocytes ↓	10/915 (1.1)	12/719 (1.7)	10/1520 (0.7)	5/254 (2.0)	3/1410 (0.2)	25/2689 (0.9)	15/2129(0.7)
Neutro (Abs.) ↓	27/915 (3.0)	29/719 (4.0)	27/1406 (1.9)	7/254 (2.8)	22/1294 (1.7)	61/2575 (2.4)	51/2013 (2.5)
Eosino (Abs.) ↑	15/915 (1.9)	11/719 (1.5)	13/1520 (0.9)	1/254 (0.4)	17/1409 (1.2)	29/2689 (1.1)	28/2128 (1.3)
AST ↑	22/915 (2.4)	16/719 (2.2)	10/1500 (0.7)	1/254 (0.4)	11/1384 (0.8)	33/2669 (1.2)	27/2103 (1.3)
ALT ↑	23/915 (2.5)	20/719 (2.8)	17/1500 (1.1)	4/254 (1.6)	15/1385 (1.1)	44/2669 (1.6)	35/2104 (1.7)
Alk phos ↑	19/915 (2.1)	16/719 (2.2)	6/1499 (0.4)	0/254 (0.0)	2/1385 (0.1)	25/2668 (0.9)	18/2104 (0.9)
Total bilirubin ↑	2/911 (0.2)	3/715 (0.4)	3/1489 (0.2)	0/254 (0.0)	1/1379 (0.1)	5/2654 (0.2)	4/2094 (0.2)
CL _{CR} ↓	37/914 (4.0)	41/717 (5.7)	72/1500 (4.8)	1/254 (0.4)	68/1384 (4.9)	110/2668 (4.1)	109/2101 (5.2)
Creatinine ↑	6/915 (0.7)	2/719 (0.3)	1/1500 (0.1)	0/254 (0.0)	2/1385 (0.1)	7/2669 (0.3)	4/2104 (0.2)
Potassium ↑	19/527 (3.6)	20/532 (3.8)	18/1499 (1.2)	2/254 (0.8)	15/1385 (1.1)	39/2280 (1.7)	35/1917 (1.8)

n/N = number of subjects with CNALV for specific analyte/number of subjects with measurement of analyte
Key: ↑ is an increased value in the analyte; ↓ is a decreased value in the analyte. Alk phos = alkaline phosphatase, CL_{CR} = creatinine clearance
TEL: telithromycin, COMP: comparators

In addition to clinically noteworthy abnormal laboratory values (CNALVs), no subject had a concomitant increase in ALT ≥ 3 x ULN and total bilirubin ≥ 1.5 x ULN. There were no meaningful differences in CNALVs between telithromycin and comparator treated subjects.

7.2.6 Assessment of the effects of telithromycin on cardiac repolarization in Phase III studies

Erythromycin and other macrolides have been shown to have an effect on cardiac repolarization resulting in a small increase of the electrocardiographic QT interval. Given its structural similarity to the macrolide class, telithromycin was also assessed for potential effects on cardiac repolarization.

Preclinical studies were performed to assess the effect of telithromycin on the repolarization current in the myocardium. These studies identified a weak inhibitory effect on the I_{kr} (HERG) channel which was comparable to, or slightly lower than, that seen with the macrolide antibiotics. Little or no evidence of early after-depolarizations was seen.

An extensive program of clinical studies has generated a significant body of data addressing the effect of telithromycin on cardiac repolarization.

7.2.6.1 QT interval findings in Phase III studies

A total of 6611 subjects evaluable for safety have been studied in 16 Phase III studies including 4472 subjects who received telithromycin and 2139 subjects who received comparator drugs. Twelve-lead ECGs were obtained routinely in 12 of these 16 studies. ECGs were recorded in all subjects at pretherapy, during therapy with the active drug/comparator, and post-therapy. Time windows were defined as follows.

- Pretherapy: Last ECG done within 72 hours prior to starting drug therapy
- On-therapy³: Last ECG done from Day 2 to the last day of active drug therapy, inclusive
- Post-therapy: First ECG done at least 1 day following cessation of active drug treatment

All ECGs were over-read by a central reader, blinded to treatment, ECG sequence, demographics and medical history. All twelve leads were manually reviewed with the longest and shortest QT interval reported. Any changes made to the ECG reading by the central reader were added to the telithromycin study database. For each ECG, QTc interval was derived by calculating the mean value of the longest and shortest QT intervals. Results are presented using descriptive statistics.

A summary of the integrated ECG data obtained for telithromycin-treated subjects from these 12 Phase III studies is provided in the following table. The table excludes information from Studies 3010, 3011, 3012, and 4003 as ECGs were not performed systematically in all subjects at entry in those studies, but only in a selected population of at-risk subjects for monitoring purposes. Data on outlier values observed in those studies are detailed in Table 7-13.

Table 7-12. QT interval data for telithromycin-treated subjects in Phase III studies^a

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

Data are mean ± SD; QTc was calculated following Bazett

^a Excludes Studies 3010, 3011, 3012 and 4003 where ECGs were performed only in selected subjects

^b Represents number of subjects with both a pre-therapy and on-therapy ECG

^c Represents number of subjects from the on-therapy group who also had a post-therapy ECG

^d ΔQTc represents interval on-therapy minus QTc interval pre-therapy

^e ΔQTc represents QTc interval post-therapy minus QTc interval pre-therapy

³ Investigators were requested to obtain the on-therapy ECGs within 2 to 3 hours after dose.

The mean on-therapy change in QTc was 1.5 ms. The frequency of telithromycin-treated subjects with QTc increase ≥ 30 ms and < 60 ms, as well as ≥ 60 ms, was similar on-therapy and post-therapy. The proportion of subjects considered to have a QTc outlier value was similar or higher at pretherapy than either on-therapy or post-therapy. No change in QT dispersion was observed.

Details of the telithromycin- and comparator-treated subjects with QTc values above 500 ms in all Phase III studies (including Studies 3010, 3011, 3012, and 4003) are provided in the table below.

Table 7-13. Subjects with QTc values ≥ 500 ms in Phase III studies

Investigator/Subject No.	QTc value (ms)			
	Pretherapy	On-therapy	Change between baseline and on-therapy	Post-therapy
Telithromycin-treated subjects				
Study 3001				
0501/001	526.5	410.3	-116.2	374.9
1002/021	516.1	517.8	+1.7	503.8
Study 3003				
1403/002	488.1	531.2	+43.1	466.9 (Day 12) 485.1 (Day 19) 482.8 (Day 36)
1405/006	504.2	470.8	-33.4	446.1
Study 3009				
0340/003	500.8	- a	- a	- a
Study 3009OL				
0355/149	432.9	508	+75	-
Study 3010				
0525/001	-	512.3	-	478.8
0534/068	522.6	-	-	-
Study 3012				
1037/001	521.5	495.5	-26.2	503.3 (Day 12) 511.2 (Day 24)
1037/002	502.6	470.1	-32.5	487.5 (Day 8) 480.8 (Day 17)
4016/017	507.8	490.6	-17.2	449.6 (Day 8) 472.3 (Day 17)
Comparator-treated subjects				
Study 3001 (AMX)				
0203/002	535.3	- a	- a	- a
0705/002	398.3	503.9	+105.6	440.0 (Day 13) 465.3 (Day 17)
Study 3003 (AMC)				
0603/006	521.5	479.8	-41.7	518.4 (Day 10) 487.7 (Day 13) 521.6 (Day 16)
1703/009	496.8	- a	- a	510.8
Study 3013 (CLA)				
0101/021	502	460.9	-41.1	436.5

AMX = amoxicillin, AMC = amoxicillin-clavulanic acid, CLA = clarithromycin

^a No follow-up QTc available as subject in recurrent atrial fibrillation

As outlined in the table above, 8 of the 11 telithromycin-treated subjects with QTc >500 ms had this prolongation at the baseline (pretherapy) visit. A single subject from both the telithromycin and comparator (amoxicillin) treated groups had an on-therapy QTc >500 ms associated with a change of ≥60 ms from baseline. Brief details for these 2 subjects are given below.

- Subject 0355/149 in CAP Study 3009OL: a 69-year-old male with COPD, asthma, hypertension, benign prostatic hypertrophy, fibrositis and Berger’s disease. The subject had a baseline QTc of 433 ms associated with a heart rate of 52; the uncorrected QT interval was 500 ms. On-therapy QTc increased to 508 ms, with an uncorrected QT interval of 520 ms. This subject had no cardiac adverse events.
- Subject 0705/002 in CAP Study 3001: an 88 year old male with medical history of COPD and coronary artery disease. The subject had a prolonged QTc (398 ms) at baseline (HR 47 bpm), which increased to 504 ms on-therapy with amoxicillin (HR 72 bpm). Uncorrected QT intervals for the baseline and on-therapy ECGs were 440 ms and 480 ms, respectively. At subsequent post-therapy assessment, the QTc value had decreased to 440 ms. The subject had a TEAE of heart failure of moderate intensity on Day 2 of active treatment that was considered unrelated to the study medication by the investigator.

7.2.6.2 Comparison with clarithromycin

Data derived from 3 controlled Phase III studies (Studies 3006, 3008 and 3013) provided an opportunity to compare QT interval data to clarithromycin. The QTc findings are summarized in the table below.

Table 7-14. QT interval data for telithromycin vs. clarithromycin (controlled Studies 3006, 3008 and 3013)

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

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

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

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

^c ΔQTc represents interval on-therapy minus QTc interval pretherapy

^d ΔQTc represents QTc interval post-therapy minus QTc interval pretherapy

Consistent with the preclinical findings, telithromycin was comparable to clarithromycin with respect to QTc interval changes.

The frequency of subjects with a QTc increase of ≥ 60 ms at on-therapy was low and similar between treatment groups, as was the frequency of subjects with QTc outliers.

The frequency of subjects with a QTc outlier value was similar in the telithromycin and clarithromycin treatment groups following drug administration. No subject in either treatment group in Studies 3006, 3008 or 3013 had an on-therapy or post-therapy QTc value ≥ 500 ms.

7.2.6.3 Comparison of telithromycin to non-macrolide antibiotics

QTc interval data for telithromycin compared with other comparators not known to impact cardiac repolarization (penicillin, amoxicillin, amoxicillin-clavulanic acid, cefuroxime, trovafloxacin) are summarized in the table below for those subjects with ECGs performed for all 3 study periods.

Table 7-15. QT interval data for telithromycin vs. non-macrolide comparators in controlled Phase III studies

Variable	Pre-therapy		On-therapy		Post-therapy	
	TEL (N=792)	COMP (N=576)	TEL (N=792) ^a	COMP (N=576) ^a	TEL (N=792) ^b	COMP (N=576) ^b
QTc (ms)	408.7 \pm 23.4	409.4 \pm 23.5	409.8 \pm 22.2	406.6 \pm 22.2	405.4 \pm 22.2	404.9 \pm 23.6
Δ QTc (ms)	-	-	1.1 \pm 21.6 ^c	-2.9 \pm 22.0 ^c	-3.3 \pm 22.7 ^d	-4.6 \pm 22.6 ^d
QTc increase (n/N (%) subjects)						
≥ 30 and < 60 ms	-	-	73/792 (9.2)	52/576 (9.0)	51/792 (5.6)	32/576 (5.6)
≥ 60 ms	-	-	3/792 (0.4)	2/576 (0.3)	1/792 (0.1)	3/576 (0.5)
QTc outlier (n/N (%) subjects)						
≥ 450 ms (men)	19/390 (4.9)	21/290 (7.2)	17/390 (4.4)	10/290 (3.4)	8/390 (2.1)	9/290 (3.1)
≥ 470 ms (women)	6/402 (1.5)	2/286 (0.7)	4/402 (1.0)	1/286 (0.3)	5/402 (1.2)	0/286 (0.0)
≥ 500 ms (men or women)	4/792 (0.5)	2/576 (0.3)	2/792 (0.3)	1/576 (0.2)	1/792 (0.1)	2/576 (0.3)
QT dispersion (ms)	23.0 \pm 9.9	22.2 \pm 9.9	21.6 \pm 9.3	21.4 \pm 9.8	22.8 \pm 9.6	22.5 \pm 9.8

Data are mean \pm SD. TEL = telithromycin; COMP = non-macrolide comparators: amoxicillin, amoxicillin-clavulanic acid, penicillin, trovafloxacin, cefuroxime

^a Represents number of subjects with both a pre-therapy and on-therapy ECG

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

^c Δ QTc interval on-therapy minus QTc interval pre-therapy

^d Δ QTc represents QTc interval post-therapy minus QTc interval pre-therapy

There was a small change in QTc of ~ 1 ms observed in telithromycin-treated subjects, which is consistent with what was seen in the other Phase III studies. Although a small difference was noted in comparison to the non-macrolide comparators, this would appear to be of minimal clinical significance in light of the observed variability. There was no difference in the frequency of subjects with changes in QTc ≥ 30 ms or ≥ 60 ms, nor in the frequency of QTc outliers, between the 2 groups.

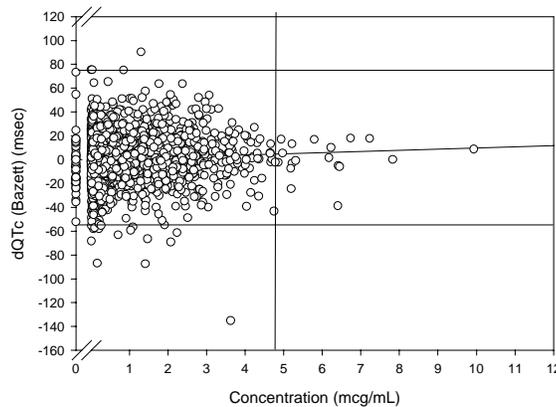
7.2.6.4 Relationship between telithromycin exposure and QTc interval

The relationship between plasma concentration and QT interval was determined in 8 of the Phase III studies (3000, 3001, 3002, 3003, 3005, 3006, 3007 and 3008). For the subjects enrolled in these Phase III studies who received telithromycin and had an ECG recording, a plasma telithromycin level was to be obtained. These plasma levels were used to determine the relationship of plasma level to corrected QT interval (described below).

This analysis was done to delineate the relationship of telithromycin exposure to corrected QT interval in the 1715 subjects in 8 Phase III studies who had matched data (within 1 hour) for both ECG and plasma concentration (73% of the entire population).

A total of 1611 observations obtained on-therapy from 1557 subjects were available. For this population, the mean telithromycin plasma concentration was $1.08 \pm 1.18 \mu\text{g/mL}$. Mean baseline QTc was $406 \pm 22 \text{ ms}$ and remained virtually unchanged after treatment at $407 \pm 22 \text{ ms}$; mean heart rate decreased from $78 \pm 16 \text{ bpm}$ (baseline) to $75 \pm 13 \text{ bpm}$ after treatment. The figure below shows the relationship between plasma telithromycin concentration and change in QTc for the on-therapy period in subjects with matched data.

Figure 7-1. Relationship between telithromycin plasma concentration and change in QTc



N=1611 data points from 1557 subjects

$r^2=0.003$

$P<0.05$

Slope=0.98 ms/ $\mu\text{g/mL}$

Mean conc $1.08 \pm 1.18 \mu\text{g/mL}$

A linear best-fit between concentration and ΔQTc was described by the relationship shown in the above figure. A very shallow slope was observed over a wide range of plasma concentrations (0.05 to $9.9 \mu\text{g/mL}$).

The levels shown in the graph above encompass the levels observed when telithromycin elimination pathways were impaired (see *Section 5.4, Pharmacokinetics in populations of special interest*). As shown in *Section 5.4.4, Subjects >60 years of age with impairment of multiple elimination pathways*, for the population with multiple impairment where high telithromycin exposures were seen, there were no QTc outliers, which is consistent with the relationship shown above for Phase III subjects.

In addition, analyses were done on high risk subgroups in Phase III, and a brief summary of the findings are shown in the following table. While a small sample size in some of the sub groups limited the conclusion that could be drawn, the shallow slope of the relationship ΔQTc vs. concentration was similar to that seen for the population as a whole.

Table 7-16. Regression analysis of on-therapy telithromycin plasma concentration and Δ QTc in at-risk subgroup populations

Subgroup	N	Mean \pm SD (range) TEL plasma conc (μ g/mL)	Slope	Intercept	r ²
Elderly (≥ 65 years)	175	1.48 \pm 1.46	-0.37	0.11	0.00054
Elderly with CR _{CL} \leq 50 mL/min	18	2.55 \pm 2.38	1.75	-5.4	0.072
Females	802	1.16 \pm 1.23	0.48	0.97	0.0009
Elderly Females	81	1.65 \pm 1.72	-0.59	3.63	0.0029
Females with CR _{CL} \leq 50 mL/min	11	2.44 \pm 3.04	1.85	-10	0.058
Females Taking CYP3A4 Inhibitors	100	1.31 \pm 1.36	-0.05	2.7	0.0001
Subjects with CR _{CL} \leq 50 mL/min	23	2.17 \pm 2.29	1.75	-7.3	0.039
Subjects with CR _{CL} >50 mL/min to <80 mL/min	181	1.37 \pm 1.24	-1.11	0.08	0.0031
Subjects with cardiovascular disease	298	1.20 \pm 1.27	-0.42	0.65	0.00069
Subjects taking concomitant diuretics and with potassium \leq 3.5 mEq/L	139	1.44 \pm 1.43	-1.08	-0.78	0.0047
Subjects taking concomitant CYP3A4 substrates	555	1.26 \pm 1.32	0.61	1.04	0.0014
Subjects taking concomitant CYP3A4 inhibitors	132	1.27 \pm 1.30	0.2	3.02	0.00035

N = number of matched data points, TEL = telithromycin

7.2.7 Summary of safety in Phase III studies

- The incidence and nature of the most frequently reported TEAEs were, in general, similar between telithromycin and comparators. TEAEs of the gastrointestinal disorders SOC (e.g. diarrhea NOS, nausea and vomiting) were most frequently reported and were generally mild or moderate in intensity.
- Blurred vision, which was generally mild, transient, and fully reversible, was rarely reported (0.4%) in Phase III clinical trials and appeared at higher incidence in subjects under 50 years of age. The mechanism of blurred vision is consistent with a transient delay in accommodation. The effect had a short duration (2 to 3 hours). There was no evidence of retinal toxicity or change in intraocular pressure or anterior chamber angle as explored in Phase I studies.
- The overall incidence of death was the same (0.4%) in both telithromycin and comparator groups. None of the deaths were assessed by the investigator as being possibly related to study medication.
- Adverse events requiring discontinuation of study medications were uncommon and balanced between treatment groups: telithromycin (119/2702, 4.4%) and comparators (92/2139, 4.3%). The most frequently reported TEAEs leading to discontinuation in both telithromycin- and comparator-treated subjects were diarrhea NOS (0.9% vs. 0.6%, respectively), vomiting NOS (0.8% vs. 0.5%, respectively) and nausea (0.7% vs. 0.5%, respectively).
- In Phase III studies, hepatic laboratory values (such as combined total bilirubin and ALT increases and CNALVs for ALT and AST) were balanced between telithromycin and comparators. There was 1 case of granulomatous hepatitis with eosinophilic infiltration on biopsy that resolved with

an asymptomatic recurrence 9 months later without further telithromycin exposure suggesting a pre-existing and undiagnosed autoimmune disorder as a cause.

- At therapeutic dose, telithromycin was associated with a small (1.5 ms) mean increase in QTc interval. QTc outlier values were uncommon and similar in frequency to those seen with clarithromycin and non-macrolide antibiotics. No excess in risk for significant QTc interval prolongation was noted, even in at-risk populations.

7.3 Study 3014

Study 3014 was a large trial performed in a usual care setting which allowed the assessment of telithromycin safety in a large number of subjects, including significant numbers with associated comorbidities and taking a variety of concomitant medications.

This study was a randomized, open-label, comparative study performed in the usual care setting, which enrolled and treated 24140 subjects, including 12161 subjects in the telithromycin arm.

This large trial was designed in consultation with the FDA. Telithromycin was administered at 800 mg once daily for 5 days in the treatment of AS, and for 7 to 10 days in CAP. To enhance potential safety signal detection, the treatment duration for AECB was extended from 5 days (the usual telithromycin AECB dosing duration) to 7 to 10 days as recommended by the FDA. Amoxicillin-clavulanic acid (AMC) was administered at 875 mg amoxicillin in combination with 125 mg clavulanic acid 3 times daily for 7 to 10 days for all 3 indications, as recommended in its US labeling. Doses were reduced for severe renal insufficiency with both study medications. Consistent with a usual care design, exclusion criteria were kept to a minimum. Subjects were excluded if they had a known history of congenital long-QTc syndrome, were pregnant or breast-feeding, had hypersensitivity to telithromycin, or beta-lactam or macrolide classes of antibiotics, required treatment during the study with ergot alkaloid derivatives, terfenadine, cisapride, astemizole, or pimozide, had previously participated in this study or had a previous history of cholestatic jaundice or hepatic dysfunction associated with AMC. The study targeted subjects with comorbidities and was planned to enroll $\geq 35\%$ subjects aged 50 years or older, and 40% of subjects with CAP or AECB.

On-site office visits were planned at pretherapy (Visit 1, occurring on Day 1) and post-therapy (Visit 2, occurring between Days 17 to 22). Contact at late post-therapy (Visit 3, planned for Days 30 to 35) could be conducted either by phone or office visit. However, to facilitate capture of detailed adverse event information, all subjects with adverse events of special interest (AESIs) or serious adverse events (SAEs) were asked to return to the office at late post-therapy. In all other cases, whether this visit was a site or office visit was left to the clinical discretion of the investigator.

The main focus of this study was clinical safety, with the intent to exclude an increased risk of rare clinical events. AESIs were subject to detailed reporting and follow-up. AESI included clinically overt hepatic events; cardiac events related to QT prolongation or potentially representing malignant ventricular arrhythmias, including all deaths in the period of observation; vasculitic events; and events of blurred vision.

Investigators were instructed to report all adverse events occurring within the 30 to 35 day window of observation, with a particular focus on identifying all AESIs. All adverse events reported during the period of observation were reviewed on a regular basis by the responsible pharmacovigilance medical officer and Clinical Review Team officer to ensure that no serious events or AESI had been missed.

To ensure the capture of all potential hepatic cases, hepatic laboratory tests were performed at pretherapy and post-therapy.

The investigator completed the relevant AESI form for each such event, including a questionnaire that elicited various history and physical exam findings relevant to the diagnosis. Its purpose was to provide a standardized set of information to substantiate the diagnosis and investigate the etiology of the event. In addition, for each AESI, the investigator was instructed to perform a minimum standard evaluation in all subjects. While this guidance was not intended to define the extent of work-up of the event, it provided a robust body of information on each AESI. The broader work-up of these events was directed by the investigator and any other physicians treating the subject as dictated by clinical judgement and the standard of medical care. The events of interest were followed by the Sponsor representative through the study-defined period of observation, and for longer as necessary, including the collection of additional laboratory samples until, for example, resolution of hepatic analyte abnormalities, or until the investigator deemed follow-up was no longer required. The Sponsor representative generated the case information, along with other pertinent case findings, into an individual case narrative. The narratives were forwarded every 2 months to an expert clinical events committee (CEC) for blinded review. A case data summary, the questionnaire completed by the investigator and any other available documentation was also provided for each subject with an AESI. This package of information was used by the CEC to evaluate if the case met the predefined study endpoint definitions.

7.3.1 Subject exposure

A total of 24140 subjects were treated in Study 3014. Two telithromycin-treated subjects and one AMC treated subject had no post-baseline assessment. Therefore, 24137 (>99.9%) subjects had a post-baseline assessment and constitute the safety-evaluable population.

An additional stratification of the safety-evaluable population is comprised of subjects with available adverse event information for at least 28 days or more after the start of treatment. A high percentage of subjects, 99.5% of telithromycin-treated subjects and 99.2% of AMC-treated subjects are in this category. This population is used to estimate the incidence of rates for the primary safety events adjudicated as positive by the CEC. (see *Section 7.3.6, Adverse events of special interest*).

Table 7-17. Safety evaluable population in Study 3014

Demographic variable	Number (%) of subjects ^a			
	TEL		AMC	
Total treated	12161	(100)	11979	(100)
Safety evaluable	12159	(>99.9)	11978	(>99.9)
Total with Follow-up to Day 28 or later				
Vital (alive or dead) status	12138	(99.8)	11941	(99.7)
Adverse event information	12096	(99.5)	11883	(99.2)

TEL: telithromycin, AMC: amoxicillin-clavulanic acid

7.3.2 Demographics of population in Study 3014

Study 3014 focused enrollment on a target population of potentially at-risk subjects, with 5671 (46.6%) ≥50 years of age, 2273 (18.6%) ≥65 years of age, and 892 (7.3%) ≥75 years of age. The following table shows the age and sex characteristics of the 3014 population.

Table 7-18. Demographic characteristics for safety-evaluable population in Study 3014

Demographic variable		Number (%) of subjects			
		TEL		AMC	
Total treated and safety evaluable		12159		11978	
Sex	Male	4755	(39.1)	4786	(40.0)
	Female	7404	(60.9)	7192	(60.0)
Age (years)	Subjects <50	6481	(53.3)	6436	(53.7)
	Subjects ≥50	5671	(46.6)	5536	(46.2)
	Subjects 50 - 64	3398	(27.9)	3333	(27.8)
	Subjects 65 - 74	1381	(11.4)	1330	(11.1)
	Subjects 75 - 84	766	(6.3)	747	(6.2)
	Subjects ≥85	126	(1.0)	126	(1.1)
	Mean ± SD	49.3 ± 15.7		49.1 ± 15.9	
Median (Range)	48.0 (18 - 99)		48.0 (16 - 100)		

TEL = telithromycin; AMC = amoxicillin-clavulanic acid

7.3.3 Exposure by indication and treatment duration

A total of 24137 subjects were evaluable for safety analyses. This total included 12159 subjects who received telithromycin and 11978 subjects who received AMC. The following table shows by indication, the number of subjects in the safety-evaluable population exposed to telithromycin.

Table 7-19. Subjects exposed to telithromycin in Study 3014

Indication	Telithromycin			Amoxicillin-clavulanic acid		
	Treatment Regimen (Days)	No. of Subjects	Mean ± SD duration (days)	Treatment Regimen (Days)	No. of Subjects	Mean ± SD duration (days)
CAP	7 to 10	1092	10 ± 2	7 to10	1053	10 ± 2
AECB	7 to 10	3786	10 ± 2	7 to10	3668	10 ± 2
Acute sinusitis	5	7281	6 ± 2	7 to10	7257	10 ± 2
Total number of subjects		12159			11978	

CAP = community-acquired pneumonia; AECB = acute exacerbation of chronic bronchitis
Subjects with missing values were excluded.

As the table above shows, there is extensive experience with telithromycin for both 5-day and 7- to 10-day regimens, and there are comparable exposure numbers by indication for telithromycin and AMC subjects.

7.3.4 Treatment-emergent adverse events

The definition of TEAEs was the same in Study 3014 as for the integrated Phase III studies (see *Section 7.2.3, Treatment-emergent adverse events in Phase III studies*). In Study 3014, the treatment period encompassed the period from the first day of study medication to 7 days after the last dose was taken.

The frequency and profile of TEAEs was comparable between telithromycin-treated subjects (2807/12159, 23.1%) and AMC-treated subjects (2745/11978, 22.9%).

The following table shows the 5 MedDRA SOCs for which all TEAEs and possibly related TEAEs were most commonly reported.

Table 7-20. System organ classes for which all and possibly related TEAEs were most commonly reported in Study 3014

MedDRA System organ class	Number (%) of subjects	
	Telithromycin N=12159	AMC N=11978
All TEAEs^a		
Subjects with TEAEs	2807 (23.1)	2745 (22.9)
Gastrointestinal disorders	1292 (10.6)	1417 (11.8)
Nervous system disorders	581 (4.8)	238 (2.0)
Infections and infestations	501 (4.1)	728 (6.1)
Respiratory, thoracic and mediastinal disorders	204 (1.7)	190 (1.6)
Skin and subcutaneous tissue disorders ^b	151 (1.2)	170 (1.4)
Possibly related TEAEs^a		
Subjects with possibly related TEAEs	1901 (15.6)	1932 (16.1)
Gastrointestinal disorders	1106 (9.1)	1260 (10.5)
Nervous system disorders	416 (3.4)	118 (1.0)
Infections and infestations	243 (2.0)	467 (3.9)
Skin and subcutaneous tissue disorders	117 (1.0)	128 (1.1)
Investigations ^c	85 (0.7)	54 (0.5)

AMC = amoxicillin-clavulanic acid

^a Based on the 5 most frequently affected SOCs in each treatment group.

^b TEAEs were also reported in 151 (1.2%) telithromycin subjects and 93 (0.8%) AMC treated subjects for the general disorders and administration site conditions SOC.

^c Investigations includes asymptomatic laboratory abnormalities

In both treatment groups, the most frequently affected SOC was the gastrointestinal system. Nervous system disorders appeared to be more common in telithromycin-treated subjects, whereas TEAEs of the infections and infestations SOC were more common in subjects treated with AMC.

TEAEs by decreasing frequency

The following table presents the most common individual TEAEs reported.

Table 7-21. All and possibly related TEAEs by decreasing frequency in Study 3014

Preferred term	Number (%) of subjects	
	Telithromycin N=12159	AMC N=11978
All TEAEs^a		
Subjects with TEAEs	2807 (23.1)	2745 (22.9)
Diarrhea NOS	423 (3.5)	813 (6.8)
Nausea	382 (3.1)	286 (2.4)
Headache NOS	230 (1.9)	144 (1.2)
Dizziness (excl. vertigo)	192 (1.6)	59 (0.5)
Vomiting NOS	102 (0.8)	115 (1.0)
Possibly related TEAEs^b		
Subjects with possibly related TEAEs	1901 (15.6)	1932 (16.1)
Diarrhea NOS	384 (3.2)	776 (6.5)
Nausea	345 (2.8)	244 (2.0)
Headache NOS	154 (1.3)	73 (0.6)
Dizziness (excluding vertigo)	149 (1.2)	32 (0.3)
Vaginosis fungal NOS	54 (0.4)	159 (1.3)

^a Based on a frequency of all TEAEs of $\geq 2.0\%$ in telithromycin or AMC treatment groups.

^b Based on a frequency of possibly related TEAEs of $\geq 1.0\%$ in telithromycin or AMC treatment groups.
NOS = not otherwise specified, AMC = amoxicillin-clavulanic acid

Diarrhea NOS was the most common individual TEAE and was more frequent in AMC-treated subjects than in the telithromycin group. Headache NOS and dizziness (excluding vertigo) were more common in telithromycin-treated subjects than AMC-treated subjects. The majority of these events were considered as possibly related to study medication.

The profile of events was consistent with that observed in the controlled Phase III trials. The adverse event reporting rate with telithromycin in study 3014, while lower than that seen in the Phase III studies, was comparable to that observed with comparator, amoxicillin-clavulanic acid. The lower reporting rate in this study likely reflects the differences in study design. The differential effect of design on reporting rates has been observed with other large trials performed in a usual care setting (PB Iannini et al, ICAAC, 2002, Abstract L-374). Of note, as presented below, reporting rates for adverse events of special interest (the focus of this large study), drug-related serious adverse events, and discontinuations due to adverse events, were comparable between the two study populations.

TEAEs by intensity

As shown in the following table, the majority of subjects with TEAEs had events of mild or moderate intensity in both the telithromycin and AMC treatment groups. The frequency of severe TEAEs was low and was reported at a similar rate in each treatment group.

Table 7-22. All and possibly related TEAEs by intensity in Study 3014

Intensity	Number (%) of subjects			
	All TEAEs		Possibly related TEAEs	
	Telithromycin N=12159	AMC N=11978	Telithromycin N=12159	AMC N=11978
Mild	1985 (16.3)	1944 (16.2)	1380 (11.3)	1382 (11.5)
Moderate	858 (7.1)	831 (6.9)	538 (4.4)	544 (4.5)
Severe	170 (1.4)	153 (1.3)	91 (0.7)	86 (0.7)

AMC = amoxicillin-clavulanic acid

Diarrhea NOS was the most common severe TEAE and was reported in 25/12159 (0.2%) telithromycin-treated subjects and 36/11978 (0.3%) AMC-treated subjects.

7.3.4.1 TEAEs in subgroups of interest

Study 3014 provided an opportunity to look at the safety of telithromycin in subgroups of interest due to the significant number of subjects that is generally not seen in traditional Phase III studies. The safety profile of at-risk subgroups (older subjects, subjects with diabetes, cardiac, hepatic and renal diseases) was generally similar between treatment groups. The following table shows the TEAE frequency in some of the subgroups of interest.

Table 7-23. Frequency of all TEAEs by subgroup in Study 3014

Subjects with TEAEs by subgroup	n/N (%) of subjects			
	TEL		AMC	
Safety evaluable population	2807/12159	(23.1)	2745/11978	(22.9)
Men	935/4755	(19.7)	860/4786	(18.0)
Women	1872/7404	(25.3)	1885/7192	(26.2)
Aged <50 years	1493/6481	(23.0)	1459/6436	(22.7)
Aged ≥50 years	1314/5671	(23.2)	1284/5536	(23.2)
Aged ≥= 65	518/2273	(22.8)	526/2203	(23.9)
Diabetes	256/1126	(22.7)	249/1075	(23.2)
History of cardiovascular disease	793/2965	(26.7)	737/2915	(25.3)
History of arrhythmia	100/305	(32.8)	94/274	(34.3)
History of congestive heart failure	83/277	(30.0)	65/270	(24.1)
Any renal impairment	19/78	(24.4)	16/76	(21.1)
Hepatic impairment	31/97	(32.0)	41/119	(34.5)
Taking CYP3A4 inhibitors	632/2309	(27.4)	651/2201	(29.6)
Taking drugs metabolized by CYP3A4	1499/5834	(25.7)	1542/5795	(26.6)
Taking simvastatin/atorvastatin/lovastatin	347/1420	(24.4)	305/1341	(22.7)

TEL = telithromycin, AMC = amoxicillin-clavulanic acid

n = number of subjects with event, N= total number of subjects in population or subgroup

The number of subjects by age may not sum to the total as some subjects had missing age data

The overall frequency of TEAEs was similar between groups and unaffected by subgroup. In each treatment group, TEAEs were more common in women than men. No clinically relevant differences were observed in TEAE frequency between the different age subgroups. Further details are provided below for some of these subgroups of interest.

Subjects with cardiovascular disease, arrhythmia or congestive heart failure

Subjects with a history of cardiovascular disease showed a slight increase in incidence of TEAEs in both treatment groups compared to the overall safety population, although the incidence of treatment related events for telithromycin and AMC was similar to those in the overall safety population. The pattern of TEAEs in the cardiovascular subgroup was also similar to that observed in the overall safety population. In the smaller subgroups of subjects with a history of arrhythmia or of congestive heart failure, the incidence of TEAEs also appeared to be increased in both groups compared with the overall safety population; further conclusions are limited by the small subgroup size.

Subjects taking CYP3A4 inhibitors

Given that telithromycin is partly metabolized by CYP3A4, an analysis of the TEAEs in subjects taking concomitant CYP3A4 inhibitors was performed. The frequency of TEAEs was comparable between treatment groups but in both groups was slightly higher in those subjects taking a concomitant CYP3A4 inhibitor (telithromycin: 632/2309, 27.4%; AMC: 651/2201, 29.6%) than in the overall safety evaluable population. This finding was similar between the 2 groups although AMC is not metabolized by CYP3A4. TEAEs were most common in the gastrointestinal disorders SOC.

Subjects taking HMG CoA reductase inhibitors of interest

Simvastatin, atorvastatin and lovastatin are primarily metabolized by CYP3A4. The incidence of TEAEs in subjects with concomitant use of these statins was similar in both treatment groups and comparable to the overall population.

The frequency of TEAEs of the musculoskeletal and connective tissue disorders SOC in subjects taking HMG CoA reductase inhibitors of interest (telithromycin: 12/1420, 0.8%; AMC: 15/1341, 1.1%) was similar to the overall safety evaluable population in both treatment groups (telithromycin: 127/12159, 1.0%; AMC: 89/11978, 0.7%). The frequency of individual musculoskeletal events was low and similar between treatments in those subjects taking HMG CoA reductase inhibitors of interest: myalgia (telithromycin 1/1420; AMC 2/1341), muscle cramps (telithromycin 3/1420; AMC 3/1341), musculoskeletal pain (telithromycin 1/1420; AMC 0/1341). No events of rhabdomyolysis or severe myositis were reported during the study and no telithromycin-treated subject had a TEAE of blood creatinine phosphokinase increased (compared with 1/1341 AMC-treated subject).

Subjects with hepatic impairment

In subjects with a history of hepatic impairment, the frequency of gastrointestinal disorders was slightly lower for telithromycin-treated subjects (10/97, 10.3%) than for AMC-treated subjects (18/119, 15.1%), with diarrhea NOS being the most frequently reported gastrointestinal event in each group (4.1% and 8.4%, respectively). The other most common TEAEs in this subgroup were liver function tests NOS abnormal (telithromycin: 4/97, 4.1%; AMC: 3/119, 2.5%) and alanine aminotransferase increased (telithromycin: 3/97, 3.1%; AMC: 7/119, 5.9%).

Subjects with renal impairment

In subjects with any renal impairment recorded at entry, TEAEs were reported in 19/78 (24.4%) telithromycin-treated subjects and 16/76 (21.1%) AMC-treated subjects, rates comparable with the overall safety population

Severe renal impairment was defined as a known creatinine clearance <30 mL/min at study enrollment. Determination of creatinine clearance at randomization was not required as this study was

meant to reflect the practice in a community setting. Five subjects (5/23) in the telithromycin group and none of the 17 AMC-treated subjects experienced TEAEs. The incidence of TEAEs in this subgroup is consistent with the overall incidence in the safety population with no major differences in individual events; further conclusions are limited by the small subgroup size.

7.3.5 Deaths, Serious Adverse Events and Discontinuations due to TEAEs

7.3.5.1 Deaths

A total of 35 subjects died; 24 between Days 1 and 35, 11 after Day 35. The incidence of death was very low and similar between the telithromycin (15/12159, 0.1%) and AMC (20/11978, 0.2%) treatment groups. None of the deaths were considered possibly related to study medication by the investigator. All deaths occurring between Days 1 and 35 (the observation period for the study) were considered cardiac adverse events of special interest and were reviewed by the cardiac CEC (see Section 7.3.6.2, *Assessment of cardiac effects*). Narratives for these subjects can be found in Appendix 8, *Deaths in Study 3014*.

Table 7-24. Deaths occurring during Days 1 to 35 by indication in Study 3014

	Number of subjects	
	TEL	AMC
Deaths occurring during Days 1 to 35		
All indications	10	14
AECB	4	7
AS	5	4
CAP	1	3

TEL = telithromycin, AMC = amoxicillin-clavulanic acid

7.3.5.2 Serious TEAEs

The frequency of serious TEAEs was balanced between treatment groups (telithromycin: 155/12159, 1.3%; AMC: 133/11978, 1.1%). The incidence of possibly related serious TEAEs was very low in each treatment group (telithromycin: 26/12159, 0.2%; AMC: 9/11978, 0.1%) and consistent with the findings from the controlled Phase III studies.

As in the controlled Phase III studies, the most frequently reported serious event criteria in both treatment groups in Study 3014 were required/prolonged hospitalization (telithromycin: 118/12159, 1.0%; AMC: 108/11978, 0.9%) and medically important (telithromycin: 54/12159, 0.4%; AMC: 34/11978, 0.3%).

The following table shows the SOCs for which all serious TEAEs were most commonly reported.

Table 7-25. System organ classes for which all TEAEs were most commonly reported in Study 3014

System organ class	Number (%) of subjects	
	Telithromycin (N=12159)	AMC (N=11978)
Subjects with all serious TEAEs^a	155 (1.3)	133 (1.1)
Infections and infestations	42 (0.3)	49 (0.4)
Respiratory, thoracic and mediastinal disorders	34 (0.3)	27 (0.2)
Cardiac disorders	26 (0.2)	17 (0.1)
Gastrointestinal disorders	15 (0.1)	10 (0.1)
Pregnancy, puerperium and perinatal conditions	6 (0.0)	7 (0.1)

^a Based on the 5 most frequently affected SOCs in each treatment group.

SAEs were balanced between telithromycin and AMC treatment groups. As seen in the Phase III studies, infections not related to drug were the most common SAEs reported.

7.3.5.3 Discontinuations due to TEAEs

Discontinuation of study medication due to a TEAE was uncommon for both treatment groups (telithromycin: 467/12159, 3.8%; AMC: 557/11978, 4.7%) and was most commonly due to gastrointestinal events. The discontinuation rates are comparable to that seen in controlled Phase III studies (telithromycin: 119/2702, 4.4%). The frequencies of the most common TEAEs that led to discontinuation of study medication are presented in the following table.

Table 7-26. TEAEs resulting in discontinuation of study medication in Study 3014

Preferred term	Number (%) of subjects			
	Telithromycin (N=12159)		AMC (N=11978)	
Subjects with TEAEs resulting in discontinuation of study medication^a	467	(3.8)	557	(4.7)
Nausea	83	(0.7)	88	(0.7)
Diarrhea NOS	75	(0.6)	224	(1.9)
Vomiting NOS	40	(0.3)	57	(0.5)
Dizziness (excl vertigo)	38	(0.3)	10	(0.1)
Headache NOS	36	(0.3)	21	(0.2)
Vision blurred	23	(0.2)	2	(0.0)
Abdominal pain NOS	22	(0.2)	29	(0.2)
Rash NOS	12	(0.1)	23	(0.2)
Urticaria NOS	10	(0.1)	18	(0.2)

^a Based on a frequency of TEAEs leading to discontinuation of $\geq 0.2\%$ in telithromycin or AMC groups.
AMC = amoxicillin-clavulanic acid; NOS = not otherwise specified

In the telithromycin treatment group, the most common TEAE leading to discontinuation of study medication was nausea but the proportion of subjects discontinuing therapy for this event was similar to the AMC group. In the AMC group the most common TEAE leading to discontinuation was diarrhea NOS, which occurred in a higher proportion of subjects than in the telithromycin group.

7.3.6 Adverse events of special interest

Assessment of specific events of interest (cardiac, hepatic, visual and vasculitic) was a major focus of this study to ensure and facilitate adjudication of all study endpoints, and is presented in this section. The specific safety endpoint definitions established with external experts are provided at the start of the appropriate section. The goal of such definitions was the establishment of likely drug-related endpoints. The CEC used their expertise to provide the final opinion on each case.

7.3.6.1 Assessment of hepatic effects

7.3.6.1.1 Hepatic adverse events of special interest

Hepatic AESIs included all reports of hepatitis, jaundice, or any worsening of a pre-existing hepatic condition. In addition, all cases of ALT >3x ULN were designated AESIs. The occurrence of hepatic AESIs was balanced between telithromycin and comparator, with 111/12046 (0.9%) and 98/11883 (0.8%) hepatic AESI, respectively. Those AESI confirmed as endpoints by the CEC are discussed in *Section 7.3.6.1.2, Hepatic endpoints*. The majority of these AESIs (telithromycin: 80/111, 72.1%; amoxicillin-clavulanic acid: 75/98, 76.5%) were reported to be asymptomatic liver enzyme elevations captured through routine screening of all subjects. Symptomatic hepatic adverse events were also balanced between treatment groups, with 21 cases in the telithromycin group and 23 in the AMC group. The most common symptoms in each treatment group were fatigue and nausea. Three subjects (2 in the telithromycin group and 1 in the AMC group) had jaundice recorded as a symptom of the hepatic AESI; all were confirmed by laboratory results and all 3 recovered.

Of the 209 subjects with hepatic AESIs, 196 had documented resolution of their laboratory abnormalities. Of the 13 subjects that remained: 3 died of unrelated causes, 10 either refused follow-up or had other medical illnesses, or were taking concomitant medications which accounted for the lack of complete resolution of their hepatic event. None had signs or symptoms suggesting clinical hepatitis, apart from one subject on AMC who was adjudicated as a positive end-point and refused follow-up. Thus, there was no evidence of chronic hepatic injury in the 24137 subjects enrolled and treated in Study3014.

7.3.6.1.2 Hepatic endpoints

In Study 3014, the hepatic endpoint was predefined as possible drug-related significant hepatic injury: clinically overt, symptomatic liver insult, with associated ALT values of at least 3x ULN in the absence of other causes. New onset of symptoms on or later than Day 5 of therapy was specified, so as to differentiate drug-related effects from symptoms of an underlying disease. A decrease in ALT $\geq 50\%$ was expected within 30 days of drug cessation.

The incidence of hepatic endpoint cases following blinded CEC adjudication was balanced between telithromycin and AMC, with rates of 0.025% and 0.017%, respectively. Brief narratives of the 3 telithromycin and 2 AMC cases are presented below.

Telithromycin

Subject 3440/001 (telithromycin), a 75-year-old white female, with a medical history of coronary artery disease, angina/myocardial infarction, hypertension, cholecystectomy, gastroesophageal reflux disorder, degenerative joint disease, hyperlipidemia and hypothyroidism was enrolled in the study on 21 January 2002, with acute sinusitis (AS). She had no history of liver disease. The subject reported a history of use of acetaminophen and recently Extra-Strength Tylenol for joint pain. The last dose of

study medication was taken on 25 January 2002. On 06 February 2002, the subject experienced liver function tests NOS abnormal (verbatim term: elevated LFT) as detailed in the table below, and abdominal pain NOS (verbatim term: abdominal pain). Associated symptoms included fatigue, nausea, fever and severe epigastric pain. While jaundice was noted as a symptom of the event, peak bilirubin value was only 1.7 mg/dL. The epigastric pain began suddenly while eating breakfast and was initially relieved with TUMS. The subject was hospitalized on 07 February 2002 for worsening pain. On admission, she was in no distress. Temperature was 100.2°F to 101.0°F with a pulse of 88 beats per minute. Exam was notable for right upper quadrant and epigastric tenderness. She was kept on nothing by mouth and given intravenous fluids. Her pravastatin was withheld. Hepatitis A, B and C serology, ANA, anti-smooth muscle, anti-double stranded DNA, and anti-mitochondrial antibodies were all negative. Acetaminophen level was 2 (no units given). An abdominal CT scan was notable for signs of previous cholecystectomy. There was no noted common bile duct dilation (per investigator, report not available). She continued to improve, felt better and was discharged from the hospital on 10 February 2002. Discharge diagnosis was hepatitis with possible etiologies including drug and passed stone. The investigator assessed the events to be serious as they required or prolonged inpatient hospitalization, of severe intensity, and possibly related to study medication. The investigator also provided alternative explanations for the events: possibly associated with concomitant drugs or due to stone in the common bile duct. Abdominal pain resolved without sequelae on 25 March 2002. The event resolved with the return of ALT and alkaline phosphatase to within the normal range.

Laboratory data for Subject 3440/001 (telithromycin)

Analyte (units)	Normal range	Base-line (21 Jan 2002)	Date (07 Feb 2002; 07:04)	Date (07 Feb 2002; 02:29)	Date (08 Feb 2002; 07:15)	Date (09 Feb 2002)	Date (18 Feb 2002)	Date (26 Mar 2002)
ALT (U/L)	6-32	9.0					33.0/H	18.0
ALT (U/L) ^a	25-65		969.0/H	531.0/H	629.0/H			
AST (U/L)	9-34	16.0					18.0	17.0
AST (U/L) ^a	15-37		1357.0/H	782.0/H	396.0/H	108.0/H		
Alkaline phosphatase (U/L)	35-164	74.0					103.0	71.0
Alkaline phosphatase (U/L) ^a	50-136		285.0/H	260.0/H	282.0/H	243.0/H		
Total bilirubin (µmol/L)	3-21	7.0					5.0	7.0
Total bilirubin (µmol/L) ^b	0-17		31/H	15	19/H	12		

H = high - above the upper limit of the normal range, L = low - below the lower limit of the normal range

^a Local laboratory measurement. ^b Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL=17 µmol/L.

Subject 1567/009 (telithromycin), a 58-year-old black female, was enrolled in the study on 05 December 2001, with AECB. The last dose of study medication was taken on 14 December 2001, and hepatic laboratory tests performed on 21 December 2001 were normal. On 27 December 2001, the subject was seen in the emergency room and diagnosed with pyelonephritis. Symptoms included fatigue, fever, abdominal pain, and hematuria. Urinalysis revealed 2+ bilirubin with 10 to 20 WBC/high power field. She was begun on ciprofloxacin. Repeat bloodwork performed on 30 December 2001 revealed elevated liver function tests as shown in the table. The investigator assessed the event as nonserious, of mild intensity, and possibly related to study medication. Increased bilirubin and pyelonephritis resolved without sequelae on 01 February 2002.

Laboratory data for Subject 1567/009 (telithromycin)

Analyte (units)	Normal range	Baseline (05 Dec 2001)	Date (21 Dec 2001)	Date (30 Dec 2001)	Date (01 Feb 2002)
ALT (U/L)	6-34	14.0	16.0		22.0
ALT (U/L) ^a	8-35			66/H	
AST (U/L)	9-34	19.0	21.0		19.0
AST (U/L) ^a	8-37			88/H	
Alkaline phosphatase (U/L)	35-123	91.0	90.0		89.0
Alkaline phosphatase (U/L) ^a	30-120			196/H	
Total bilirubin (µmol/L)	3-21	3.0	9.0		9.0
Total bilirubin (µmol/L) ^{a, b}	1.7-17			82.1/H	

H = high - above the upper limit of the normal range, L = low - below the lower limit of the normal range

^a = Local laboratory data not entered in the database.

^b = Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL=17 µmol/L.

Subject 2004/002 (telithromycin), a 72-year-old male, with a medical history of type II diabetes mellitus, hypertension, prostate cancer without known metastases, chronic lower left extremity lymphedema, congestive heart failure (systolic and diastolic dysfunction), coronary artery disease, diastolic and systolic dysfunction, chronic pleural effusion, and chronic anticoagulation for questionable clot in the heart was enrolled in the study on 19 December 2001, with CAP. Concomitant medications were Aceon, Coumadin, Glyburide, Lasix, Promethazine/codeine, Spironazide, Levaquin, Robitussin A-C, Vitamin K, Ambien, Milk of Magnesia, Unasyn and Aldactone. The subject completed treatment on 28 December 2001. On 10 January 2002, the subject experienced elevated liver function tests, with peak ALT of 270 U/L, AST of 162 U/L, and total bilirubin of 104 U/L in conjunction with an elevated alkaline phosphatase (461 U/L) on that date, and with peak alkaline phosphatase of 617 U/L noted 6 days later. He otherwise felt well, but was noted on examination to have jaundice. Epstein Barr Virus titers, ANA, anti-dsDNA, and hepatitis A, B, and C titers were all negative. The CT scan revealed bilateral pleural effusion and segmental atelectasis at the right lung base anterior segment, mild eventration of the right dome of the diaphragm, with increased wall thickness of the gallbladder and increased density suggestive of the gallbladder filled with stones and/or a significant amount of sludge. A sonogram of the gallbladder, performed on 17 January 2002, revealed increased gallbladder wall thickness of up to 0.9 cm. There was also some sludge, small low density calculi varying between 1.0 to 2.0 mm and 1 large 5.0 mm of higher density. The sonogram confirmed a significant degree of cholelithiasis and increased gallbladder wall thickness. It was considered that the increased wall thickness was probably secondary to chronic cholecystitis. The subject was admitted on 18 January 2002 with the diagnosis of jaundice. The subject started Levaquin on the same day (18 January 2002) for a complication of the primary infection. On 23 January 2002 the subject underwent a laparoscopic cholecystectomy, and the pathological report was consistent with cholelithiasis and cholecystitis. A post-procedure, intraoperative cholangiogram revealed no common bile duct stones, and this was confirmed on endoscopic retrograde cholangiopancreatography. A biopsy of the liver was performed intraoperatively and showed cholestasis with normally maintained parenchyma, and no significant portal inflammatory changes or lobular inflammation.

Laboratory data for Subject 2004/002 (telithromycin)

Analyte (units)	Normal range	Baseline (19 Dec 2001)	Date (10 Jan 2002)	Date (16 Jan 2002)	Date (01 Feb 2002)	Date (14 Jun 2002)
ALT (U/L)	6-35	17.0	270.0/H	158.0/H	50.0/H	25.0
AST (U/L)	11-36	19.0	162.0/H	100.0/H	36.0	25.0
Alkaline phosphatase (U/L)	35-156	148.0	461.0/H	617.0/H	210.0/H	127.0
Total bilirubin (µmol/L)	3-21	17.0	104.0/H	79.0/H	-	8.5
Absolute eosinophils (cells/MCL)	50-550 cells/MCL	-	-	-	658.0/H (12 Feb 2002)	-
Eosinophils (%)	0.0-6.8	-	-	6.6	-	-

H = high - above the upper limit of the normal range, L = low - below the lower limit of the normal range

The investigator considered this event to be serious, of mild intensity and not related to study medication. The event resolved without sequelae on 28 January 2002, with a final diagnosis of choledocolithiasis.

AMC

Subject 0604/004 (AMC), a 43-year-old white male, was enrolled in the study on 15 January 2002, with AS. His only other medication was Zovirax. The subject completed treatment on 25 January 2002. On 01 February 2002, the subject experienced alanine aminotransferase increased (verbatim term: elevated ALT) with a peak value of 154.0/H and an AST of 68.0/H. Associated symptoms included rash/pruritus. Laboratory values for liver-related tests are shown in the table below. The investigator assessed the event to be nonserious, of mild intensity, and not related to study medication. The subject withdrew from the study on 11 February 2002, and refused to return for follow-up lab work

Laboratory data for Subject 0604/004 (AMC)

Analyte (units)	Normal range	Baseline (15 Jan 2002)	Date (01 Feb 2002)
ALT (U/L)	6-43	50.0/H	154.0/H
AST (U/L)	11-36	35.0	68.0/H
Alkaline phosphatase (U/L)	31-129	67.0	66.0
Total bilirubin (µmol/L)	3-21	7.0	9.0

H = high - above the upper limit of the normal range, L = low - below the lower limit of the normal range

Subject 2326/004 (AMC), a 64-year-old white female was enrolled in the study on 09 January 2002 with AECB. Concomitant medications were Zocor, Miacalcin, Prilosec, Serevent, Flovent, and Calcium with vitamin D. The subject completed treatment on 19 January 2002. The subject had been doing well but returned for follow up on 05 February 2002 complaining of dark urine, nausea, and itching; she was noted on examination to be jaundiced. Laboratory results at that time demonstrated elevated transaminases associated with an elevated total bilirubin and alkaline phosphatase (ALT (U/L): 571/H, AST (U/L): 348/H, Alkaline phosphatase (U/L): 182/H, Total bilirubin (µmol/L): 86.7/H). Hepatitis A, Band C serology were negative. All results returned to normal by 19 March 2002. The investigator treated the subject with tapering doses of prednisone over 16 days starting at 40 mg daily. The investigator assessed the event to be nonserious, of mild intensity, and possibly related to study medication. He also commented that the event may also have been caused by the subject's longstanding treatment with Zocor.

Laboratory data for Subject 2326/004 (AMC)

Analyte (units)	Normal range	Baseline (09 Jan 2002)	Date (26 Jan 2002)	Date (06 Feb 2002)	Date (11 Feb 2002)	Date (19 Mar 2002)
ALT (U/L)	6-34	19.0	21.0		384.0/H	24.0
ALT (U/L) ^a	10-60			571/H		
AST (U/L)	9-34	18.0	22.0		162.0/H	25.0
AST (U/L) ^a	10-42			348/H		
Alkaline phosphatase (U/L)	35-123	38.0	38.0		143.0/H	46.0
Alkaline phosphatase (U/L) ^a	42-121			182/H		
Total bilirubin (µmol/L)	3-21	10.0	10.0		44.0/H	9.0
Total bilirubin (µmol/L) ^{a, b}	3.4-17			86.7/H		
Eosinophils (%)	0.0-6.8	-	-	6.4	3.0	4.4
Absolute eosinophils (GG/L)	0.0-0.57	-	-	-	0.27	0.35

H = high - above the upper limit of the normal range, L = low - below the lower limit of the normal range

^a Local laboratory data not entered in the database.

^b Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL=17 µmol/L.

7.3.6.1.3 Laboratory assessment of the effects of telithromycin on hepatic function

An extensive assessment of the potential for hepatic injury had been performed in Phase III studies enrolling and treating 4472 safety evaluable subjects in telithromycin treatment groups. Increases in transaminases >5 x ULN were balanced between telithromycin and pooled active comparators. No subject in the all integrated Phase III studies had a concomitant increase in ALT ≥3 x ULN and total bilirubin ≥1.5 x ULN. There was 1 case of granulomatous hepatitis with eosinophilic infiltration on biopsy that resolved with an asymptomatic recurrence 9 months later suggesting a pre-existing and undiagnosed autoimmune disorder as a cause.

The large size of Study 3014 allows a thorough assessment of the potential for rare clinical hepatic adverse events. This assessment focused on observed clinical events, and hepatic enzyme and bilirubin measurements were performed to ensure complete case ascertainment. These data include all follow-up tests obtained through August, 2002.

Frequency of clinically noteworthy values for hepatic laboratory tests

As defined in the protocol, hepatic laboratory tests (ALT, AST, alkaline phosphatase, and total bilirubin) were to be performed in all subjects at baseline and post-therapy (Days 17 to 22) to ensure complete documentation of all potential hepatic adverse events, with follow-up to continue until resolution was documented. Fewer than 1% of subjects (telithromycin: 65 subjects, AMC: 95 subjects) had no hepatic laboratory assessment performed, and these subjects were balanced between treatment groups.

Clinically noteworthy abnormal laboratory values

The overall frequency of CNALVs for hepatic enzymes at any post-therapy visit, irrespective of baseline status, was low and similar between telithromycin and AMC.

Table 7-27. Clinically noteworthy hepatic laboratory analytes in Study 3014 at any post-therapy visit

Analyte Criterion	n/N (%) Subjects			
	Telithromycin		Amoxicillin-clavulanic acid	
ALT >3x ULN	110/11570	(1.0)	96/11311	(0.8)
ALT >8x ULN	19/11570	(0.2)	10/11311	(0.1)
ALT ≥3x ULN and total bilirubin ≥1.5x ULN	3/10864	(0.0)	6/10600	(0.1)

n/N = number of subjects with CNALV for specific analyte/number of subjects with measurement of analyte.

As stated in the protocol, all hepatic AESIs were to be monitored for resolution. Predetermined resolution levels were defined as follows: if a subject had normal transaminase levels at pretherapy/entry, investigators were advised to follow the subject until the ALT value had returned to normal; if the hepatic enzymes were abnormal at pretherapy/entry, the recommendation was to follow the subject until the ALT level was within pretherapy/entry value + 2x ULN. The final decision for additional laboratory tests was left to the discretion of the investigator, based on their clinical judgement on the overall condition of the subject.

ALT elevations of 3x ULN were similar between treatment groups. Subjects with ALT >8x ULN at any point during the study were uncommon in both treatment groups, but were slightly more frequent with telithromycin (19 vs. 10 subjects). Most of these elevations were moderate, in the range of 300 to 500 U/L. Elevations above 1000 U/L were noted in 3 telithromycin subjects: 1 had acute hepatitis B infection, and a second had hypoperfusion liver injury (“shock liver”) secondary to acute myocardial infarction. The third subject, with a peak ALT value of 1173 U/L, had a sample questionable for validity (AST not read because of hemolyzed sample); a repeat analysis performed 3 days later revealed an ALT value of 399 U/L.

Fourteen of the 19 telithromycin subjects with ALT >8x ULN had asymptomatic enzyme elevations. For the 5 subjects with symptoms, 2 had jaundice, 1 had symptoms associated with an ovarian cyst, and the remaining 2 had non-specific symptoms. Seventeen of the 19 subjects recovered during subsequent follow-up. Resolution was not documented for 2 subjects: 1 was a 49-year-old female with a history of alcohol abuse and hepatitis C who had a baseline ALT value of 7.5x ULN (254 U/L) and refused further blood sampling for hepatic tests; however, at the late post-therapy visit on Day 31, this subject reported no adverse events. The other subject is mentioned above; that subject had hypoperfusion liver injury whose ALT value was resolving (2.9 ULN) at the time of his death from unrelated cardiac causes.

Three telithromycin subjects and 6 AMC subjects had concomitant ALT >3x ULN and total bilirubin ≥1.5x ULN. In the telithromycin group, only 1 of these subjects, who had acute hepatitis B, had these combined elevations in the absence of significant alkaline phosphatase elevations. The other 2 subjects had alkaline phosphatase elevations consistent with a mixed or cholestatic pattern. One of these had gallstones and was an endpoint case. All 3 subjects recovered. In the AMC group, 4 of the 6 subjects had combined elevated ALT and bilirubin values in the absence of significant alkaline phosphatase elevations. One of the 4 subjects was a positively adjudicated endpoint case. A second subject had hepatitis C with moderate increase in transaminases and new hyperbilirubinemia. A third subject had an abnormal ALT at baseline with minimal change in transaminases post treatment but a new hyperbilirubinemia. The remaining subject had normal baseline transaminases with no alternative explanation for the elevated laboratory values. All 4 of these subjects recovered. The remaining 2 subjects had concurrent alkaline phosphatase elevations consistent with cholestatic injury; 1 subject died of metastatic cancer, the other subject recovered.

7.3.6.2 Assessment of cardiac effects

Study 3014 was a usual care setting study enriched in subjects with underlying diseases. Of the 24137 subjects in the safety population, 1709 (7.1%) subjects had coronary artery disease and 4379 (18.1%) had other cardiovascular diseases. ECGs, as well as other appropriate investigations, though not performed routinely in this study, were nonetheless conducted for subjects who presented with cardiac AESIs if deemed appropriate by the investigator, and data were reviewed by the CEC.

7.3.6.2.1 Cardiac adverse events of special interest

Cardiac AESIs included torsades de pointes and other ventricular arrhythmias, syncope defined as a complete loss of consciousness, cardiac arrest, and all unwitnessed or unexplained deaths. Additionally, any death occurring between Days 1 and 35 was designated a cardiac AESI and forwarded to the expert committee for evaluation for potential ventricular arrhythmia. AESIs adjudicated as endpoints are presented in *Section 7.3.6.2.2, Cardiac endpoints* and cardiac deaths are described in *Section 7.3.6.2.3, Analyses of deaths*.

Cardiac AESIs were identified in 39 subjects (0.3 %) receiving telithromycin and 34 subjects (0.3%) receiving AMC. Of the 73 subjects who experienced a cardiac AESI, more than 80% (59/73) were ≥ 50 years of age; the median age was 66 years (telithromycin: 65 years; AMC: 69.5 years). A similar number of subjects in each treatment group with cardiac AESIs had a history of cardiac disease.

The number of subjects with cardiac AESIs were evenly distributed between treatment groups, gender, indications, and treatment duration (treatment duration analyzed for AECB subjects only). Cardiac AESIs tended to be more common in both treatment groups in the following subgroups: subjects ≥ 50 years of age, in subjects with a history of coronary artery disease, cardiovascular disease, in subjects taking antiarrhythmic drugs, in subjects taking strong CYP3A4 inhibitors and in subjects without a history of hepatic or renal impairment.

The most common outcome of cardiac AESIs reported in either treatment group was recovery without sequelae (26/39 subjects for telithromycin and 17/34 subjects for AMC). Cardiac AESIs resulting in death were reported for 10/12159 (0.08%) telithromycin-treated subjects and 16/11978 (0.13%) AMC-treated subjects.

7.3.6.2.2 Cardiac endpoints

In Study 3014, the cardiac endpoint was predefined as events likely to represent malignant ventricular arrhythmias: torsades de pointes, sustained ventricular tachycardia, syncope, cardiac arrest, and unwitnessed or unexplained death which occurred after first ingestion of study medication through 48 hours after last study medication intake. Other likely causes for the event should have been excluded. Definitions of these component terms are as follows:

- Torsades de pointes: pause-dependent characteristic polymorphic ventricular tachycardia associated with QT interval prolongation. All 3 components were required on the expert-adjudicated ECGs to qualify as torsades de pointes.
- Sustained ventricular tachycardia: documented ventricular tachycardia (monomorphic or polymorphic) which persists for more than 30 seconds or requires termination because of hemodynamic compromise and/or symptoms of impaired perfusion
- Syncope: total loss of consciousness

- Cardiac arrest: loss of consciousness associated with resuscitation where a lethal cardiac arrhythmia has been implicated
- Unwitnessed or unexplained death: any outpatient death which has not been observed and/or where no proximal cause is obvious to the investigator on follow-up. This would not include terminally ill subjects or subjects with imminently lethal diagnoses.

Following blinded CEC adjudication, no telithromycin-treated subjects and 1 AMC-treated subject were confirmed as meeting the endpoint of events likely to represent drug-related malignant ventricular arrhythmias.

The single positively adjudicated endpoint observed in the AMC group is detailed below:

Subject 3014/1302/002 (AMC), a 73-year-old white male, with a medical history of chronic obstructive pulmonary disease, multiple episodes of pneumonia and congestive heart failure was enrolled in the study on 21 December 2001, with AECB. Concomitant medications were Fosamax, Lorazepam, Darvocet-N, Zantac, Proventil inhaler and Ultram. The subject completed treatment on 30 December 2001. On 02 January 2002, the subject experienced an unwitnessed loss of consciousness and died while at home (Investigator assessment: fatal respiratory arrest). No autopsy was performed. This event was adjudicated as a confirmed safety endpoint by the CEC.

7.3.6.2.3 Analyses of deaths

All deaths occurring in the Day 1 to 35 time window were considered cardiac AESIs and were reviewed by the blinded cardiac CEC. There were 10 such deaths in the telithromycin group and 14 in the AMC group. None were considered related to study medication by the investigator or the CEC. A single case in the AMC group (see *Section 7.3.6.2.2, Cardiac endpoints*) was positively adjudicated by the CEC.

These deaths were also reviewed by the blinded CEC and characterized as follows: 1) non-cardiac, 2) cardiac non-arrhythmic, and 3) cardiac arrhythmic (presumed and documented), following the methods of Pratt *et al* [43]. Cardiac arrhythmic deaths were those deaths that were of primary cardiac origin that occurred unexpectedly within 1 hour of symptom onset, or any unwitnessed or unexplained deaths. Cardiac non-arrhythmic deaths were deaths of cardiac origin, but not fitting the cardiac arrhythmic category. Non-cardiac deaths were those deaths that were not due primarily to cardiac causes. These categorizations do *not* imply a causal relationship to study medication. The summary of the presumed arrhythmic deaths is presented below.

Table 7-28. Subjects with presumed arrhythmic deaths in Study 3014

Subject Number	Age/ Sex	Study medication	Event as reported by Investigator	Day of event	Last day of study treatment	Medical History
1760/029	56/F	TEL	Acute MI	29	5	HT, DM, anxiety
0885/002	42/M	TEL	Cardiac arrest	22	10	Obesity, HT, CVA, narcotic addiction
0403/062	57/M	TEL	Myocardial infarction	31	5 ^b	Tobacco, hyperlipidemia, HT, CAD, COPD, dementia
0211/004	81/M	TEL	Worsening thoracic aortic aneurysm	17	10 ^b	CAD, TAA for repair week prior to death, NIDDM, BPH, GERD, hyperlipidemia, HT, COPD
0198/023	74/M	TEL	Cardiac arrest	14	3	CAD, COPD, asthma, DM HT, permanent pacemaker, CHF, CAD, dilated cardiomyopathy
1814/086	48/M	TEL	Cardiac arrest	17	4	None
1305/006	56/F	TEL	COPD exacerbation	14	5	COPD, hyperlipidemia, GERD, fibromyalgia
0728/008	62/F	AMC	Myocardial infarction	28	10	CAD, CHF, COPD, DM
0074/014	62/F	AMC	Cardiac arrest	21	10	CAD, angioplasty with stent 1 month prior, AMI 2 months prior, COPD, CHF
1302/002	73/M	AMC	Respiratory arrest ^a	12	10	COPD, CHF
1228/111	71/F	AMC	Respiratory failure	7	3	Cardiac arrhythmia, DM, left upper lobectomy, COPD with chronic hypoxia, asthma, heart failure, respiratory failure

^a CEC confirmed cardiac endpoint

^b Last day of study medication presumed per protocol where it was not possible to determine the actual last day

TEL = telithromycin, AMC = amoxicillin-clavulanic acid

Sex: M = male, F = female

Medical history: BPH = benign prostatic hypertrophy, CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, DM = diabetes mellitus, GERD = gastroesophageal reflux disease, HT = hypertension, AMI = acute myocardial infarction, NIDDM = non-insulin dependent diabetes mellitus, TAA = thoracic aortic aneurysm

Eleven presumed arrhythmic deaths were identified (7 in the telithromycin group and 4 in the AMC group). None of these cardiac deaths were considered as related to the study medication by the reporting investigator or CEC, all telithromycin cases occurred distant to end of drug therapy >7 days after last dose of study medication, and all AMC cases occurred >4 days post-therapy. One case (Subject 1302/002, treated with AMC) was positively adjudicated by the CEC.

7.3.6.3 Assessment of visual effects

7.3.6.3.1 Visual adverse events of special interest

Investigators were directed to monitor for all episodes of blurred vision occurring with study medication administration (visual AESIs). When present, these events were followed up with a detailed questionnaire. Visual AESIs occurred in 0.68% of subjects treated with telithromycin, and 0.06% of AMC subjects. These events in the telithromycin group were generally mild, transient and reversible. Visual safety endpoints were those visual AESIs adjudicated positive by an independent visual CEC that was blinded to study treatment.

7.3.6.3.2 Visual endpoints

Visual endpoints were defined as all drug-related episodes of blurred vision that occurred after first ingestion of study medication through 48 hours after last study medication intake.

Following blinded CEC adjudication, 74 telithromycin-treated subjects (0.61%) and 5 AMC-treated subjects (0.04%) were confirmed as having met the endpoint of drug-related episodes of blurred vision. The incidence rate of confirmed visual endpoints for telithromycin was consistent with the incidence rate observed with telithromycin in the Phase III studies. The most frequent CEC confirmed visual endpoint events were blurred vision, diplopia and vision abnormal NOS.

In the telithromycin group, the majority of subjects had confirmed visual endpoints that were mild to moderate in intensity. Severe drug-related blurred vision occurred in only 5 telithromycin-treated subjects and all recovered without sequelae. Most subjects required no change in their study medication, but 25/74 telithromycin-treated subjects and 1/5 AMC-treated subjects discontinued treatment due to the event.

The majority of telithromycin-treated subjects reported an episodic occurrence of visual events, which began up to a few hours (median 1 hour) after taking each dose and recovered within several hours (median 2 hours) of each dose. Fewer than half of the subjects with visual endpoint events reported significant impact on their activities, most frequently described as a transient inability to read due to the event. No subjects with blurred vision had further sequelae, there were no reports of permanent visual disturbance and no reports of any adverse event that could be related to an accidental injury associated with blurred vision.

Comparison of the incidence of visual endpoint events in telithromycin-treated subjects with and without various risk factors showed that visual events were more common in females and in subjects with AS. The reasons for the gender and indication differences are unknown. The incidence of visual endpoint events was similar between subjects aged <50 years (42/6481, 0.65%) and those aged ≥50 years (32/5671, 0.56%).

7.3.6.4 Vasculitic adverse events of special interest

Vasculitic endpoints were all drug-related episodes of vasculitis, purpura or other signs that occurred during the period of observation.

Three telithromycin-treated subjects and 1 AMC-treated subject had a vasculitic AESI but following blinded CEC adjudication, there were no subjects in either treatment group with events that were confirmed as meeting the vasculitic endpoint.

7.3.7 Summary of safety in Study 3014

In this large, usual care setting study:

- The safety profile of telithromycin in this usual care setting was comparable to that seen in the Phase III studies, with no new significant safety signals identified.
- The frequency and profile of TEAEs was similar between telithromycin (2807/12159, 23.1%) and AMC (2745/11978, 22.9%). The majority of all TEAEs were of mild or moderate intensity and discontinuation of study medication due to a TEAE was uncommon for both treatment groups (telithromycin: 467/12159, 3.8%; AMC: 557/11978, 4.7%).
- TEAEs of the gastrointestinal disorders SOC were the most common events reported in both treatment groups (telithromycin: 1292/12159, 10.6%; AMC: 1417/11978, 11.8%). Diarrhea NOS was the most common individual TEAE in both groups and occurred less frequently in the telithromycin group (telithromycin: 423/12159, 3.5%; AMC: 813/11978, 6.8%).
- The frequency of serious TEAEs was similar between treatment groups (telithromycin: 155/12159, 1.3%; AMC: 133/11978, 1.1%). A total of 35 subjects (telithromycin: 15; AMC: 20) died during the study. None of the deaths were related to study medication.
- The profile of hepatic AESIs was similar between groups. The incidence of CEC confirmed hepatic safety endpoints was low and similar between treatment groups (telithromycin 3 subjects; AMC 2 subjects). Moderate increases of primarily asymptomatic ALT elevations were rare, but slightly more common with telithromycin. These laboratory abnormalities did not lead to a meaningful increase in clinically symptomatic events, and these events resolved. No episodes of fulminant hepatitis, hepatic failure, chronic immune-mediated hepatitis, liver transplantation, or death due to liver injury were noted.
- No positively adjudicated cardiac endpoints were observed in the telithromycin group compared with one event in the AMC group. All presumed arrhythmic deaths in the telithromycin group occurred distant to treatment and occurred primarily in subjects with significant baseline cardiovascular risk factors.
- Positively adjudicated visual endpoints (blurred vision) occurred in 0.61% of telithromycin-treated subjects and 0.04% AMC-treated subjects. The events were consistent with a delay in accommodation, were transient and resolved without sequelae. There were no reports of permanent visual disturbance and no reports of any adverse event that could be related to an accidental injury associated with blurred vision.
- There were no cases of positively adjudicated drug-related systemic vasculitis in either treatment group.

7.4 Safety data from postmarketing sources

Since approval for use in the treatment of respiratory tract infections in July 2001, telithromycin has been marketed in several countries in Europe and South/Central America, including Germany, France, Italy, Spain, Brazil and Mexico. Current exposures are estimated at nearly 1 million courses of therapy⁴.

This significant exposure with marketed use allows for a confirmation of the safety profile observed in the clinical trials for telithromycin, and assessment of the potential for rare adverse events with broad use.

In the period since approval, a total of 371 postmarketing adverse events have been reported to Aventis (reporting rate of ~0.04%). These events were noted most frequently in the gastrointestinal and visual systems; no new or previously unidentified safety issues were identified.

Forty-six hepatic adverse events occurring in 25 individuals, most commonly representing asymptomatic transaminase elevations, have been reported from postmarketing sources (reporting rate of 0.003%). These events were primarily mild or moderate in intensity, with peak elevations no higher than 300 to 500 U/L. One 58 year-old female subject had ALT elevation to ~ 1200 U/L associated with nausea and fatigue. No elevations of bilirubin were noted, and the subject recovered 12 days later.

Five reports of jaundice were received, 1 of which occurred in a subject with confirmed acute mononucleosis. None of the remaining 4 jaundice cases met Hy's law criteria (transaminase elevations associated with jaundice in the absence of alkaline phosphatase elevation). Two of these cases were confounded by the use of concomitant antibiotic therapy near the time of the hepatic event. All 5 subjects recovered fully. There were no reports of hepatic failure, death from primary hepatic causes, injury requiring transplant, or immune-mediated hepatitis. The overall pattern of hepatic effects observed in the first year of marketing is consistent with that seen from previous clinical trials and with currently marketed antibiotics; no excess risk was identified.

No documented cases of drug-related sudden or unexplained death have been received. Among these ~1 million exposures, a single case of fatal ventricular arrhythmia, was reported as "torsades de pointes". However, the diagnosis of torsades de pointe could not be verified on available ECG tracings. This 59 year-old male subject had multiple cardiac risk factors, including a family history of sudden death in 2 brothers and a parent, and a history of coronary artery disease requiring stent placement in the previous year. This subject had a syncopal episode 3 days prior to starting treatment with telithromycin. While on treatment, he had another syncopal episode which resulted in a motor vehicle accident requiring hospitalization. Treatment with telithromycin was continued. While on a cardiac monitor, the subject developed ventricular tachycardia; the preceding rhythm was sinus rhythm without noted QT interval prolongation. The rhythm progressed to ventricular fibrillation (a "torsades de pointe" was not confirmed on available ECG tracing) and the subject expired. Given this subject's high risk medical history and the onset of syncope prior to drug therapy, an association to telithromycin is unlikely.

Blurred vision and related visual complaints have been reported infrequently (reporting rate of 0.01%). These events were similar to those observed in the clinical trials, with no documented reports of permanent sequelae or serious eye injury. The majority of reports occurred in younger adults (≥ 18

⁴ From Aventis internal sales data as of 01 October 2002

years of age and ≤ 40 years of age). Blurred vision was non-serious, primarily mild or moderate in intensity, and transient, with complete and rapid resolution noted. Most subjects with blurred vision reported an episodic difficulty with focusing on objects (near or far vision), occurring 1 to a few hours after dosing, and lasting a few hours.

7.5 Summary of safety

There is now extensive safety experience with telithromycin, including over 16000 subjects treated in clinical studies (Phase III studies plus Study 3014, a large study in a usual care setting) and postmarketing exposure in approximately 1 million courses of therapy. Significant experience has also been achieved in populations generally considered at risk for drug-related adverse events, including the elderly and those with a variety of co-morbid conditions. Safety data from these sources reinforce the favorable safety profile of telithromycin.

In controlled clinical trials, the frequency and profile of TEAEs observed with telithromycin subjects were comparable to other commonly prescribed antibiotics for respiratory infections, which include macrolides, β -lactams, and fluoroquinolones. The majority of TEAEs were mild to moderate in intensity with gastrointestinal events being the most commonly reported. Similar data were observed in Study 3014, with diarrhea NOS being the most common individual TEAE in both treatment groups although occurring less frequently with telithromycin than with AMC. Rates of discontinuation for adverse events were low and similar to comparator antibiotics. An extensive review of subgroups identified no population at increased risk for adverse drug-related outcomes.

The hepatic safety profile seen with telithromycin is comparable to that of widely prescribed antibiotics. Hepatic adverse events, primarily representing asymptomatic transaminase elevations, were balanced between telithromycin and pooled comparators in Phase III clinical studies. In a large safety study in a usual care setting, no excess risk in adverse hepatic events was noted and there was no detectable difference between telithromycin and AMC in the incidence of predefined hepatic safety endpoints as adjudicated by an independent and blinded expert panel. Moreover, populations at risk, such as the elderly and subjects with renal or hepatic insufficiency, did not display an increased risk for hepatic injury with telithromycin treatment. The profile of hepatic adverse events reported from marketed use (~1 million exposures over approximately a year and a half) was similar to that seen with other antibiotics. No cases of drug-related fulminant hepatic failure, deaths or transplants have been observed.

Electrocardiographic analyses in the Phase III clinical development program revealed a minimal change in QTc of 1.5 ms in subjects with respiratory infections treated with telithromycin. Cardiac adverse event rates were comparable between telithromycin and comparators, including macrolide antibiotics. These findings were confirmed in Study 3014, performed in a usual care setting with minimal exclusion criteria. No positively adjudicated cardiac endpoints were observed with telithromycin, despite enrichment with older subjects and subjects with extensive co-morbid conditions. The postmarketing experience of more than 1 million exposures to date has revealed no excess in sudden unexplained deaths or malignant ventricular arrhythmias. Taken together, the experience from the entire telithromycin development and postmarketing experience confirms the lack of excess cardiac risk.

Results from the integrated Phase III studies, Study 3014 and postmarketing sources were consistent in their characterization of blurred vision associated with telithromycin treatment. The events were characterized as not serious, transient, mild to moderate, occurring predominately in females of 18 to 40 years of age with no comorbid conditions or diseases, rare (<1% in Phase III studies and 3014),

and occurring within a few hours of dosing and lasting for a few hours after each dose. No disabling sequelae were noted. The age distribution of these events supports the Phase I findings that suggest a primary mechanism affecting accommodation.

Events of vasculitis were rarely reported and the data suggest there is no increased risk for vasculitis in subjects treated with telithromycin.

Thus, telithromycin in integrated Phase III studies, in a large risk-enhanced usual care setting study, and in more than 1 million postmarketing exposures has consistently exhibited a safety profile comparable to marketed antibiotics used to treat respiratory tract infections.

8. SUMMARY OF BENEFITS AND RISKS

Telithromycin is the first of a new class of antibacterial agents, the ketolides, developed for the treatment of community-acquired respiratory tract infections (RTIs). Submission of this dossier is to support approval of telithromycin for 3 RTI indications: acute sinusitis (AS), acute exacerbation of chronic bronchitis (AECB), and community-acquired pneumonia (CAP).

RTIs are among the most frequent infectious diseases encountered among outpatients and can be associated with significant morbidity. The key agents associated with these infections include common bacterial pathogens such as *Streptococcus pneumoniae* (including penicillin- and/or macrolide-resistant strains); *Haemophilus influenzae* and *Moraxella catarrhalis* (including β -lactamase-producing strains); *Staphylococcus aureus*, and *Streptococcus pyogenes*. In addition, atypical pathogens, such as *Mycoplasma pneumoniae*, and intracellular pathogens, such as *Legionella pneumophila* and *Chlamydia pneumoniae*, represent important causes of CAP that are often clinically refractory to β -lactam antibiotics. Atypical and intracellular pathogens are reported to be responsible for a substantial proportion of cases of ambulatory CAP in some settings [32].

There has been a significant increase in the prevalence of β -lactamase-producing as well as penicillin- and/or macrolide-resistant pathogens in recent years, limiting the clinical efficacy of many heretofore active oral antibiotics in the community setting for the treatment of CAP, AECB, and AS [36, 34]. Thus, the chosen therapy should be active against such antibiotic-resistant pathogens.

In contrast to macrolides, telithromycin binds tightly to 2 sites on the ribosome, domains II and V of the 23S rRNA on the 50S subunit. The affinity of telithromycin for the 50S ribosomal subunit is 10-fold higher than that of erythromycin A. As a result of its novel mechanism of action, telithromycin is active against bacteria that harbor a macrolide-lincosamide-streptogramin_B (MLS_B)-inducible type of resistance and does not induce MLS_B resistance in vitro. It is active against gram-positive cocci (*S. pneumoniae* and *S. pyogenes*) resistant to the macrolides (erythromycin A) via an efflux mechanism, is 2 to 4 times more active than clarithromycin, and 4 to 8 times more active than azithromycin against gram-positive cocci susceptible to erythromycin A. Unlike most macrolides, telithromycin also demonstrates concentration-dependent bactericidal activity against *S. pneumoniae*. Moreover, unlike the broad-spectrum penicillins and the newer fluoroquinolones, telithromycin has weak activity against enteric gram-negative anaerobes and gram-negative rods and, therefore, is less likely to select for enteric pathogens of concern [28, 33, 35].

Relative to macrolides such as azithromycin, it achieves high maximum plasma concentrations (mean C_{max} of approximately 2.27 μ g/mL) after repeated doses of 800 mg once daily. It has a relatively long half life (approximately 10 hours) and is distributed extensively in human tissue, permitting once daily dosing. Telithromycin achieves high concentrations in pulmonary epithelial lining fluid and in tonsillar tissue. Pulmonary epithelial lining fluid levels achieved by telithromycin are higher than the MIC₉₀ for *S. pneumoniae* (1 μ g/mL, 15 times higher), *H. influenzae* (4 μ g/mL, 4 times higher), and *M. catarrhalis* (0.25 μ g/mL, 60 times higher). Food has no significant effect on the rate or extent at which telithromycin is absorbed.

Telithromycin is eliminated by multiple pathways, both as unchanged drug and after metabolism by CYP450-dependant and CYP450-independent pathways. Studies have shown that the renal pathway is compensatory when metabolism is impaired. Therefore, there is limited risk for excessive drug exposure when one of the pathways is impaired either due to mild to moderate renal insufficiency, hepatic insufficiency due to liver disease, or drugs that inhibit the CYP3A4 pathway.

Telithromycin demonstrates excellent efficacy when administered once daily to subjects with CAP (7 to 10 day regimen), AECB (5 day regimen) and AS (5 day regimen). The potency of telithromycin translates to high rates of clinical cure in subjects with RTIs caused by *S. pneumoniae* (including penicillin- or macrolide-resistant strains); *H. influenzae* and *M. catarrhalis* (including β -lactamase-producing strains); *S. aureus*; as well as atypical (*M. pneumoniae*) and intracellular (*C. pneumoniae* and *L. pneumophila*) pathogens.

Of significance, telithromycin has demonstrated excellent clinical cure rates among subjects with CAP caused by macrolide-resistant (88%, 44/50) and/or penicillin G-resistant (88.9%, 24/27) strains of *S. pneumoniae*, as well as in pneumococcal bacteremia (90.2%, 74/82). Telithromycin was also highly active against *H. influenzae* (90%, 206/229) and *M. catarrhalis* (88%, 44/50) in CAP. In subjects with AECB or AS, treatment with telithromycin was also associated with excellent efficacy. In addition, it is highly effective in high-risk subjects such as the elderly or subjects with AECB and significant bronchial obstruction. In subjects with underlying conditions such as diabetes mellitus or cardiovascular disease, the cure rates are similar to those seen in the general population. Moreover, clinical cure rates with 5 days of telithromycin in AS and AECB are equivalent to those observed with 10 days for the comparators used in clinical trials. Short-course therapy has been shown to minimize the selection of antimicrobial-resistant pneumococci [44].

The adverse event profile of telithromycin, including events that were of concern with previously approved antibiotics, has been thoroughly examined in 16631 subjects in clinical studies along with 14117 subjects receiving comparator drugs. In addition, postmarketing surveillance safety data are available from approximately 1 million courses of therapy from countries where telithromycin has been launched. Overall, the adverse event profile of telithromycin is comparable to commonly prescribed antibiotics for RTIs, including β -lactams, macrolides, and fluoroquinolones.

The vast majority of treatment-emergent adverse events (TEAEs) associated with telithromycin are of mild to moderate intensity, and are related to the gastrointestinal tract, with diarrhea being the most common event. Discontinuation rates for adverse events associated with the gastrointestinal tract were low and were no different from those of comparators. Transient and self-limited blurred vision occurred in about 0.6% of subjects treated with telithromycin. It was mild or moderate in character, more common in female subjects, and resolved without sequelae within a few hours (median 1 hour). The etiology is most consistent with a slight delay of accommodation.

Electrocardiographic analysis in the clinical development program revealed a minimal, approximately 1.5 ms, increase in the QTc interval (QT corrected for heart rate by the Bazett formula). Telithromycin exhibited no meaningful increase in adverse clinical cardiovascular events, including malignant ventricular arrhythmias. Cardiac adverse events and death rates were comparable between telithromycin and active comparators.

The hepatic safety profile of telithromycin is comparable to widely prescribed antibiotics. In a large safety study performed in a usual care setting (Study 3014), there was no detectable difference between telithromycin and amoxicillin-clavulanic acid in the incidence of predefined hepatic safety endpoints as adjudicated by an independent and blinded clinical events committee. Hepatic adverse events were primarily mild to moderate asymptomatic transaminase elevations and were not associated with clinical sequelae. No cases of drug-related fulminant hepatitis, hepatic failure, or primary hepatic death were observed in either clinical trials or in the large post marketing experience of approximately 1 million exposure.

In conclusion, the benefits associated with the use of telithromycin in the treatment of subjects with CAP, AECB, or AS outweigh the risks. The results of the clinical development program for

telithromycin support its safe and effective use for the treatment of bacterial RTIs when administered once daily at a dose of 800 mg. A short treatment duration of 5 days is effective for the treatment of subjects with AEBC and AS (a feature that enhances compliance and reduces risk of selecting resistant pathogens). A 7- to 10-day treatment period is requested for the treatment of CAP.

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10. APPENDICES

- Appendix 1. Clinical pharmacology studies of telithromycin
- Appendix 2. Standardization of processes for Phase III studies
- Appendix 3. Key inclusion/exclusion criteria
- Appendix 4. Narratives for subjects with *S. pneumoniae* isolated from the blood at entry who failed therapy with telithromycin
- Appendix 5. Narratives for subjects with erythromycin and/or penicillin G-resistant *S. pneumoniae* isolated from the blood at entry who failed therapy with telithromycin
- Appendix 6. Phase II and III studies submitted to NDA 21-144
- Appendix 7. Deaths in Phase III studies
- Appendix 8. Deaths in Study 3014

Appendix 1. Clinical pharmacology studies of telithromycin

46 Clinical pharmacology studies of telithromycin, reports finalized

Study No.	Key feature of study
1001	Single-dose food interaction study in healthy men (50 to 800 mg telithromycin)
1002	Multiple-dose PK study in healthy men (100, 200, 400, 600 mg telithromycin qd 10 days)
1003	Single-dose food effect study in healthy men given 800 mg telithromycin
1004	Pilot PK study, single iv infusion and oral absolute bioavailability of telithromycin in healthy young and elderly
1005	Single- and multiple-dose (telithromycin 10 days) PK study in elderly men and women vs. healthy young men
1006	Bioavailability study of 2 oral tablet formulations of 800 mg telithromycin in healthy men
1007	Penetration in blister fluid after single dose, 600 mg telithromycin in healthy men
1008	Dose proportionality study after single/ multiple oral doses of 400, 800, 1600 mg telithromycin in healthy subjects
1009	PK and metabolism in healthy men after single oral administration of ¹⁴ C-HMR3647
1011	Effect of telithromycin on PK of theophylline in healthy men and women
1012	PK/PD interaction of telithromycin with racemic warfarin in healthy men
1013	Effects of telithromycin on PK of digoxin in healthy men
1014	Comparison of 800 mg oral telithromycin qd and 500 mg oral clarithromycin bid, on oropharyngeal and intestinal microflora in healthy men and women
1015	PK and safety in subjects with hepatic impairment given telithromycin
1016	PK and safety in subjects with renal impairment given telithromycin
1017	Bioequivalence of 400 mg telithromycin tablet formulation in healthy men
1020	Crossover study on effect of ranitidine (Zantac) and Maalox on PK in men
1022	PK interaction study of 800 mg telithromycin qd and 30 mg paroxetine qd in healthy men
1024	Tolerability and PK study in healthy men with multiple doses (300 mg bid, 800, 900, 1200 mg qd telithromycin for 10 days)
1028	Concentrations of telithromycin in tonsils after multiple 800 mg qd for 5 days in adult subjects undergoing tonsillectomy
1029	Respiratory tissue and plasma concentrations after multiple oral doses (800 mg telithromycin qd for 5 days) in healthy young men
1030	Safety, tolerability, PK of single and multiple doses (1600, 2000, 2400 mg telithromycin) in healthy men and sterilized young women; single and multiple doses (1200, 1600, 2000 mg) in elderly men and postmenopausal women
1031	3 way crossover study on 800 mg telithromycin po qd for 6 days vs. 500 mg of clarithromycin po bid for 6 days, on QT-interval duration at rest and at various heart rates during exercise in healthy young subjects
1032	4-way crossover study on single doses (800 - 1600 - 1400 mg telithromycin) on QT-interval duration at rest and at various heart rates during exercise in healthy young subjects
1037	Effect of itraconazole on PK of telithromycin in healthy men
1041	PK interaction study between telithromycin and cisapride in healthy subjects
1042	PK/PD interaction of telithromycin with low dose triphasic oral contraceptive (ethinyl estradiol/levonorgestrel) in healthy women
1043	Respiratory tissues and plasma concentrations of telithromycin after multiple oral doses (800 mg qd for 5 days) in subjects requiring fiber-optic bronchoscopy
1401	Placebo-controlled tolerance and PK study after rising single iv infusions (1000 mg, 2000 mg over 2 hours) of telithromycin in healthy young subjects
1044	Oral absolute bioavailability of telithromycin (400 mg tablet) after single administration in healthy young and elderly subjects
1045	4-way crossover on effect of concomitant multiple doses of ketoconazole and telithromycin on PK and ECG measures
1046	Safety, tolerability and PK of single oral doses (2400 and 3200 mg telithromycin) in healthy young men and women
1047	Concomitant administration of grapefruit juice on the single dose PK of telithromycin in healthy men
1048	PK interaction between telithromycin and simvastatin in healthy men
1049	Safety, tolerability and PK of single doses of telithromycin (800, 1600 mg qd) vs. clarithromycin (500 mg bid) in subjects with underlying cardiovascular diseases

Study No.	Key feature of study
1050	Effective permeability of telithromycin in the human jejunum
1054	PK of telithromycin in adolescents with bacterial RTIs after multiple doses of 800 mg telithromycin qd
1056	Crossover study after multiple doses (800 mg telithromycin qd) on PK of midazolam, after single iv infusion or single oral dose, in healthy men
1057	Single oral dose (800 mg of telithromycin) on sotalol-induced prolongation of ventricular repolarization after single oral dose (160 mg sotalol) in healthy women
1058 *	Crossover study on effect of multiple doses of rifampicin (600 mg qd) on single-dose and multiple-dose PK of telithromycin (800 mg qd) in healthy men
1059 *	Blurred vision induced by telithromycin at single supraclinical dose (2400 mg) vs. therapeutic single dose (800 mg) in younger and older healthy subjects
1060 *	PK and safety of telithromycin in subjects with hepatic impairment vs. healthy subjects after multiple oral administration of 800 mg qd for 7 days.
1061 *	Open study on oral doses of telithromycin (800 mg qd) and single oral dose of metoprolol (100 mg) in healthy volunteers.
1062 *	PK and safety of telithromycin in subjects with renal impairment after multiple doses of 400, 600, 800 mg qd for 5 days
1063 *	Effects of ketoconazole and renal impairment on PK of telithromycin after multiple doses of 800 mg qd for 5 days in subjects ≥ 60 years of age.
1064 *	Blurred vision induced by telithromycin at single supraclinical dose (2400 mg) vs. therapeutic single dose (800 mg) in healthy subjects

* Study submitted to the FDA in Amendment 2 of July 2002.

2 Additional studies: Data finalized, report not completed

Study No.	Study title
1065	Crossover study on effect of dosing interval on the PK interaction of telithromycin on simvastatin in healthy men
1067	Crossover study on effect of dosing interval on the PK interaction of clarithromycin on simvastatin in healthy men

Appendix 2. Standardization of processes for Phase III studies

STANDARDIZATION OF PROCESSES FOR PHASE III STUDIES

A. Clinical evaluation

Time windows for assessment of outcome (Western studies)

There were 5 visits in each study: pretherapy/entry, on-therapy, end-of-therapy, post-therapy/TOC and late post-therapy. Efficacy was analyzed at the post-therapy/TOC and late post-therapy visits. Similar time windows were used for these visits in the studies for the 4 indications. They were established following the recommendations of the FDA Draft Guideline - Evaluating Clinical Studies of Antimicrobials in the Division of Anti-infective Drug Products (February 1997), the FDA Draft Guideline - Developing Antimicrobial Drugs - General Considerations for Clinical Trials, July 1998, and taking into account the pharmacokinetic profiles of the study medication used in the studies.

A time window of Days 17 to 24 was used for the assessment of efficacy at TOC. A time window of Days 31 to 45 was used for the efficacy analyses at late post-therapy. This extended window was used to accommodate the more erratic visit timing at late post-therapy compared to post-therapy/TOC, and to ensure that relapses occurring later would be included in the per protocol analysis performed at late post-therapy.

In the studies comparing a 5-day and 10-day treatment period (3003, 3007, 3013 in AECB, 3002, 3005, 3011 in acute sinusitis, 4003 in pneumonia), the TOC assessment was performed at the same point after the start of study medication in both groups. Therefore, the interval between the end of therapy and the post-therapy/TOC and late post-therapy visits was up to 5 days longer for the telithromycin 5-day regimen vs. comparator, and early relapses in subjects receiving a short duration of active treatment were thus counted as failure at post-therapy/TOC.

Time windows for assessment of outcome (Japanese Study 2105)

The time windows used to assess outcome in Study 2105 differed from the Western studies in that the main end point was performed at the end of treatment (Day 7) to comply with Japanese guidelines for evaluating the efficacy of anti-infectives. However, a second end point was evaluated 7 days after the end of treatment, corresponding to a time window of 14 to 21 days after commencing treatment. This second end point was close to the time window used for test of cure evaluation in Western studies (Days 17 to 24).

Study variables

Infection-related signs and symptoms

The investigator assessed the presence or absence of infection-related signs and symptoms specific for each indication, as detailed below. A severity scale was established to allow for more consistent

follow-up throughout the study (intensity of signs and symptoms were to be rated [mild, moderate, or severe] or documented as a value).

Categorization of clinical outcome

The clinical outcome was assessed by the investigator based on the evolution of clinical signs and symptoms and X-ray findings. The investigator was asked to classify the outcome as cure, failure, or indeterminate. In addition, of the subjects classified as cures, the investigator was asked to distinguish between subjects who had returned to their preinfection state (classified as “cure/returned to preinfection state”), and subjects whose residual symptoms represented a normal course of clearance of the inflammatory process (classified as “cure/improved or postinfectious stigmata”). On the contrary, subjects with residual symptoms requiring subsequent treatment with other antibiotics were classified as “failure.”

Discontinuation of subjects with a resistant causative pathogen isolated at pretherapy/entry was not mandatory; these subjects were discontinued at the discretion of the investigators depending on clinical status or evaluation. Susceptibility of causative pathogens at the investigator’s site was based on inhibition zone values obtained by the disk diffusion method at local laboratories during the study. In controlled studies, discontinuation could result from isolation of a pathogen resistant to either telithromycin or the comparator drug.

Treatment was also considered a failure if subjects discontinued study medication due to an adverse event and the investigator decided that the anti-infective treatment should be continued with a subsequent antibiotic. However, subjects who discontinued study medication with no need for a subsequent antibiotic because their disease was sufficiently improved were not counted as failures.

B. Bacteriological evaluation

Isolation of causative pathogens

A sample for bacteriological diagnosis was taken before the treatment where possible in all studies.

In CAP and AECB studies, sputum cultures and blood cultures (except Study 2105) were performed where possible. Respiratory secretion smears were analyzed by direct microscopy and Gram stain. Gram-stained smears were to be examined for the presence of bacteria, squamous epithelial cells, and polymorphonuclear cells.

In the acute sinusitis studies, sinus puncture cultures were performed on all subjects in Study 3002 at pretherapy/entry, for subjects at selected centers in Study 3005, and for subjects at US sites in Study 3011. In Studies 3002 and 3011, a quantitative culture of the sinus aspiration samples was performed when possible for *Staphylococcus aureus*. This pathogen was considered causative only if the bacterial count was $\geq 10^4$ colony forming units per milliliter (cfu/mL) or classified as “+++” using semiquantitative methods.

Susceptibility testing

Susceptibility to telithromycin was tested by disk diffusion (15 µg disk) at the investigator's local laboratory for the primary cultures (for the tonsillitis Study 3004, all the primary cultures were sent to a single laboratory). Subcultures of primary isolates were then sent to a central laboratory (US studies: Clinical Microbiology Institute, Inc. [CMI], Wilsonville, Oregon, US; EU studies: GR Micro Ltd, London, UK) for identification and simultaneous testing of the disk zone inhibition and MIC using National Committee for Clinical Laboratory Standards (NCCLS) methodology against telithromycin, the comparator, and selected other antibiotics. A cross-validation study between the 2 laboratories showed that comparable results were obtained. For the Japanese Study 2105, isolates were tested according to NCCLS procedures at a central laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories Inc., Tokyo, Japan); *S. pneumoniae* isolates were subsequently retested for susceptibility to telithromycin, penicillin G and erythromycin A at CMI. Only the CMI data are presented in this briefing document.

Local microbiology data were used for the identification of the bacteriological per protocol population (PPb) and the analysis of bacteriological outcome. Central laboratory data on concordant isolates were used to assess the correlation between clinical outcome and MIC, bacteriological outcome and MIC, disk zone inhibition and MIC, and to define penicillin-resistant and erythromycin-resistant pathogens and the bacteriological outcome in these subjects.

Genotyping

Genotyping of strains of *S. pneumoniae* and *S. pyogenes* resistant to erythromycin was performed. The occurrence of *erm(A)*-, *erm(B)*-, *erm(TR)*- and *mef(E)*-related sequences was studied in *S. pneumoniae* and *S. pyogenes* that were causative of infection at entry. The genotype of these clinical isolates was determined using a polymerase chain reaction (PCR) method.

Categorization of bacteriological outcome

Bacteriological response by causative pathogen was categorized at post-therapy/TOC, as defined below:

- Eradication: the causative pathogen was absent.
- Presumed eradication (except in tonsillitis/pharyngitis): the subject had improved clinically to such an extent that a proper follow-up culture could not be obtained.
- Persistence: the causative pathogen was still present whether or not signs of infection were still present.
- Presumed persistence: a subsequent antimicrobial was started before a post-therapy/TOC culture was obtained.
- Recurrence: reappearance of the causative pretherapy/entry pathogen after eradication from the original site of infection.

When new pathogens were isolated, culture results were classified as follows:

- Colonization (eradication with colonization): a new pathogen emerged between the first day of study drug administration and the post-therapy/TOC visit in a subject free of new symptoms.
- Superinfection: a new pathogen emerged during therapy (from the second day of treatment) or within 3 days after treatment had been completed, either at the site of infection or at a distant site with the emergence or worsening of associated clinical or laboratory evidence of infection, and a new systemic anti-infective treatment was prescribed.
- Eradication and reinfection (designated “reinfection” in the clinical study reports): elimination of the initial infecting organism followed by replacement with a new species or with a new serotype or biotype of the same organism at the same site in the presence of signs and symptoms of infection after completion of therapy.

Bacteriological response by subject was assessed at post-therapy/TOC as satisfactory (eradication, eradication with colonization, presumed eradication) or unsatisfactory (all other categories) based on the by-pathogen bacteriological response at post-therapy/TOC and the presence of new pathogens.

Diagnosis and evaluation of outcome due to atypical and intracellular organisms

The diagnosis of atypical infection is mainly indirect (based on serology data) given the poor sensitivity of current culture methods. Subjects who had positive diagnoses of atypical infection (by serology or positive PCR) and had no bacteria isolated were not considered to be bacteriologically evaluable (i.e., were not included in the PPb population), even if the indirect diagnosis of infection by atypical pathogen represented evidence of a bacterial etiology of the disease in these subjects. Instead, the clinical outcome of the subjects was analyzed separately and presented as a subgroup analysis.

The following methods were used to detect the presence of:

- *Chlamydia pneumoniae* - Culture of nasopharyngeal swabs (in selected centers of Studies 3006 and 3009); acute (pretherapy/entry visit) and convalescent (post-therapy/TOC or late post-therapy visit) serology by a microimmunofluorescence method; sputum samples tested by PCR.
- *Mycoplasma pneumoniae* - Acute and convalescent serology by an enzyme-linked immunosorbent assay (ELISA) method; sputum samples tested by PCR.
- *Legionella pneumophila* - Serology using indirect fluorescence antibody testing after a screening ELISA (US studies) or microagglutination (EU studies); urine samples tested for the presence of serogroup I urinary antigen using an ELISA technique.

Diagnostic criteria were established (based on results obtained before the database was unblinded) after interaction with the FDA to increase the specificity of the diagnoses. These more restrictive definitions of atypical infection considered subjects to have a positive diagnosis if there was a negative aerobic culture for any “typical” pathogen and the following criteria were met:

- *Chlamydia pneumoniae* - Positive culture when available, 4-fold increase in microimmunofluorescence IgG (polyclonal) titers of paired samples, or a single IgM titer $\geq 1:32$ by microimmunofluorescence in combination with a positive PCR for *C. pneumoniae*.

- *Mycoplasma pneumoniae* - Positive culture when available, fourfold increase in serum IgG in paired samples, or a single IgM titer $\geq 1:16$ by microimmunofluorescence in combination with a positive PCR for *M. pneumoniae*.
- *Legionella pneumophila* - Positive culture when available, 4-fold increase in paired serum of IgG or IgM titers, or a positive urine antigen for *L. pneumophila* serogroup I.

Appendix 3. Key inclusion/exclusion criteria

Key inclusion diagnostic criteria

Indication [a]	Protocols	Criteria
CAP	HMR3647A/3006 HMR3647A/3009 HMR3647A/3001 HMR3647A/3000 HMR3647A/3009OL HMR3647A/3010 HMR3647A/3012 HMR3647A/4003	<ul style="list-style-type: none"> • Clinical diagnosis of CAP in protocols HMR3647A/3006, HMR3647A/3009, and HMR3647A/3000 based on at least 2 of the following clinical signs/symptoms including: <ul style="list-style-type: none"> [1] new onset of cough; [2] production of purulent sputum or change in sputum character; [3] auscultatory findings such as rales and/or evidence of pulmonary consolidation; [4] dyspnea or tachypnea; [5] fever (oral temperature >38°C); [6] elevated total peripheral white blood cell (WBC) count >10,000/mm³ or >15% immature neutrophils; and [7] a positive Gram stain on an adequate sputum sample (optional in HMR3647A/3006 and HMR3647A/3009). <p>At least 3 clinical signs/symptoms of CAP were required in protocol HMR3647A/3001 including at least 2 from 1-4 listed above and at least 1 from 5-7 listed above. In Study 3009 OL, consolidation on chest X-ray was required. In Study 3010, at least 1 criterion from 5-7 above was required.</p> <ul style="list-style-type: none"> • Chest X-ray with presence of presumably new infiltrates supporting a diagnosis of bacterial pneumonia. [b] • Specimens (respiratory and blood) collected for bacteriological assessments within 48 hours prior to enrollment whenever possible.
AECEB	HMR3647A/3007 HMR3647A/3003 HMR3647A/3013	<ul style="list-style-type: none"> • Documented history of chronic bronchitis characterized by cough and excessive sputum production for more than 2 consecutive years with symptoms most days in a consecutive 3-month period. • FEV₁/FVC<70% based on lung function tests within the previous 12 months (HMR3647A/3003 only). • Clinical diagnosis of AECEB based on at least 2 (HMR3647A/3007) or 3 (HMR3647A/3003, HMR3647A/3013) of the following clinical signs/symptoms including increased cough or dyspnea, increased sputum volume, and increased sputum purulence. • Chest X-ray negative for acute pulmonary infiltrates within 2 days prior to initiation of study treatment. • Specimens collected for bacteriological assessments at inclusion.

Key inclusion diagnostic criteria

Indication [a]	Protocols	Criteria
Sinusitis	HMR3647A/3005 HMR3647A/3002 HMR3647A/3011	<ul style="list-style-type: none"> • Clinical diagnosis of acute maxillary sinusitis based on at least 1 of the following clinical signs/symptoms (<28 days in duration) including purulent nasal discharge (postnasal or visualized in the middle meatus); maxillary tenderness; maxillary pain at percussion; maxillary toothache; facial pain, pressure, or tightness; or nasal congestion with poor response to nasal decongestants. • Abnormal maxillary sinus X-ray performed within 48 hours prior to initiation of study treatment indicating the presence of air fluid level, mucosal thickening ≥ 6 mm (HMR3647A/3005 only) or ≥ 10 mm (HMR3647A/3011 only), and/or total sinus opacity.[b,c] • Sinus puncture for bacteriological documentation performed at inclusion (required for all subjects in HMR3647A/3002 and for selected centers in HMR3647A/3005). In Study 3011, sinus puncture was performed at all US sites, sinus endoscopy was performed at all non-US sites.

^a CAP = community-acquired pneumonia, AECEB = acute exacerbation of chronic bronchitis.
^b Diagnosis confirmed by a board certified radiologist in U.S. studies (CAP protocols HMR3647A/3006 and HMR3647A/3009, and sinusitis protocol HMR3647A/3005).
^c Sinus X-ray performed as follows: occipitomenal, occipitofrontal, and lateral views obtained in HMR3647A/3005; occipitomenal view obtained in HMR3647A/3002.

Selected CAP exclusion criteria

Subjects who had CAP requiring either intensive care unit admission, parenteral antibiotic treatment or who had at least 1 of the following conditions were excluded from CAP studies:

- Respiratory frequency >30 breaths/minute
- Chest radiograph showing bilateral or multiple lobe involvement, or an increase in the size of the opacity by $\geq 50\%$ within 48 hours of the evaluation
- Shock (systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg)
- Altered mental status (disorientation to person, place or time that was not known to be chronic, lethargy, stupor, or coma)
- <90% O₂ saturation (by pulse oximetry) or PaO₂ <60 mm Hg
- Total peripheral white blood cell count <4,000/mm³
- Required mechanical ventilation
- Required vasopressors for more than 4 hours
- Urine output lower than 20 mL/h or total urine output lower than 80 mL in 4 hours, unless another explanation was available, or acute renal failure that required dialysis

Appendix 4. Narratives for subjects with *S. pneumoniae* isolated from the blood at entry who failed therapy with telithromycin

Subject 3000/701/1450 (age 61, Fine score II, with consolidation on the pretherapy/entry chest X-ray) presented with *S. pneumoniae* susceptible to telithromycin (MIC of 0.015 µg/mL), and susceptible to penicillin G and to erythromycin A, isolated in blood, and 2 other causative pathogens isolated from respiratory specimens, *K. pneumoniae* and *E. coli* resistant to telithromycin. No subsequent blood cultures were performed. This subject received an intravenous antibiotic treatment (cefotaxime sodium and gentamycin sulfate) because of unchanged status at Day 4. The subsequent antibiotic therapy was successful.

Subject 3000/605/1091 (age 78, Fine score III, with consolidation on the pretherapy/entry chest X-ray) presented with *S. pneumoniae* resistant to penicillin G (MIC of 2 µg/mL) and erythromycin A (MIC of 32 µg/mL, genotype of resistance *erm*[B]), but susceptible to telithromycin (MIC of 0.03 µg/mL), isolated in blood, associated with 2 other causative pathogens isolated from respiratory specimens, *H. influenzae* (MIC of 1 µg/mL) and *M. catarrhalis* (MIC was not performed, pathogen was susceptible by disk diffusion). After initial improvement, this subject was administered intravenous antibiotics for a recurrence of symptoms (dyspnea and fever) associated with a diagnosis by the investigator of urinary infection due to *S. aureus*. The subject's clinical status at TOC was improved and the blood culture was negative but the *S. pneumoniae* was considered to be presumed persistent because of the additional antibiotics required to treat *S. aureus* in the urine.

Subject 3000/1201/1245 (age 43, Fine score I, with consolidation on the pretherapy/entry chest X-ray) presented with *S. pneumoniae* susceptible to telithromycin (MIC of 0.015 µg/mL) and to penicillin G and erythromycin A, isolated in blood and respiratory specimen. After improvement this subject had a recurrence of fever associated with a pleural effusion and was categorized clinical failure.

Subject 3009OL/0369/105 (age 37, Fine score II, with bilateral pneumonia and consolidation in 1 lobe on the pretherapy/entry chest X-ray) presented with *S. pneumoniae* resistant to penicillin G (MIC of 2 µg/mL) and erythromycin A (MIC of 4 µg/mL, genotype of resistance *mef*[E]), but susceptible to telithromycin (MIC of 0.12 µg/mL), isolated in blood and respiratory specimens. The HIV status of this South African subject is unknown (the prevalence of HIV infection is approximately 30% in this population). The subject received telithromycin for 4 days and was then treated with intravenous antibiotics of penicillin G (1.2 million units every 6 hours) and cefoxitin (1 gram every 8 hours) because her clinical status was described as unchanged by the investigator. A blood culture was performed on Day 4, before the change in antibiotics, that showed a *S. pneumoniae* susceptible to telithromycin (MIC of 0.5 µg/mL). The clinical outcome after the subsequent antimicrobial treatment was cure.

Subject 3012/3011/004 was a 37-year-old black male enrolled with moderate CAP. Relevant medical history included current smoking status. At pretherapy/entry, *S. pneumoniae* was isolated from both sputum and blood. The *S. pneumoniae* urinary antigen test was positive at pretherapy/entry. Chest X-ray showed right single lobe alveolar picture and consolidation. At the on-therapy and end-of-therapy visits, it was impossible to obtain sputum specimens for culture and no organism was isolated from repeat blood cultures. On Day 12 at the end-of-therapy/early withdrawal visit, the subject had signs and symptoms of mild rhonchi and mild tachypnea. Chest X-ray showed right single lobe alveolar picture and consolidation, which was assessed an improvement compared to pretherapy/entry. This subject was classified as a clinical failure at the end of therapy visit even though both clinical and chest X-ray findings had improved. In spite of evidence that the *S. pneumoniae* was eradicated from blood based on negative blood cultures from 2 consecutive visits, the subject was assigned a bacteriological outcome of presumed persistence because a subsequent antibiotic was initiated at the end-of-therapy visit.

Subject 3012/4002/006 was a 30-year-old multiracial male enrolled with moderate CAP. Relevant medical history included current smoking status. At pretherapy/entry, *H. influenzae* was isolated from sputum and *S. pneumoniae* was isolated from blood. The *S. pneumoniae* urinary antigen test was negative at pretherapy/entry. The Ziehl-Neelsen stain was negative for mycobacteria. Chest X-ray showed right single lobe alveolar picture and consolidation. At the on-therapy visit, no organism was isolated from sputum and blood cultures were not repeated. On Day 8 at the end-of-therapy visit, no sputum culture was performed due to the absence of sputum production and blood cultures were negative for *S. pneumoniae*. The investigator's overall assessment was that of improved. On Day 17 at the post-therapy/TOC visit, all clinical signs and symptoms were absent with the exception of mild tachypnea and as a result an adequate sputum specimen was not obtained. In addition, blood samples for culture were not collected. Chest X-ray showed right single lobe alveolar picture and consolidation, which was assessed as worsened compared to pretherapy/entry. Clinical outcome was failure and bacteriological outcome was presumed eradication for both *H. influenzae* and *S. pneumoniae* (blood and sputum). No subsequent antimicrobial treatment was reported.

Subject 3012/4004/052 was a 35-year-old black male enrolled with moderate CAP. Relevant medical history included past history of smoking. At pretherapy/entry, no organism was isolated from sputum and *S. pneumoniae* was isolated from blood. The *S. pneumoniae* urinary antigen test was positive at pretherapy/entry. The Ziehl-Neelsen stain was negative for mycobacteria. Chest X-ray showed bilateral multiple lobe consolidation with right multiple lobe cavitory process. At the end-of-therapy visit, blood cultures were negative for *S. pneumoniae*. On Day 18 at the post-therapy/TOC visit, the chest X-ray showed bilateral multiple lobe alveolar picture and infiltrates with right single lobe cavitory process, which was assessed as worsened compared to pretherapy/entry. Sputum production was absent at this visit and, as a result, an inadequate sputum culture was collected. In addition, blood cultures obtained at this visit were negative for *S. pneumoniae*. Clinical outcome was failure and bacteriological outcome was eradication for *S. pneumoniae* in blood. No subsequent antimicrobial treatment was reported and the subject was not referred for possible follow-up of tuberculosis.

Subject 3012/4004/083 was a 34-year-old black male enrolled with mild CAP. Relevant medical history included current smoking status. At pretherapy/entry, *S. pneumoniae* (PISP) was isolated from both sputum and blood. The *S. pneumoniae* urinary antigen test was positive at pretherapy/entry. Chest X-ray showed right single lobe alveolar picture and consolidation. At the on-therapy and end-of-therapy visits it was impossible to obtain sputum specimens for culture and no organism was isolated from repeat blood cultures. At the post-therapy/TOC visit, all clinical signs and symptoms were absent with the exception of mild cough and rales. As a result, an inadequate sputum culture was collected. In addition, blood cultures obtained at this visit were negative for *S. pneumoniae*. Chest X-ray showed right single lobe consolidation and atelectasis with right single lobe cavitory process, which was assessed as worsened compared to pretherapy/entry. Clinical outcome was failure and bacteriological outcome was presumed eradication for *S. pneumoniae* in sputum and eradication for *S. pneumoniae* in blood. No subsequent antimicrobial treatment was reported. However, the subject was referred to a tuberculosis (TB) clinic for assessment of a new right single lobe cavitory process that was evident on the post-therapy/TOC chest X-ray.

**Appendix 5. Narratives for subjects with erythromycin and/or penicillin G-resistant
S. pneumoniae isolated from the blood at entry who failed therapy with telithromycin**

Subject 3000/605/1091 (also described in Appendix 4) (age 78, Fine score III, with consolidation on the pretherapy/entry chest X-ray) presented with *S. pneumoniae* resistant to penicillin G (MIC of 2 µg/mL) and erythromycin A (MIC of 32 µg/mL, genotype of resistance *erm*[B]), but susceptible to telithromycin (MIC of 0.03 µg/mL), isolated in blood, associated with 2 other causative pathogens isolated from respiratory specimens, *H. influenzae* (MIC of 1 µg/mL) and *M. catarrhalis* (MIC was not performed, pathogen was susceptible by disk diffusion). After initial improvement, this subject was administered intravenous antibiotics for a recurrence of symptoms (dyspnea and fever) associated with a diagnosis by the investigator of urinary infection due to *S. aureus*. The subject's clinical status at TOC was improved and the blood culture was negative but the *S. pneumoniae* was considered to be presumed persistent because of the additional antibiotics required to treat *S. aureus* in the urine.

Subject 3009OL/0369/105 (also described in Appendix 4) (age 37, Fine score II, with bilateral pneumonia and consolidation in 1 lobe on the pretherapy/entry chest X-ray) presented with *S. pneumoniae* resistant to penicillin G (MIC of 2 µg/mL) and erythromycin A (MIC of 4 µg/mL, genotype of resistance *mef*[E]), but susceptible to telithromycin (MIC of 0.12 µg/mL), isolated in blood and respiratory specimens. The HIV status of this South African subject is unknown (the prevalence of HIV infection is approximately 30% in this population). The subject received telithromycin for 4 days and was then treated with intravenous antibiotics of penicillin G (1.2 million units every 6 hours) and cefoxitin (1 gram every 8 hours) because her clinical status was described as unchanged by the investigator. A blood culture was performed on Day 4, before the change in antibiotics, that showed a *S. pneumoniae* susceptible to telithromycin (MIC of 0.5 µg/mL). The clinical outcome after the subsequent antimicrobial treatment was cure.

Appendix 6. Phase II and III studies submitted to NDA 21-144

Phase II and III studies submitted to NDA 21-144

Study included in:		Indication/Study No.	Study Design	Treatment Regimen		
Efficacy	Safety					
Community-acquired pneumonia						
X	X	3000	Open label	7 to 10 d	TEL	800 mg qd
X	X	3001	Double-blind	10 d	TEL	800 mg qd
				10 d	AMX	1000 mg tid
X	X	3006	Double-blind	10 d	TEL	800 mg qd
				10 d	CLA	500 mg bid
X	X	3009	Double-blind	7 to 10 d	TEL	800 mg qd
				7 to 10 d	TVA	200 mg qd
X	X	3009OL	Open label	7 to 10 d	TEL	800 mg qd
X	X	3010	Open label	7 d	TEL	800 mg qd
X	X	3012	Open label	7 d	TEL	800 mg qd
X	X	4003	Double-blind	5 d	TEL	800 mg qd
				7 d	TEL	800 mg qd
				10 d	CLA	500 mg bid
X		2105 (Japan)	Double-blind	7 d	TEL	600 mg qd
				7 d	TEL	800 mg qd
X		3107 (Japan)	Double-blind	7 d	TEL	600 mg qd
				7 d	LVF	100 mg tid
Acute exacerbation of chronic bronchitis						
X	X	3003	Double-blind	5 d	TEL	800 mg qd
				10 d	AMC	500 mg/125 mg tid
X	X	3007	Double-blind	5 d	TEL	800 mg qd
				10 d	CXM	500 mg bid
X	X	3013	Double-blind	5 d	TEL	800 mg qd
				10 d	CLA	500 mg bid
Acute sinusitis						
X	X	3002	Double-blind	5 d	TEL	800 mg qd
				10 d	TEL	800 mg qd
X	X	3005	Double-blind	5 d	TEL	800 mg qd
				10 d	TEL	800 mg qd
				10 d	AMC	500 mg/125 mg tid
X	X	3011	Double-blind	5 d	TEL	800 mg qd
				10 d	CXM	250 mg bid
Large Safety Trial						
X	X	3014	Open-label	5 d in AS	TEL	800 mg qd ^a
				7 to 10 d in CAP/AECB	TEL	800 mg qd ^a
				7 to 10 d in all indications	AMC	875 mg/125 mg tid ^b
Tonsillitis/Pharyngitis						
	X	3004	Double-blind	5 d	TEL	800 mg qd
				10 d	PEN	500 mg tid
	X	3008	Double-blind	5 d	TEL	800 mg qd
				10 d	CLA	250 mg bid

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

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

^b In subjects with known severe renal impairment, the dose was reduced to 500 mg amoxicillin (500/125 mg tablet) bid if creatinine clearance was between 10 and 30 mL/min, and to 500 mg qd if creatinine clearance was <10 mL/min.

Appendix 7. Deaths in Phase III studies

Deaths in integrated Phase III studies

Subject Number	Age/ Sex	Study drug	Event as reported by Investigator	Day of event	Last day of study treatment	Medical History
Controlled Studies						
3001/1002/027	71/F	TEL	Multiorgan failure	4	4	COPD, CAD, dorsal scoliosis
3001/1301/004	80/M	TEL	Cardiac insufficiency	10	10	CAD, atrial fibrillation, cerebrovascular disease, diabetes, liver disease
3001/0111/004	52/M	TEL	Bronchospasm	34	8	Asthma
3006/0386/018	43/F	CLA	Pneumonia	30	?10	Diabetes
3006/0060/002	70/F	CLA	malignant bronchial neoplasm	>150	?10	schizophrenia, hypothyroidism, seizures, COPD, tobacco use, and small bowel resection
3004/1306/008	55/F	PEN	acute lymphoid leukemia	48	4	mild hearing loss, splenectomy, elevated leukocytes pretherapy
3013/1203/004	79/F	TEL	Probable MI following severe acute precordial chest pain	127	?5	COPD and tobacco use
3013/1403/004	81/F	TEL	Probable MI	127	?5	cigarette smoking and chronic airway obstruction
3013/0101/022	90/F	CLA	Probable neoplasm	48	?10	neoplasm of an unspecified origin
3013/0601/003	79/F	CLA	severe exacerbation of chronic obstructive pulmonary disease and cardiac dysrhythmia	54	10	cigarette smoking, neoplasm, coronary atherosclerosis, congestive heart failure, and chronic airway disease
3013/1403/003	88/F	CLA	Cardiopulmonary arrest	82	10	cigarette smoking, chronic airway obstruction, and other pulmonary insufficiency
4003/3657/025	41/M	TEL	Septicemia	3	3	alcohol dependency and hemoptysis
4003/3410/004	78/F	TEL	Cardiac arrest	3	3	heart failure treated with furosemide and unspecified ventricular arrhythmia treated with amiodarone, renal insufficiency (estimated creatinine clearance = 29 mL/min) and a chest X-ray showing cardiac enlargement
4003/3652/003	30/M	TEL	Suspected acute meningitis	8	5	None
4003/3402/007	83/F	CLA	MI	13	10	Angina pectoris
4003/3128/002	57/M	CLA	Lung cancer	39	?10	Prostate cancer
Uncontrolled Studies						
3000/0703/1466	57/M	TEL	Sepsis and adult respiratory distress syndrome	?	3	None

Subject Number	Age/ Sex	Study drug	Event as reported by Investigator	Day of event	Last day of study treatment	Medical History
3000/0803/1520	65/M	TEL	Gram negative septicemia	9	31	CAD, diabetes, COPD, chronic osteomyelitis and stroke
3009OL/0369/108	37/F	TEL	respiratory failure, cardiomyopathy, liver failure, and immunosuppression	12	7	HIV positive
3010/0473/009	77/M	TEL	acute aspiration/foreign body in larynx	5	5	Mild renal insufficiency; CHF
3010/0537/009	44/M	TEL	acute myocardial infarction	2	2	new myocardial infarction pretherapy, sinus tachycardia at 130 bpm
3012/2004/004	84/F	TEL	Respiratory arrest	1	1	Hypertension
3012/4002/022	70/F	TEL	Heart failure	3	3	COPD, heart failure, cor pulmonale
3012/4003/013	46/M	TEL	Pneumonia?	7	8	HIV infection
3012/4003/040	56/M	TEL	Pneumonia	12	7	Chronic obstructive airways disease, pneumoconiosis (1987), unspecified visual and hearing loss
3012/4003/022	43/M	TEL	Pneumonia?	17	7	AIDS-related complex immunocompromized status and tobacco use

TEL = telithromycin, AMC = amoxicillin-clavulanic acid
Sex: M = male, F = female

Narratives: Deaths in Controlled Phase III Studies

Study 3001

Telithromycin 10-day for CAP

3001/1002/027

Subject 3001/1002/027 was a 71-year-old white female with history of COPD, coronary artery disease (CAD) and dorsal scoliosis, who was admitted to a frail nursing care unit at study entry. Pretherapy chest X-ray showed single lobe consolidation on the right side. Sputum cultures were positive for *S. pneumoniae*, β -lactamase-producing *H. influenzae*, and *S. aureus* (subsequently identified resistant to telithromycin). The following day, the subject's clinical condition worsened (severe lobar pneumonia, with associated hypotension, cyanosis, and altered mental state). Antimicrobial therapy with iv gentamycin and Rocephin (ceftriaxone) was started. Severe multiorgan (circulatory, kidney, and respiratory) failure developed and was the primary cause of death on Day 4.

3001/1301/004

Subject 3001/1301/004 was an 80-year-old white male with history of CAD, atrial fibrillation, cerebrovascular disease, diabetes mellitus and unspecified liver disease. On Day 10 the subject

developed dyspnea and hypotension (BP: 100/70 mm Hg). Intensive medical care was given, but the subject died that day with the primary cause of death as cardiac insufficiency.

Amoxicillin for CAP

3001/0111/004

Subject 3001/0111/004 was a 52-year-old white male with a longstanding history of asthma. Study medication was discontinued on Day 8 due to low creatinine clearance at study entry (exclusion criteria). Subsequent amoxicillin therapy was started on 3 August 1998 to treat the pneumonia. On Day 34, the subject experienced severe bronchospasm and died while being transported to the hospital. No autopsy was performed.

Study 3006

Clarithromycin for CAP

3006/0386/018

Subject 3006/0386/018 was a 43-year-old white female with a history of diabetes. Pretherapy sputum culture revealed normal flora. Three days after completing study medication, the subject developed worsening pneumonia. Therapy with ceftriaxone was started. On Day 21, the subject was hospitalized for worsening pneumonia with associated dyspnea, tachypnea, increased sputum production, chest pain, nausea, and mild pleural effusion. Antimicrobial therapy with clindamycin, cefotaxime, ceftazidime, and amikacin was started to treat the pneumonia. The subject died on Day 30, with the primary cause of death as pneumonia (organism not identified).

3006/0060/002

Subject 3006/0060/002 was a 70-year-old white female with a medical history of schizophrenia, hypothyroidism, seizures, COPD, 2 ½ pack-per-day tobacco use, and small bowel resection. The subject died 5 months post-treatment of malignant bronchial neoplasm.

Study 3004

Penicillin VK for tonsillitis/pharyngitis

3004/1306/008

Subject 3004/1306/008 was a 55-year-old white female with a history of mild hearing loss and splenectomy and elevated leukocytes ($215 \times 10^9/L$) pretherapy. On Day 2, the subject had fever and weakness. The subject was diagnosed with severe acute lymphoid leukemia, treatment was changed to amoxicillin (Day 4), the subject was withdrawn from the study (Day 5) and transferred to another hospital. She died 44 days after the last dose of study medication of acute lymphoid leukemia.

Study 3013

Telithromycin 5-day for AECB

3013/1203/004

Subject 3013/1203/004 was a 79-year-old white female with a history of COPD and tobacco use. On Day 127 (post-treatment) she died following severe acute precordial chest pain that had started that day. No autopsy was performed, but the investigator considered myocardial infarction the most likely cause of death.

3013/1403/004

Subject 3013/1403/004 was a 81-year-old white female who experienced a severe acute myocardial infarction on Day 127 (post-treatment) that resulted in death on the same day. Although an autopsy was not performed, the investigator considered the myocardial infarction as the most likely cause of death. The subject's medical history included cigarette smoking and chronic airway obstruction.

Clarithromycin for AECB

3013/0101/022

Subject 3013/0101/022 was a 90-year-old white female who died on Day 48 (post-treatment) with the cause tentatively diagnosed as a neoplasm. An autopsy was not performed. Two weeks prior to the subject's death, all medications were stopped due to swallowing problems. The subject had been cachectic with a deteriorating overall condition. The subject's medical history included neoplasm of an unspecified origin.

3013/0601/003

Subject 3013/0601/003 was a 79-year-old white female who died on Day 54 (post-treatment) due to a severe exacerbation of chronic obstructive pulmonary disease and cardiac dysrhythmia with onset on the day of death. Study medication had been completed on Day 10. The subject's medical history included cigarette smoking, neoplasm, coronary atherosclerosis, congestive heart failure, and chronic airway disease.

3013/1403/003

Subject 3013/1403/003 was an 88-year-old white female who experienced cardiopulmonary arrest on Day 82 (post-treatment) that resulted in death on the same day. Study medication was completed on Day 10. An autopsy was not performed. The subject's medical history included cigarette smoking, chronic airway obstruction, and other pulmonary insufficiency. The subject had been taking multiple concomitant medications including diltiazem, pantoprazole, Duo-CVP[®], ipratropium/albuterol, prednisone, Ravotril[®], Aerogastrol[®], and Hidrium[®]. The cardiopulmonary arrest was assessed by the investigator as not related to study medication.

Study 4003

Telithromycin 5-day

4003/3657/025

Subject 4003/3657/025 was a 41-year-old male, with a history of alcohol dependency and hemoptysis, who experienced gram negative septicemia due to *Klebsiella spp* and subsequently died. On Day 1, prior to study entry, the subject presented to the hospital with worsening respiratory signs, tachypnea, crepitations, and delirium. The subject was enrolled into the study before laboratory results were available. On Day 3, the culture results showed *Klebsiella pneumoniae* resistant to telithromycin and clarithromycin. Study medication was discontinued and therapy with cefuroxime iv and gentamycin iv was started but the subject died on Day 3 due to septicemia.

Telithromycin 7-day

4003/3410/004

Subject 4003/3410/004 was a 78-year-old white female who experienced an adverse event of cardiac arrest on Day 3 that resulted in death. On study entry, this subject had CAP with a Fine score of IV and clinical findings including renal insufficiency (estimated creatinine clearance = 29 mL/min) and a chest X-ray showing cardiac enlargement. An ECG done 4.5 hours after the first dose of study medication showed 1st degree atrioventricular block (PR interval = 0.22 sec) and a QTc interval of 440 ms, within normal limits. Medical history included heart failure treated with furosemide and unspecified ventricular arrhythmia treated with amiodarone. Concomitant medications included heparin, salbutamol and oxygen (all begun on Day 1 at time of hospitalization). Sputum culture results identified *S. pneumoniae* as the causative pathogen with a telithromycin MIC of 0.008 µg/mL and sensitive to penicillin G, erythromycin A, and clarithromycin. On the morning of Day 3, the subject was found with no pulse and no spontaneous respiration. The cause of death was listed as cardiac arrest. An autopsy was not performed.

4003/3652/003

Subject 4003/3652/003 was a 30-year-old black male who developed a headache, vomiting and then convulsions on the evening of Day 7 (he had discontinued study medication 2 days earlier). The subject was brought to the hospital the following morning in extremis where he continued to convulse. Treatment with diazepam, cefazolin iv, gentamycin iv, and iv fluids of lactated ringers solution were initiated. On Day 8, 15 hours after the convulsions began, the subject died from suspected acute meningitis. No autopsy was performed.

Clarithromycin

4003/3402/007

Subject 4003/3402/007 was a 83-year-old white female with a history of angina pectoris who experienced myocardial infarction (MI) resulting in death on Day 13, 3 days after the last dose of study medication. The subject presented to the emergency room (ER) with edema, shortness of breath, and altered consciousness. She was treated in the ER (unspecified) and an ECG indicated a myocardial infarction.

4003/3128/002

Subject 4003/3128/002 was a 57-year-old white male with prostate cancer who was diagnosed with lung cancer (type and stage unspecified) on Day 30 (post-treatment) resulting in death on Day 39.

Narratives: Deaths in Uncontrolled Phase III Studies

Study 3000

Telithromycin

3000/0703/1466

Subject 3000/0703/1466 was a 57-year-old white male who was diagnosed on Day 3 with acute leptospirosis (confirmed by serology) associated with renal failure, hemolytic anemia, sepsis, and liver insufficiency. The subject subsequently died of sepsis and adult respiratory distress syndrome (ARDS).

3000/0803/1520

Subject 3000/0803/1520 was a 65-year-old white male, with history of CAD, diabetes, COPD, chronic osteomyelitis and stroke, who completed study treatment with a return to the preinfection state. On Day 12 (3 days post-treatment) he presented with a nonpruritic rash on upper and lower extremities, confirmed as leukocytoclastic vasculitis on biopsy. Urinalysis showed microscopic hematuria and chest X-ray showed bilateral infiltrates, which were identified in the chest CT scan as pleural fluid. On Day 20, the subject had an acute myocardial infarction and died on Day 31 due to gram-negative septicemia.

Study 3009OL

Telithromycin

3009OL/0369/108

Subject 3009OL/0369/108 was a 37-year-old black female who experienced a worsening of pneumonia with severe dyspnea and respiratory distress on Day 5. On Day 6 she developed clinical jaundice and complained of painful lower legs. Laboratory test results revealed abnormal liver function tests (AST 806 U/L, ALT 1235 U/L, alkaline phosphatase 326 U/L, total bilirubin 26 µmol/L). The following day, she became dyspneic with peripheral edema and hepatomegaly, HIV tests were positive. The subject was withdrawn from the study and transferred to another hospital, and died on Day 12, 5 days after the last dose of study medication. The investigator assessed these events as unrelated to the study medication. The reported cause of death was respiratory failure, cardiomyopathy, liver failure, and immunosuppression, considered due to the underlying/concomitant illness.

Study 3010

Telithromycin 7-day

3010/0473/009

Subject 3010/0473/009 was a 77-year old white male who presented to the emergency room at study entry with increased shortness of breath, cough with productive purulent sputum, chest discomfort, and mild chills for 2 to 3 days. An entry diagnosis of mild renal insufficiency was initially felt to be compromised due to pneumonia and underlying congestive heart failure. On Day 3 the subject showed improvement in clinical signs and symptoms of pneumonia (confirmed by chest X-ray). However, renal insufficiency increased from mild to moderate secondary to vomiting and poor intake. On Day 5 the subject experienced labored respirations and shortness of breath secondary to acute aspiration, was transferred to the intensive care unit and died a short time later due to acute aspiration, later changed to foreign body in larynx.

3010/0537/009

Subject 3010/0537/009 was a 44-year old black male who experienced acute myocardial infarction on Day 1. Pretherapy, the subject was hospitalized due to presentation with pleuritic chest pain, cough, dyspnea, tachypnea, fever and chest X-ray revealing consolidation. No causative pathogen was isolated. Review of the pretherapy/entry ECG indicated evidence of a new myocardial infarction (Q waves in leads V1-V3, ST segment elevation s in leads V1-V4, PR segment depressions in lead II, QTc of 470 ms) and sinus tachycardia at 130 beats per minute. The subject died on Day 2. The investigator assessed the event as not related to the study medication, but rather to an underlying or concomitant illness (acute myocardial infarction).

Study 3012

Telithromycin 7-day

3012/2004/004

Subject 3012/2004/004 was an 84-year-old white female with a history of hypertension who was treated with study medication approximately 18 hours after hospital admission for suspected pneumonia. Approximately 1.5 hours later the subject's clinical condition deteriorated with worsening respiratory distress, subsequent arrest, unsuccessful resuscitative attempts and death approximately 8 hours later.

3012/4002/022

Subject 3012/4002/022 was a 70-year-old female with medical history of chronic obstructive pulmonary disease, heart failure, and cor pulmonale. On Day 1 the subject started furosemide for her heart failure, which worsened on Day 3, and resulted in death the same day despite counteractive measures.

3012/4003/013

Subject 3012/4003/013 was a 46-year-old black male with a history of HIV infection. Initial clinical improvement was noted on Day 3, but the subject subsequently worsened and died on Day 8.

3012/4003/040

Subject 3012/4003/040 was a 56-year-old black male with medical history of chronic obstructive airways disease, pneumoconiosis (1987), unspecified visual and hearing loss, and nonsmoking status. Study medication was completed on Day 7. On Day 12, the subject was hospitalized for worsening bilateral upper lobe pneumonia and died the same day.

3012/4003/022

Subject 3012/4003/022 was a 43-year-old black male with history of AIDS-related complex with immunocompromized status and tobacco use. On Day 8, the subject developed diarrhea attributed to an unspecified toxic herbal treatment. On Day 11, the subject visited his Sangoma (witch doctor) who advised him not to continue the study as the study medication was considered poison. The investigator suspected that the subject drank a toxic substance provided by the Sangoma. On Day 15, the pneumonia worsened, CD4 count was 44 U/L. On Day 17, the subject was prescribed ciprofloxacin and an unspecified tuberculosis therapy, but died before treatment was started.

Appendix 8. Deaths in Study 3014

Deaths in Study 3014

Deaths were categorized according to time to onset of death: deaths occurring up to and including Day 17, deaths occurring up to and including Day 35, and all deaths reported. This latter group included 3 deaths discovered during additional follow-up that are not included in the clinical database as they occurred remote to study drug therapy. There were 17 subjects with at least 1 TEAE with an outcome of death: 9 (9/12159, 0.1%) in the telithromycin group and 8 (8/11978, 0.1%) in the AMC group. In 1 AMC-treated subject (0427/004), the primary cause of death was a post-treatment SAE and the TEAE with an outcome of death was not reported as serious. Only 9 subjects died during Days 1 to 17: 6 in the telithromycin group and 3 in the AMC group. None of these deaths were considered possibly related to treatment by the investigators. All AEs leading to death are presented below.

Study 3014: All events leading to death

Subject number	Age/Sex[a]/ Race	Period[b]	Last day on study drug	Day of death [c]	Primary cause of death according to investigator	Relationship of death to study drug [d]
Telithromycin - acute exacerbation of chronic bronchitis						
Day 1 to 17						
1766/018	52/M/White	On	3	3	Cerebrovascular accident NOS	no
2827/002	66/M/White	On	5	7	Cardiac arrest	no
		On	5	7	Pneumonia NOS	no
		On	5	7	Sepsis NOS	no
0211/004	81/M/White	On		17	Coronary artery disease aggravated	no
		On		17	Aortic aneurysm	no
Day 18 to 35						
0885/002	42/M/White	Post	11	30	Cardiac arrest	no
Other deaths						
1987/001	74/F/White	Post	11	41	Cerebrovascular accident NOS	no
0136/025	63/F/White	Post	11	44	Respiratory failure (excl neonatal)	no
1766/013	81/F/White	On	11	46	Pressure sore	no
		Post	11	46	Chronic obstructive airways disease exacerbated	no
0639/022*	37/M/White	Post	11	52	Cardiopulmonary arrest	NR
0406/051	71//M/White	On	11	66	Respiratory failure (excl neonatal)	no
		Post	11	66	Encephalopathy NOS	no
		Post	11	66	Renal failure NOS	no
Telithromycin - acute sinusitis						
Day 1 to 17						
0198/023	74/M/White	On	2	14	Myocardial infarction	no
		On	2	14	Hepatorenal failure	no
1305/006	56/F/White	On	11	14	Chronic obstructive airways disease exacerbated	no
Day 18 to 35						
1760/029	56/F/White	Post	11	31	Acute myocardial infarction	no
0403/062	57/M/White	On		32	Cardiac arrest	no

Subject number	Age/Sex[a]/ Race	Period[b]	Last day on study drug	Day of death [c]	Primary cause of death according to investigator	Relationship of death to study drug [d]
0639/056	67/F/White	Post	11	33	Death NOS	no
Telithromycin - community-acquired pneumonia						
Day 1 to 17						
1814/086	48/M/White	On	4	17	Empyema NOS	no
		On	4	17	Pneumonia NOS	no
		Post	4	17	Cardiac arrest	no
Amoxicillin-clavulanic acid - acute exacerbation of chronic bronchitis						
Day 1 to 17						
1228/111	71/F/White	On	3	7	Respiratory failure (excl neonatal)	no
1302/002	73/M/White	On	11	13	Respiratory arrest (excl neonatal)	no
Day 18 to 35						
0098/011	72/F/White	Post	11	23	Acute myocardial infarction	no
0728/008	62/F/Black	Post	11	28	Myocardial infarction	no
1769/018	89/M/White	Post	11	30	Acute respiratory failure	no
		Post	11	30	Pneumonia pseudomonal	no
0050/015	46/M/White	Post	8	31	Carcinoma NOS	no
0728/059	68/M/Black	On		32	Cardiac failure NOS	no
Other deaths						
0443/002	82/F/White	Post	8	42	Cerebrovascular accident NOS	no
Amoxicillin-clavulanic acid - acute sinusitis						
Day 18 to 35						
0074/014	62/F/White	Post	11	21	Cardiac arrest	no
		Post	11	21	Blood bilirubin increased	no
2792/019	82/M/White	Post	11	27	Cerebral hemorrhage	no

Subject number	Age/Sex[a]/ Race	Period[b]	Last day on study drug	Day of death [c]	Primary cause of death according to investigator	Relationship of death to study drug [d]
0838/037	81/M/White	Post	11	29	Myocardial infarction	no
0787/005	80/M/White	Post	11	32	Sepsis NOS	no
Other deaths						
0884/001	59/F/White	On	11	36	Lung cancer stage unspecified(excl metastatic tumors to lung)	no
		Post	11	36	Arterial thrombosis limb	no
1339/034*	47/F/White	Post	11	52	Respiratory failure	no
Amoxicillin-clavulanic acid - community-acquired pneumonia						
Day 1 to 17						
3168/003	88/M/White	On	1	15	Intestinal perforation NOS	no
		On	1	15	Pneumonia NOS	no
Day 18 to 35						
0590/002	90/M/White	On	8	21	Pneumonia aggravated	no
		On	8	21	Pulmonary edema NOS	no
0427/004	82/M/White	On	11	26	Chronic obstructive airways disease exacerbated	no
		Post	11	26	Sepsis NOS	no
Other deaths						
1921/002*	68/M/White	Post	1	37	Metastatic carcinoma	NR
1696/015	80/F/White	Post	11	37	Aortic aneurysm	no
0249/070	80/F/White	On	3	78	Chronic obstructive airways disease	no
		On	3	78	Pneumonia aggravated	no

Brief narratives for all subjects who died are provided below.

Narratives: Deaths in Study 3014

Telithromycin - Acute Exacerbation of Chronic Bronchitis

Day 1 to 17

Subject 1766/018 (telithromycin), a 52-year-old white male, with a medical history of chronic obstructive pulmonary disease and cardiovascular disease, impaired vision, allergy to codeine and hypertension, was enrolled in the study on 25 January 2002, with AECB and having experienced confusion with headache and cold congestion from the previous day. The subject took telithromycin from 25 January 2002 to 26 January 2002. He was hospitalized for altered mental status on 26 January 2002 with elevated blood pressure, loss of vision, cold, congestion, and headache and subsequently became agitated and restless with a progressive loss in alertness and decline in neurologic function. He lapsed into a coma and experienced decerebrate posturing and significant brain stem dysfunction. The subject died on 27 January 2002 of cerebral vascular accident NOS as a consequence of basilar artery thrombosis. The event was severe and not related to study medication. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Hydroxyzine, Zolofit, Felodipine, Robaxin Hydrochlorothiazide, Naproxen, Fosinopril, Butalbital with paracetamol (Cephadyn), Duratuss G, Dimetane DX, Anaplex.

3014/2827/002

Subject 2827/002 (telithromycin), a 66-year-old white male, with a medical history of chronic obstructive pulmonary disease, chronic lymphocytic leukemia and tobacco use, was enrolled in the study on 18 December 2001, with AECB. The subject took telithromycin from 18 December 2001 to 22 December 2001. On 23 December 2001, the subject developed sepsis, gram-negative bacteremia and pneumonia with fever, cough, respiratory distress and decreased level of consciousness. The investigator assessed the events to be serious, of severe intensity, and not related to study medication. Study medication was discontinued. The subject required full mechanical ventilation. After intubation he had episodes of pulseless electrical activity and required cardiopulmonary resuscitation. On 24 December 2001, the subject experienced severe, serious cardiac arrest with shortness of breath and ventricular tachycardia. The event was not related to study medication. An ECG, performed on 24 December 2001, revealed sinus tachycardia with sinus arrhythmia, right superior axis deviation and inferior-posterior infarct. A chest X-ray revealed right lower lobe consolidation. The subject died on 24 December 2001 of sepsis, with secondary causes given as pneumonia and cardiac arrest. Cardiac arrest was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Flovent, Combivent, other anti-asthmatics, inhalants, Prednisone, Advair.

3014/0211/004

Subject 0211/004 (telithromycin), an 81-year-old white male, with a medical history of coronary artery disease (ongoing), a 9 cm thoracic aortic aneurysm (diagnosed on 16 October 2001 and treated with atenolol since 08 November 2001), persistent chronic bronchitis, reflux esophagitis, non-insulin dependent diabetes mellitus, benign prostatic hypertrophy, and hyperlipidemia, was enrolled in the study on 08 November 2001, with AECB. The subject took telithromycin from 08 November 2001. The date and time of the last dose of study medication was unknown. On 14 November 2001 investigations revealed normal left ventricular function, 3 vessel coronary artery disease and aortic aneurysm. The

subject was scheduled for a thoracic aneurysm repair on 28 November 2001. On 24 November 2001, the subject experienced serious worsening thoracic aortic aneurysm and coronary artery disease aggravated (verbatim term: worsening thoracic aortic aneurysm) of severe intensity. The subject was found dead on 24 November 2001. The events were not related to study medication. Postmortem was not performed. Coronary artery disease aggravated was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Gemfibrozil, Atenolol, Loratadine, Esomeprazole, Metformin hydrochloride, Terazosin, Proton pump inhibitors NOS.

Day 18 to 35

3014/0885/002

Subject 0885/002 (telithromycin), a 42-year-old white male, with a medical history of obesity, hypertension, narcotic addiction, and cerebrovascular accident (2001), was enrolled in the study on 26 December 2001, with AECB. The subject completed telithromycin treatment on 04 January 2002. The subject had an ALT level above the normal range on 26 December 2001 (pretherapy/entry) that was further elevated on 16 January 2002 (Visit 2). On 24 January 2002, the subject experienced serious cardiac arrest (verbatim term: cardiac arrest). The subject was discovered in bed and was unresponsive, apneic and without pulse. Cardiopulmonary resuscitation was started. The subject was pronounced dead upon arrival at the Emergency Department later the same day. The investigator assessed the event to be of severe intensity, and not related to study medication. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Ambien, Covera, Methadone.

Other deaths

3014/1987/001

Subject 1987/001 (telithromycin), a 74-year-old white female, with a medical history of diabetes mellitus, diabetic neuropathy, chronic atrial fibrillation, chronic obstructive pulmonary disease, degenerative joint disease, chronic pain, chronic post-shingles neuropathy and goiter operation, was enrolled in the study on 04 December 2001, with AECB and a recent history of frequent falls and head trauma. The subject completed telithromycin treatment on 13 December 2001. On 05 January 2002, the subject was hospitalized for severe, serious cerebrovascular accident NOS with confusion, slurred speech, visual hallucinations and weakness on 1 side. The event was not related to study medication. A CT scan of the brain was normal. Chest X-ray revealed cardiomegaly. ECG showed atrial fibrillation, poor R wave progression and occasional PVCs. The subject died on 13 January 2002 of cerebrovascular accident and chronic obstructive pulmonary disease. No autopsy was performed. Concomitant medications were Albuterol, Bisoprolol with hydrochlorothiazine, Celebrex, Dipyridamole, Glucophage, Neurontin, Propoxyphene napsylate with acetaminophen, Prozac, Salmeterol, Triamcinolone, Zaroxolyn.

3014/0136/025

Subject 0136/025 (telithromycin), a 63-year-old white female with a medical history of chronic obstructive pulmonary disease, was enrolled in the study on 18 January 2002, with AECB and completed study medication on 28 January 2002. On 04 February 2002, the subject experienced serious severe pneumonia, with bronchospasm, wheezing and dyspnea, that required hospitalization and was not related to study medication. The subject was also diagnosed with lung carcinoma cell type unspecified stage IV, a squamous cell carcinoma with metastases to the liver. On 02 March 2002 the subject developed serious

severe respiratory failure (excl neonatal) that was not related to study medication and that resulted in death that same day. Concomitant medications were not reported.

3014/1766/013

Subject 1766/013 (telithromycin), an 81-year-old white female, with a medical history of chronic obstructive pulmonary disease, asthma and allergies to Claritin and Celebrex, was enrolled in the study on 17 January 2002, with AECB. The subject took telithromycin from 17 January 2002 to 23 January 2002. On 22 January 2002, the subject experienced severe, serious deeply infected sacral decubitus secondary to being wheelchair bound. The event was not related to study medication. The subject was hospitalized for the event and discharged in a stable condition on 29 January 2002. On 18 February 2002, the subject experienced serious chronic obstructive airways disease exacerbated with chest pain, shortness of breath, cough, and weakness. The event was of severe intensity, and not related to study medication. The subject became comatose on 28 February 2002, was placed in a hospice on 01 March 2002 and received comfort measures only. The subject experienced atrial fibrillation with rapid ventricular rate, unresponsive to digoxin, and died on 03 March 2002 of chronic obstructive pulmonary disease, pulmonary fibrosis, stage IV decubitus and rheumatoid arthritis. The event of chronic obstructive airways disease was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Cipro, Ancef, Flagyl, Levaquin, Lortab, Clonazepam, Prednisone, Ethinylestradiol with norethindrone, Calcium with vitamin D 2, Muco-Fen-DM, Chlorphenamine/hydrocodone/phenylephedrine HCl, Gentamycin.

3014/0639/022

Subject 0639/022 (telithromycin), a 37-year-old white male with a medical history of chronic obstructive pulmonary disease, asthma, pneumonia, heavy tobacco use, alcohol abuse and bullous emphysematous radiological changes but negative bronchoscopy, was enrolled in the study on 26 November 2001 with AECB. On 27 November 2001 the subject presented with serious moderate pneumonia NOS that required hospitalization and was not related to study medication. Associated symptoms included fever, diarrhea, vomiting, dehydration, persistent cough, bronchospasm, hemoptysis and slight anemia. The subject completed study treatment on 06 December 2001 and the pneumonia resolved without sequelae on that day. Further information on this subject was obtained through follow-up, but not included in the clinical database. On 27 December 2001 the subject presented with depression, cough, nausea, gastritis-type symptoms, anorexia, weight loss and alcohol abuse. He was given Zoloft and Ambivent, advised to avoid alcohol and scheduled for follow-up in 3 weeks or sooner. On 16 January 2002 the subject died from cardiopulmonary arrest. As death occurred remote to treatment this was not reported as an SAE and the investigator's assessment of relationship was not obtained.

3014/0406/051

Subject 0406/051 (telithromycin), a 71-year-old white male, with a medical history of coronary artery disease, other cardiovascular disease, arrhythmia and chronic obstructive pulmonary disease, was enrolled in the study on 16 January 2002, with AECB. The subject completed telithromycin treatment on 24 January 2002. On 01 February 2002, the subject was hospitalized for serious dissecting aortic aneurysm and serious respiratory failure (excl. neonatal). The aneurysm resolved without sequelae, following a Hemashield graft, on 05 February 2002. On 03 February 2002, the subject experienced serious cardiac tamponade, which required 2 days of open chest exploratory surgery and resolved without sequelae on 05 February 2002. A tracheostomy was performed for respiratory failure on 14 February

2002. On 16 February 2002, the subject experienced serious renal failure NOS requiring dialysis 3 times per week. On 20 February 2002, the subject experienced serious encephalopathy NOS. All events were of severe intensity and were unrelated to study medication. The subject died on 22 March 2002 from respiratory failure, renal failure and encephalopathy. Concomitant medications were Warfarin sodium, Lanoxin, Salbutamol with ipratropium bromide, Pravastatin sodium, Diltiazem, Quinapril hydrochloride, Zantac, Insulin, Ritalin, Clonidine, calcium carbonate, Erythropoietin, Zoloft, Lovenox, Labetalol, Docusate sodium, Heparin, Nitroglycerin, Esmolol, protamine sulfate.

Telithromycin - Acute Sinusitis

Day 1 to 17

3014/0198/023

Subject 0198/023 (telithromycin), a 74-year-old white male, with a medical history of diabetes mellitus, hypertension, coronary artery disease, severe non-ischemic dilated cardiomyopathy, mild multi-valve heart disease, angina, COPD, asthma, arrhythmia with permanent (DDD) pacemaker implant, and hyperlipidemia, was enrolled in the study on 08 January 2002 with AS and received telithromycin from 08 to 09 January 2002. Liver function tests were normal at pretherapy/entry. In the week prior to enrollment the subject complained of orthopnea and paroxysmal nocturnal dyspnea but denied chest pain, palpitations, near syncope or syncope. On the night of 08 January 2002 the subject had a fall and the family thought he had mental status changes. On 09 January 2002 he was taken to the emergency room where he was mildly hypoxic (O₂ saturation of 92%) and mildly hypertensive (BP 151/71). Chest X-ray revealed mild cardiomegaly with mild pulmonary vasculature fullness with no acute changes. ECG showed a paced ventricular rhythm. He was found to have acute renal failure (creatinine of 3.4 mg/dL from 1.3 mg/dL in 2000) and acute liver dysfunction (ALT 2081, AST 2519) consistent with the AE of hepatorenal failure reported in the database, with normal alkaline phosphatase and total bilirubin. Initial troponin I was elevated at 3.4 with myoglobin of 33% from acute coronary syndrome. There are no records of interrogation of the subject's pacemaker. The subject was admitted to the ICU and begun on nitroglycerine. Echocardiogram showed depression of ejection fraction to 20%. Troponin I level peaked at 4.4 with peak myoglobin of 600. On 14 January 2002 (5 days after discontinuation of telithromycin) he was noted to have runs of non-sustained ventricular tachycardia and was begun on amiodarone. His acute renal failure was determined to be secondary to pre-renal azotemia by the consulting nephrologists and he was treated with iv fluid hydration and daily hemodialysis was begun. Normalization of AST occurred on 17 January 2002, with improvement in ALT to 162. He was begun on Zosyn for acute bronchitis with WBC of 29000. Treatment was changed to Levaquin, vancomycin, Flagyl and Cefepime. The WBC initially improved but subsequently rose again, peaking at 46100 on 19 January 2002. On 21 January 2002 the subject suffered a cardiac arrest and died. Note that this narrative combines information from the original narrative submitted to the CEC and late follow-up information submitted separately to the CEC before final adjudication.

3014/1305/006

Subject 1305/006 (telithromycin), a 56-year-old white female, with a medical history of chronic obstructive pulmonary disease, fibromyalgia, GERD, hypocholesterolemia and collagen vascular disease, was enrolled in the study on 26 December 2001, with AS. The subject completed telithromycin treatment on 30 December 2001. On 05 January 2002, the subject experienced serious chronic obstructive airways

disease exacerbated (verbatim term: COPD exacerbation) with loss of consciousness. The event was of moderate intensity, and not related to study medication. The subject was hospitalized for hypoxia with cough, productive sputum and shortness of breath on 07 January 2002. The subject experienced nonserious diabetes mellitus NOS (verbatim term: diabetes) of mild intensity, and not related to study medication, on 07 January 2002. The subject died on 08 January 2002 due to respiratory failure (immediate cause of death) and chronic obstructive airways disease exacerbated (secondary cause of death). Chronic obstructive airways disease exacerbated was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Paxil, Other anti-asthmatics, inhalants, Prilosec, Lipitor, Ambien, Premarin, Tonocard, Flonase, Meclizine, Atrovent, Xopenex, Allegra, Celebrex, Advair.

Day 18 to 35

3014/1760/029

Subject 1760/029 (telithromycin), a 56-year-old white female, who was a heavy smoker with a medical history of 'other' cardiovascular disease, hypertension, diabetes, and anxiety, was enrolled in the study on 14 December 2001, with AS. The subject completed telithromycin treatment on 19 December 2001. AST levels were within the normal range at pretherapy/entry but was mildly elevated at 39 U/L 31 December 2001. On 12 January 2002, the subject experienced severe, serious acute myocardial infarction with chest pain, transient angina pain, shortness of breath, nausea, and palpitations. The event was not related to study medication. Early on 13 January 2002, the angina pain returned; the subject died on the way to the emergency room. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications: Lopressor, Vioxx, Glipizide, Premarin, Tranxene, Ultram, Elavil, Glucophage, Nizoral, Hydrochlorothiazide, Neurontin, Proton pump inhibitors NOS, Effexor, Orphenadrine, Pseudoephedrine, Nexium.

3014/0403/062

Subject 0403/062 (telithromycin), a 57-year-old white male, with a medical history of smoking, hyperlipidemia, hypertension (10 years), coronary artery disease, left ventricular hypertrophy, ventricular arrhythmia, loss of consciousness, chronic obstructive pulmonary disease, and dementia, was enrolled in the study on 05 December 2001 with AS and ongoing cardiac disease. The subject took telithromycin from 05 December 2001. The last dose of study medication is unknown. An ECG performed on 01 January 2002, showed probable inferior infarction and left ventricular hypertrophy with secondary ST-T changes. On 05 January 2002, the subject experienced severe, serious myocardial infarction resulting in cardiac arrest and death. The subject had a sudden onset of chest pain with shortness of breath and lightheadedness. The subject lost consciousness for 15 minutes and died 30 minutes after the onset of the event. The event was not related to study medication. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications: Lipitor, Prinivil, Humabid - slow release, Nasonex, Lopressor, Aricept, Singulair, Aspirin.

3014/0639/056

Subject 0639/056 (telithromycin), a 67-year-old white female, with a medical history of chronic obstructive pulmonary disease, hypertension, hyperlipidemia, asthma, peripheral vascular disease, cholecystectomy, depression, stent replacement for coronary artery disease, paroxysmal atrial fibrillation, endarterectomy, femoropopliteal bypass, multiple falls, nocturnal confusion and gastrointestinal bleeds,

was enrolled in the study on 17 December 2001, with AS and ongoing cardiac disease. The subject completed telithromycin treatment on 21 December 2001. The subject experienced a series of hospitalizations for moderate, serious respiratory failure (22 to 25 December 2001), moderate, serious acute bronchitis NOS (26 to 30 December 2001), moderate, serious acute exacerbation of COPD and moderate, serious atrial fibrillation (09 to 13 January 2002). The events associated with these hospitalizations resolved without sequelae. Later on 13 January 2002, the subject was re-admitted to hospital with difficulty breathing. The subject died on 18 January 2002, of an unknown cause. The investigator assessed the death to be due to the subject's underlying illness. All AEs were unrelated to study medication. Atrial fibrillation and death NOS were AESIs but were not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Atrovent, Proventil, Flovent, Prednisone, Zyprexa, Coumadine, Lopressor, Lanoxin, Ecotrin, Paxil, Dyazide, Serevent, Pantoprazole.

Telithromycin - Community-Acquired Pneumonia

Day 1 to 17

3014/1814/086

Subject 1814/086 (telithromycin), a 48-year-old white male, with no known relevant medical history, was enrolled in the study with CAP on 28 January 2002. The subject took telithromycin from 28 January 2002 to 31 January 2002. On 28 January 2002, the subject was hospitalized for severe, serious pneumonia NOS (verbatim term: worsening CAP requiring hospitalization) and moderate, nonserious alanine aminotransferase increased. Both events were unrelated to study medication. Study medication was discontinued on 31 January 2002 due to the pneumonia. On 01 February 2002, the subject experienced severe, serious empyema NOS, which was not related to study medication. The subject was discharged from hospital in a stable condition on 11 February 2002. On 13 February 2002, the subject experienced severe, serious cardiac arrest with shortness of breath and loss of consciousness. The event was not related to study medication. He was intubated and given atropine and epinephrine. Some idioventricular rhythm returned, but no pulse or respirations. The subject died on 13 February 2002. The death certificate gave the cause of death as acute myocardial infarction due to hypertensive cardiomyopathy. An autopsy revealed the subject had cardiomegaly with acute myocardial infarction (postero-lateral), coronary artery disease, hypertension, bronchopneumonia and hepatosplenomegaly. Cardiac arrest was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Zithromax, Antibiotics, Acetaminophen with hydrocodone bitartrate, Terramycin, Azithromycin, Lo/ovral-28.

AMC - Acute Exacerbation of Chronic Bronchitis

Day 1 to 17

3014/1228/111

Subject 1228/111 (AMC), a 71-year-old white female, with a medical history of cardiac arrhythmia, diabetes, left upper lobe lobectomy, chronic obstructive pulmonary disease, anemia, gastrointestinal bleeding, chronic hypoxia, asthma, heart failure, smoking, left shoulder fracture, left hip fracture, other cardiovascular disease and respiratory failure was enrolled in the study with AECB on 08 January 2002. The treatment was discontinued on 10 January 2002 for 'other' reasons. On 11 January 2002, the subject experienced nonserious, mild hypoglycemia NOS (verbatim term: insulin reaction) was transported to the

hospital for low blood sugar. At that time her lungs were clear to auscultation and breath sounds were equal, with no wheezes, rales, or rhonchi. She was discharged from the hospital the same day. The investigator assessed the event as not related to study medication. The subject recovered without sequelae. On 14 January 2002, the subject experienced respiratory failure (excl neonatal) (verbatim term: respiratory failure). The investigator assessed the event to be serious as it resulted in death on the same day. The event was of severe intensity, and not related to study medication.

3014/1302/002

Subject 1302/002 (AMC) 73-year-old white male, with a medical history of chronic obstructive pulmonary disease, multiple episodes of pneumonia and congestive heart failure was enrolled in the study on 21 December 2001, with AECB. Concomitant medications were Fosamax, Lorazepam, Darvocet-N, Zantac, Proventil inhaler and Ultram. The subject completed treatment on 30 December 2001. On 02 January 2002, the subject experienced an unwitnessed loss of consciousness and died while at home (Investigator assessment: fatal respiratory arrest). No autopsy was performed. This event was adjudicated as a confirmed safety endpoint by the CEC.

Day 18 to 35

3014/0098/011

Subject 0098/011 (AMC), a 72-year-old white female, with a medical history of coronary artery disease with vessel occlusion, angina pectoris, oxygen-dependent severe chronic obstructive pulmonary disease, congestive heart failure, mild hyperlipidemia, and smoking was enrolled in the study with AECB on 20 November 2001. An echocardiogram on 06 June 2001 had revealed normal left ventricular systolic function, mild mitral and tricuspid insufficiency, aortic valve sclerosis, mitral calcification, and borderline left ventricular hypertrophy. Coronary angiogram on 07 June 2001 showed preserved LV function with EF 55 to 60% and totally occluded RCA and non-obstructive lesions in the LAD and circumflex arteries. The subject had an ECG within 1 year (abnormal ECG on 02 November 2001, which showed normal sinus rhythm with a short PR interval, right atrial enlargement, and voltage criteria for left ventricular hypertrophy). She completed the treatment on 29 November 2001. On 08 December 2001, the subject was hospitalized for exacerbation of COPD, following a fall and facial trauma. On 10 December 2001, while hospitalized, the subject experienced chest pain; ECG was unremarkable. On 12 December 2001, the subject experienced acute myocardial infarction (verbatim term: acute MI) and died the same day. Associated symptoms included chest pain, shortness of breath and collapse. The subject lost consciousness. The onset of symptoms was sudden, and the symptoms lasted for 1 hour after which the subject died. The investigator assessed the event to be serious as it resulted in death, of severe intensity, and not related to study medication. The death certificate noted respiratory failure as the immediate cause of death with contributing conditions of end-stage chronic obstructive lung disease and acute myocardial infarction. The myocardial infarction was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were other anti-asthmatics, Fosamax, Plavix, Prednisone, Pravachol, Norvasc, Lasix, Ambien, Albuterol, oxygen and Accolate.

3014/0728/008

Subject 0728/008 (AMC), a 62-year-old black female, with a medical history of coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease and diabetes, was enrolled in the study with AECB on 05 December 2001. The subject completed the treatment on 14 December 2001. On

25 December 2001, the subject experienced nausea, dyspnea NOS, and pulmonary congestion. The investigator assessed all of the events as nonserious, of mild intensity, and not related to study medication. On 01 January 2002, the subject experienced myocardial infarction (verbatim term: MI) at home and died. The investigator listed the causes of death as myocardial infarction, end-stage congestive heart failure, coronary artery disease, hypertension, and insulin dependent diabetes mellitus. The subject's death certificate listed the cause of death as congestive heart failure. The investigator assessed the event to be serious as it resulted in death, of severe intensity, and not related to study medication. The event of myocardial infarction was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Nitroglycerin, Clopidrogel, Digoxin, Quinidine, Propoxyphene HCl, Furosemide, Insulin Lispro, Albuterol, Potassium Chloride, analgesics, Piglitazone HCl, Oxcarbazepine, Rabeprazole, Guaifenesin and Montelukast sodium.

3014/1769/018

Subject 1769/018 (AMC), an 89-year-old white male, with a medical history of asthma, emphysema, chronic obstructive pulmonary disease, hypothyroidism, diverticulosis, diverticulitis, anemia and respiratory failure was enrolled in the study with AECB on 17 December 2001. He completed the treatment on 27 December 2001. The subject had an ECG within 1 year (02 July 2001) that showed incomplete left axis deviation, right bundle branch block and an anterior myocardial infarction. On 22 December 2001, the subject experienced nonserious, mild dyspepsia. Study medication was not changed. The investigator assessed the event as possibly related to study medication. The event resolved without sequelae on 22 December 2001. On 11 January 2002, the subject experienced serious, moderate pneumonia pseudomonal. The investigator assessed the event as not related to study medication. On the same day, the subject experienced acute respiratory failure (verbatim term: acute respiratory failure). Associated symptoms included shortness of breath, change in mental status with slight drowsiness, and left-sided chest pain. The onset of symptoms was progressive, and the symptoms lasted for an unknown period of time. The subject did not lose consciousness. The subject was brought to the emergency room on 11 January 2002, where blood gases using 3 liters of oxygen were pH 7.26, pO₂ 87, pCO₂ 85. A chest X-ray showed possible infiltrates and marked changes of chronic obstructive pulmonary disease, and ECG showed a right bundle branch block. The subject was hospitalized due to the event for further evaluation. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. Both events resulted in death on 15 January 2002. Acute respiratory failure was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Levoxyl, Cardura, Duratuss, Uniphyl, Lasix, Flovent, Serevent, Atrovent, Decadron, Prevacid, Prednisone, Medrol, Biaxin, Rocephin and Medrol.

3014/0050/015

Subject 0050/015 (AMC), a 46-year-old white male, with a medical history of smoking, alcohol use and leg fracture was enrolled in the study with AECB on 10 December 2001. The subject had no known history of liver disease, abnormal liver tests or cardiac disease. On 17 December 2001 (the last day of treatment), the subject experienced, nonserious, mild AECB. Study medication was discontinued due to the failure of treatment. The investigator assessed the event to be not related to study medication. The event resolved with sequelae on 20 December 2001. On 18 December 2001, the subject experienced 3 events: Moderate serious pneumonia NOS (verbatim term: pneumonia) that required hospitalization, was not related to study medication and resolved without sequelae on 20 December 2001; mild nonserious abnormal liver function that was not related to study medication, and serious mild cholelithiasis that was

not related to study medication. The pathology report showed non specific inflammation of the gallbladder without any evidence of malignancy. The subject was discharged from the hospital on 22 December 2002 with abnormal liver functions. The subject was readmitted to hospital on 26 December 2002. His signs and symptoms included increasing chest pain and back pain, cough, fever of 102°F, no bowel movement in 10 days, anorexia, gastroesophageal reflux disease, chills, sweats, sleeplessness, nausea and vomiting. A CAT scan of the thorax performed on 26 December 2001 revealed a left lung infiltrate and nonspecific mediastinal adenopathy, and no other masses or enlarged nodes identified. On a CT-scan of the abdomen, liver parenchyma, spleen, pancreas, kidneys and adrenals appeared normal, and there was no evidence of biliary obstruction. A whole body bone scan on 27 December 2001 showed multiple areas of increased activity involving the pelvis, spine, ribs, skull, left hip that could be related to metastases. The subject was diagnosed with severe carcinoma NOS (verbatim term: cancer). The event was considered serious as it required hospitalization, was significantly disabling and resulted in death. The onset of associated symptoms (jaundice) was progressive. The investigator assessed the event as not related to study medication. . An MRI of the brain also showed abnormalities. Bone marrow biopsy was positive for metastatic adenocarcinoma. On 31 December 2001 the subject was in poor general condition and noted to have anemia and thrombocytopenia. The subject's weight had decreased by 10 pounds, fever and constipation were still present with mild confusion and shortness of breath. . Despite aggressive treatment that included antibiotherapy, the subject gradually declined over the course of the next 2 weeks, and died on 09 January 2002. . Carcinoma NOS was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Muco-Fen-DM and Claritin.

3014/0728/059

Subject 0728/059 (AMC), a 68-year-old black male, with a medical history of coronary artery disease, other cardiovascular disease, heart failure, chronic obstructive pulmonary disease, hypertension, increased lipids, increased PSA, aortic stenosis, myocardial infarction, old CVA, and osteoarthritis, was enrolled in the study with AECB on 29 January 2002. On 24 February 2002, the subject went to the emergency room with symptoms of shortness of breath, sinus drainage, coughing, profuse sweating and bilateral rales. The subject was in respiratory distress and had noted jugular venous distension. He reported having had a history of orthopnea for 2 nights. The subject's blood pressure was 220/120 mm Hg, with pulse 112, respiratory rate 30, and oxygen saturation was 76% on room air. An ECG showed ST-T elevation and was consistent with anterior infarction and chest X-ray revealed acute congestive changes bilaterally. Serial cardiac enzymes and complete blood count were normal, potassium was 2.8, and digoxin level 0.2. The subject was thought to have acute congestive heart failure with pulmonary edema, hypokalemia, and hypertension. The subject was hospitalized and was diagnosed with an acute myocardial infarction. He was transferred to another hospital where it was found that the subject had a blocked artery. Open-heart surgery was performed on 01 March 2002 and the subject died during the surgery. The cause of death on the death certificate was given as cardiac failure due to hypertrophic left ventricle. The investigator assessed the event to be serious as it resulted in death, of severe intensity, and not related to study medication. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Simvastatin, serum lipid reducing agents, Valsartan and Clopidrogel.

Other deaths

3014/0443/002

Subject 0443/002 (AMC), an 82-year-old white female, with a medical history of coronary artery disease, other cardiovascular disease and chronic obstructive pulmonary disease was enrolled in the study with AECB on 19 November 2001. On 20 November 2001, the subject experienced nonserious, severe abdominal pain upper. Study medication was discontinued due to the event on 27 December 2001. The investigator assessed the event was possibly related to study medication. The subject recovered without sequelae. On 30 December 2001, the subject was hospitalized for a cerebrovascular accident NOS (verbatim term: massive cerebrovascular accident). A non-contrast CAT scan of the brain revealed massive left cerebral hemorrhage with associated intraventricular and subdural blood with diffuse brain edema and midbrain hydrocephalus on the right. The event resulted in death on 31 December 2001. The cause of death was massive cerebrovascular accident, coronary artery disease and chronic obstructive pulmonary disease. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Evista, Pantoprazole sodium, Plavix, Isosorbide, Vioxx, Zolof, Mevacor, Bentyl, Fosamax, Darvocet-N and Despiramine.

AMC - Acute Sinusitis

Day 18 to 35

3014/0074/014

Subject 0074/014 (AMC), a 62-year-old white female, with a medical history of coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, angina/myocardial infarction, tobacco abuse, and stent placement was enrolled in the study with AS on 17 January 2002. She completed the treatment on 26 January 2002. Cardiac disease was ongoing at time of study entry. The subject had suffered an anterolateral MI with cardiogenic shock in 04 January 1999. She had a stent placed in the proximal LAD and did well until December 2001 when she was involved in a motor vehicle accident and while examining the damage developed pulseless ventricular tachycardia requiring CPR. Angiography showed severe 2-vessel CAD with thrombosed stents from 1999 in the proximal LAD and chronic total occlusion of the proximal RCA. Collateral flow from the LAD to RCA was compromised. There was inadequate collateral flow from the circumflex/ramus branch to the LAD and RCA. Attempts to open the LAD stent were unsuccessful. The subject was considered a poor surgical risk at that time. On 06 February 2002, the subject experienced a cardiac arrest. The subject arrived at the emergency room with vital signs absent. Her ECG was "straight line" in the ambulance with occasional disordered electrical activity. The subject was intubated and an external pacemaker was applied. She was treated with epinephrine intracardiac with no improvement in rhythm, and was pronounced dead. The immediate cause of death was myocardial infarction with coronary artery disease as the underlying contributing cause. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Ecotrin, Digoxin, potassium chloride, Coreg, Proventil inhaler, Flovent, Vasotec, Plavix, Pepcid, Lasix, Ambien and Epinephrine.

3014/2792/019

Subject 2792/019 (AMC), an 82-year-old white male, with a medical history of hypertension, type 2 diabetes, urinary problems, dysarthria and left shoulder injury, was enrolled in the study with AS on 08 January 2002. The subject had a family history of hypertension and stroke. The subject completed the treatment on 12 January 2002. Post-treatment, the subject experienced nonserious, moderate muscle spasms. The investigator assessed the event as possibly related to study medication. The event was ongoing at the time of the subject's death. On 30 January 2002, the subject was hospitalized for cerebral hemorrhage (verbatim term: cerebral hemorrhage). He had experienced sudden onset right sided weakness and collapse. His blood pressure was 210/120 mmHg, pulse was 96 bpm, temperature was 36°C and respiration rate was 20. Neurologically, he was unresponsive and there was dense right hemiparesis. CAT scan of the head showed a large left intracerebral hemorrhage extending into the ventricle. The investigator assessed the event as serious, of severe intensity, and not related to study medication. The event resulted in the death of the subject on 03 February 2002. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Demadex and Motrin.

3014/0838/037

Subject 0838/037 (AMC), an 81-year-old white male, with a medical history of coronary artery disease, angina/myocardial infarction, hypertension, and other cardiovascular disease was enrolled in the study with AS on 28 December 2001. Cardiac disease was ongoing at the time of study entry. Hypertension has been treated with losartan potassium, on an ongoing basis. There was no known history of heart failure. On 18 January 2002, the subject experienced nonserious, mild alanine aminotransferase increased. There were no associated symptoms. The investigator assessed the event as not related to study medication. On 25 January 2002, the subject experienced myocardial infarction (verbatim term: myocardial infarction). Associated symptoms included chest pain and shortness of breath. The onset of symptoms was sudden, and the symptoms lasted for an unknown period of time. The subject was hospitalized on 25 January 2002. The subject died in the hospital on 26 January 2002. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. This event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Losartan potassium, Dipyridamole and Ascriptin.

3014/0787/005

Subject 0787/005 (AMC), an 80-year-old white male, with a medical history of bronchial asthma, congestive heart failure, coronary artery disease, coronary artery bypass grafting, colon cancer, prostate cancer, chronic sinusitis, chronic depression, chronic arthritis, exogenous obesity, peptic acid disease of stomach, hypothyroidism, iron deficiency anemia and vertebrobasilar insufficiency with recurrent falling was enrolled with AS on 16 January 2002. On 30 January 2002, the subject experienced a patella fracture. The investigator assessed the event to be serious as it was significantly disabling/incapacitating and required or prolonged inpatient hospitalization. The event was of severe intensity, and not related to study medication. The event was considered to have resolved with sequelae on the same day. The subject subsequently developed chronic diarrhea, fever and hypotensive episodes and on 16 February 2002 this was diagnosed as sepsis NOS (verbatim term: septicemia suspected not proven). The investigator assessed the event to be serious as it resulted in death on 16 February 2002. The event was of severe intensity, and not related to study medication. Concomitant medications were Pantoprazole sodium,

Synthroid, Flonase, Alphagan, ferrous sulfate, Celexa, Serevent inhaler, Maxair, Lasix, Levaquin, activated charcoal, Mycostatin oral suspension, Imodium, Paragoric, Flagyl, Darvocet-N, Tigan, Beano and Lotrisone.

Other deaths

3014/0884/001

Subject 0884/001 (AMC), a 59-year-old white female, with a medical history of allergy to codeine, cholecystectomy, hypertension, a melanoma excised from the back in 1990, and recent chronic cough for 5 months was enrolled with AS on 03 January 2002. On 10 January 2002, the subject was diagnosed with lung cancer stage unspecified. The subject's cough had aggravated since 09 January 2002, and the subject had dyspnea. Chest X-ray showed new evidence of atelectasis and consolidation in the right middle lobe. There was a suggestion of more focal mass density in the region of the inferior aspect of right hilum, which could be the cause of atelectasis. A CT scan of chest and abdomen showed a hilar lesion and multiple metastatic lesions in the liver and an obstructing lesion of right bronchus. Study medication was continued unchanged. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. On 21 January 2002, the subject experienced nonserious moderate abdominal pain NOS that was considered not related to study medication. A liver biopsy from 29 January 2002 confirmed metastatic malignant melanoma. On 02 February 2002, the subject presented to an emergency room with dyspnea and sudden pain in the right arm, due to an acute occlusion of the right brachial artery, and underwent an emergent brachial and radial thrombectomy. A large amount of thrombus and tumor thrombus was removed, however no malignancy was noted on histopathology. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. The subject subsequently deteriorated and developed mental status changes. She fell and developed hematoma on the left frontal region. An initial CAT scan of the head was negative. It was then suspected the subject's confusional state was associated with hypoxemia secondary to pulmonary embolism. The subject deteriorated and died on 07 February 2002. The death certificate states that the primary cause of death is extensive metastatic malignancy, with unknown primary source. Lung cancer stage unspecified was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Claritin-D, Methylprednisolone, Humibid, morphine sulphate, Compazine suppositories and Phenergan.

3014/1339/034

Subject 1339/034 (AMC), a 47-year-old white female, with elevated AST, ALT and alkaline phosphatase at pretherapy/entry, was enrolled in the study on 16 January 2002, with AS. She completed study medication on 26 January 2002, returned for Visit 2 on 21 February 2002 when liver function tests had improved, and had Visit 3 on 25 February 2002. No AEs were reported at these visits. Further information on this subject was obtained through follow-up, but not included in the clinical database. On 08 March 2002 the subject presented with pneumonia and flu-like symptoms treated with Depomedrol, Claforan im, Guaifed/P-EPHED, Tamiflu, and A-Tuss HD Liquid ATL. Later that evening she experienced respiratory failure associated with shortness of breath, chest pain, excessive coughing and hemoptysis and was in asystole by the time the EMS arrived. CPR was started and continued until the subject was pronounced dead at the hospital. According to the family, the subject had vaginal bleeding for the previous 30 days, and in the previous 2 weeks had diarrhea and had stopped taking Synthroid for hypothyroidism. Autopsy revealed pulmonary edema, cirrhosis, toxic levels of chlorpheniramine and dextromethorphan, chronic bronchitis with severe squamous dysplasia, and splenomegaly. There was no evidence of myocardial infarction or pulmonary embolism. The pathologist considered the toxic levels of

chlorpheniramine and dextromethorphan, in the face of cirrhosis were significant and may have contributed to the respiratory arrest since both drugs are metabolized by the liver. The death was reported as a post-treatment SAE that was not related to study medication.

AMC - Community-Acquired Pneumonia

Day 1 to 17

3014/3168/003

Subject 3168/003 (AMC), an 88-year-old white male, with a medical history of ulcerative colitis, gastroesophageal reflux disease, right inguinal hernia surgery, prostate cancer, was enrolled in the study with CAP on 16 January 2002. The subject had undergone an ECG within 1 year which showed sinus arrhythmia. On 16 January 2002, the subject experienced pneumonia NOS (verbatim term: pneumonia). Study medication was not changed. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. On 17 January 2002, the subject experienced a perforated viscus. The onset of symptoms was sudden. Study medication was discontinued due to the event on 17 January 2002. The subject underwent surgery for this event. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. The subject died on 30 January 2002. The investigator commented that the cause of death was cardiac arrest secondary to respiratory failure resulting from postoperative pneumonia. The pneumonia was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Azulfidine, Axid and Hytrin.

Days 18 to 35

3014/0590/002

Subject 0590/002 (AMC), a 90-year-old white male, with a medical history of coronary artery disease, coronary artery bypass graft, hypothyroidism, ASCVD, hypercholesterolemia, arthralgia, arthritis, prostatism, severe aortic stenosis, was enrolled in the study with CAP on 21 January 2002. The cardiac disease was ongoing at time of study entry. On 26 January 2002, the subject experienced pulmonary edema (verbatim term: pulmonary edema). Associated symptoms included shortness of breath. The onset of symptoms was progressive. The subject went to see his physician on 26 January 2002 complaining of shortness of breath along with fever and chills and pedal edema. An ECG was performed following irregular heartbeat, which indicated atrial flutter with variable ventricular response and fibrillation with left axis deviation. The subject was hospitalized on 28 January 2002. The subject had lower extremity edema, most probably secondary to left ventricular dysfunction, along with pulmonary hypertension. During hospitalization a 2D ECG showed an aortic valve area of 0.7 cm² and his ejection fraction was 45 to 50%. Chest X-ray showed bilateral infiltrates. During hospitalization, the subject's cardiac status improved, as did his lower extremity edema and shortness of breath. His pneumonia was also clinically improved. On 01 February 2002, the subject experienced pneumonia aggravated (verbatim term: worsening pneumonia). The investigator assessed the event to be serious, of severe intensity, and not related to study medication. The subject showed further signs of shortness of breath, which worsened on 02 February 2002. There was increased cough with bloody sputum. He required increased oxygen, and was maintained on a non-rebreather. On 04 February 2002, the subject converted to sinus rhythm. He had rales on the right side, which gradually worsened. He experienced nonserious syncope on 06 February 2002. The subject had progressive associated symptoms of shortness of breath, which lasted for 30 seconds. The event resolved after 30 seconds. The subject died on 10 February 2002 due to pneumonia

and probable pulmonary edema related to severe aortic stenosis. This was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Hytrin, Synthroid, Mevacor, Refresh, Aspirin, vitamin C, vitamin E, iron, Lasix and Micro-K.

3014/0427/004

Subject 0427/004 (AMC), an 82-year-old white male, with a medical history of chronic obstructive pulmonary disease, obstructive sleep apnea, prostate carcinoma, Crohn's disease, macular degeneration, congestive heart failure, and cor pulmonale was enrolled in the study with CAP on 14 December 2001. The cardiac disease was ongoing at time of study entry. He had had an ECG within the last year. Study medication was completed on 24 December 2001. On 25 December 2001, the subject experienced nonserious, mild hypovolemia. The investigator assessed the event as nonserious, of mild intensity, and not related to study medication. The event resolved without sequelae. On 26 December 2001, the subject was hospitalized for ileus paralytic. The subject experienced accompanying symptoms of abdominal distention and diarrhea. The investigator assessed the event to be serious, of moderate intensity, and not related to study medication. On 26 December 2001, the subject experienced nonserious, moderate chronic obstructive airways disease exacerbated. The investigator assessed the event as not related to study medication. The event was ongoing when the subject died. On 28 December 2001 the subject was evaluated for abdominal distention and diarrhea. The abdomen showed bowel sounds with diffuse tympany without guarding or rebound. Abdominal X-ray showed nonspecific gaseous distention of both the small and large intestine with a large amount of gas in the ascending and transverse colon. On 29 December 2001, there was leukocytosis. Colonoscopy to the level of the hepatic flexure showed no pseudomembranes. On 07 January 2002, the subject experienced sepsis NOS (verbatim term: bacterial septicemia with fatal outcome). Symptoms included dehydration, cough, sputum production, and failure to thrive. The onset of symptoms was sudden and they lasted for 24 hours. The subject was hospitalized for this event but was not seen by a cardiac specialist. The subject had a technically difficult echo with probable preserved overall LV function and biatrial enlargement. Chest X-ray on 07 January 2002, showed atelectasis at the left base with possible small left sided pleural effusion but without infiltrate. The investigator assessed the event to be serious, of severe intensity and not related to study medication or to cardiac return. The subject died on 08 January 2002. The event of sepsis was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Rocephin, Tequin, Minitran, Theo-24, Pentasa, Altace, Prednisone, Tazac, ASA, Lasix and Lupron.

Other deaths

3014/1921/002

Subject 1921/002 (AMC), a 68-year-old white male with a medical history of diabetes, hypertension and previous smoking (cigarettes 2½ packs/day for 30 years until 10 years ago), was enrolled in the study on 17 January 2002, with CAP. On 18 January 2002, the subject experienced serious mild pneumonia aggravated (verbatim term: worsening of pneumonia) that was not related to study medication and required hospitalization. Study medication was discontinued, with no doses being taken that day. The event resolved on 01 February 2002 and the subject recovered without sequelae. Further information on this subject was obtained through follow-up, but not included in the clinical database. The subject underwent V/Q scan of the lungs, which revealed that he had moderate probability for pulmonary embolus treated with heparin. Venous Doppler of the lower extremities was negative. A CAT scan of the chest revealed osteolytic lesions involving the sternum, left pubic rami and right aspect of the sacrum, suggestive of osseous metastases. The subject also had consolidation involving the left lower lobe with a

questionable mass surrounding the left lower bronchus, bilateral pleural effusions and right lower lobe subsegmental atelectasis. Based on these findings it was thought the subject had a metastatic cancer. He was seen by a pulmonologist and underwent bronchoscopy and bronchoalveolar lavage, which revealed a poorly differentiated adenocarcinoma. The subject was seen by an oncologist. A bone scan revealed metastatic lesions in the lumbar spine and the left pubic rami and right aspect of the sacrum. The subject was a poor candidate for chemotherapy and he refused radiation therapy. He was discharged on 01 February 2002 with a poor prognosis, to a residential facility and then to a hospice. He subsequently died on 22 February 2002. As death occurred remote to treatment this was not reported as an SAE and the investigator's assessment of relationship was not obtained.

3014/1696/015

Subject 1696/015 (AMC), an 80-year-old white female, with a medical history of coronary artery disease, congestive heart failure, cardiac arrhythmia, unstable angina, ASVD, hypertension and fatigue was enrolled in the study with CAP on 20 December 2001. The cardiac disease was ongoing at time of study entry. She had had an ECG within the previous year. The subject completed the treatment on 30 December 2001. Twenty-three days post-treatment, the subject was hospitalized for an aortic aneurysm (verbatim term: thoracic aneurysm). Associated symptoms included chest pain and shortness of breath, lethargy was also present and blood pressure was 40/20. The onset of symptoms was sudden. A CT-scan of the chest confirmed the diagnosis of thoracic aneurysm. The subject died due to the event on 25 January 2002. The investigator assessed the event to be serious, of severe intensity, and not related to study medication. The event was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Hyzaar, Evista, Prevacid, Darvocet, calcium, multivitamins, Rocephin and Dexamethasone.

3014/0249/070

Subject 0249/070 (AMC group), an 80-year-old white female, with a medical history of hypertension, hypothyroid, chronic obstructive pulmonary disease (COPD), coronary artery disease and loss of consciousness and DJD was enrolled in the study with CAP on 18 December 2001. On 22 December 2001, the subject experienced pneumonia aggravated and on 23 December 2001, the subject experienced respiratory failure (excl neonatal) The subject was hospitalized. The subject reported shortness of breath over the prior 4 to 5 days and chills 2 days prior to admission. She developed a non-productive cough and denied any chest pain or dependent edema. She was intubated and treated with diuretics, iv antibiotics and inhaled beta-agonists. Several attempts to extubate were unsuccessful and the subject required a tracheotomy. Her initial congestive heart failure improved and she remained stable after initial treatment of coronary artery disease. During hospitalization she experienced marked exacerbations and remissions of acute tracheobronchitis and ventilator dependent respiratory failure. She was treated for recurrent sepsis with various organisms, and she underwent excision of a questionably phlebotic site on her right forearm. Repeat echocardiograms showed no evidence of clear valvular vegetation suggestive of endocarditis and her fever ultimately resolved. The remainder of her hospitalization was marked by progressive worsening respiratory failure and worsening pulmonary status. She developed renal failure from progressive multisystem organ failure. Associated symptoms included shortness of breath. An ECG showed moderately impaired left ventricular systolic function and she was diagnosed with non-Q wave myocardial infarction. The investigator assessed the event to be serious as it resulted in death, of severe intensity, and not related to study medication. The subject died on 05 March 2002. The expiration diagnoses were respiratory failure from end-stage COPD with recurrent pneumonia and sepsis,

Staphylococcus aureus sepsis, acute renal failure, coronary disease, ischemic cardiomyopathy, history of hypertension and history of hypothyroidism. Respiratory failure was an AESI but was not adjudicated as a confirmed safety endpoint by the CEC. Concomitant medications were Chlorazepate, Levothyroid, Ziac and Estradiol.