Aventis Pharma

KETEK™ (telithromycin)

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EXECUTIVE SUMMARY

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

- Community-acquired pneumonia (CAP)
- Acute exacerbation of chronic bronchitis (AECB)
- Acute sinusitis (AS)
- Tonsillitis/Pharyngitis (T/P) due to Group A beta-hemolytic streptococcus (GABHS)

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,* and *Streptococcus pyogenes,* as well as atypical, *Mycoplasma pneumoniae,* and intracellular pathogens such as *Legionella pneumophila* and *Chlamydia pneumoniae*.

The choice of antimicrobial regimens for the indications listed above is complex because of the varied classes of pathogens and the emergence of resistance to many of the older agents. Beta-lactams, a cornerstone of outpatient RTI therapy, are inactive against beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*; they have no activity against atypical pathogens and are increasingly threatened by the emergence of penicillin G resistance among *S. pneumoniae*. Fluoroquinolones have variable activity against *S. pneumoniae*, and their widespread use for common infections poses concerns about the long-term use of these drugs due to emergent resistance.

The recently recognized increase in the prevalence of erythromycin A resistance now threatens the utility of this class [36,83]. In 1999, 20.3% of *S. pneumoniae* strains tested were resistant to erythromycin A in the US according to the Active Bacterial Core Surveillance (ABCs) Report, Emerging Infections Program Network [14] *(*www.cdc.gov/ncidod/dbmd/abcs *)*. While there has been some debate about the clinical importance of this rise in in vitro resistance [6,61], there are an increasing number of reports of adverse clinical outcomes in patients with erythromycin A-resistant *S. pneumoniae* who were treated with macrolides [13,35,45,48,52,79]. Because most of these macrolide-resistant *S. pneumoniae* are resistant to most beta-lactams, cotrimoxazole, and tetracyclines, there remain few options for oral therapy in patients infected with these strains.

General characteristics of telithromycin (see *Section 3, Microbiology*)

Telithromycin is the first in a new chemical class of antibacterial agents, the ketolides. It is derived from erythromycin A but has three structural features which result in a unique mechanism of action. It has a 3-keto function that replaces the alpha L-cladinose, which was long thought to be essential for antibacterial activity, a C_{11}-C_{12} carbamate, and an aryl alkyl side chain. Telithromycin binds to domain II of the 23S rRNA of the 50S ribosomal subunit and interferes with assembly of the 30S ribosomal subunit. Telithromycin also exhibits additional ribosomal activity associated with macrolides: binding to domain V of the 23S rRNA and disruption of assembly of the 50S ribosomal subunit. This novel mechanism of action results in excellent activity against macrolide-sensitive strains and maintains activity against macrolide-resistant strains of *S. pneumoniae* ([40], available in *Appendix 1. Relevant references*). Telithromycin has an antibacterial spectrum of activity that is well suited to the treatment of outpatient RTIs. It is active against the major organisms encountered in

these infections, including *S. pneumoniae* (regardless of resistance phenotype), *H. influenzae*, *M. catarrhalis*, *S. aureus*, *S. pyogenes*, anaerobic bacteria, and atypical pathogens such as *M. pneumoniae* and intracellular pathogens such as *L. pneumophila* and *C. pneumoniae*.

In vitro activity (see *Section 3, Microbiology*)

Activity against *S. pneumoniae* is crucially important for a therapy for RTIs, both because of the prevalence of this pathogen and because this pathogen is more likely to be associated with comorbid sequelae than other respiratory pathogens.

Telithromycin is highly active in vitro against strains of *S. pneumoniae* sensitive to erythromycin A and penicillin G, as shown in the table below. Telithromycin retains activity against penicillin G-intermediate resistant isolates, penicillin G-resistant isolates (penicillin MIC >2 μg/mL), and erythromycin A isolates with MLS_B or efflux-type resistance as well as quinolone-resistant isolates.

Table ES-1. MIC values for telithromycin against *S. pneumoniae* strains

Strain of *S. pneumoniae:*	**N**	**MIC_{50} range**	**MIC_{90} range**
Penicillin G susceptible (Pen-S)	1495	0.004 – 0.06	0.004 – 0.06
Penicillin G intermediate (Pen-I)	365	0.01 – 0.03	0.01 – 0.06
Penicillin G resistant (Pen-R) [a]	867	0.004 – 0.12	0.007 – 2.0
Erythromycin A susceptible (Ery-S)	491	0.001 – 0.06	0.001 – 0.06
Erythromycin A resistant (Ery-R)	455	0.0001 – 0.06	0.01 – 2.0
Quinolone resistant (Quinolone-R) [b]	41	0.01 – 0.03	0.03 – 0.06

[a] Includes macrolide-resistant strains.
[b] Includes macrolide-susceptible and macrolide-resistant strains. Telithromycin activity is independent of quinolone MIC values.

Therapy for community-acquired RTIs must be effective against all major pathogens, including common, atypical and intracellular pathogens, associated with these infections. The table below shows the high in vitro activity of telithromycin against the pathogens most frequently causative of these infections.

Table ES-2. MIC values for telithromycin against pathogens associated with community-acquired RTIs

Pathogen	**N**	**MIC_{50} range (μg/mL)**	**MIC_{90} range (μg/mL)**
H. influenzae	2300	0.025 – 2.0	0.5 – 4.0
M. catarrhalis	1108	0.02 – 0.25	0.03 – 0.5
S. pyogenes	1145	≤0.008 – 0.03	0.01 – 0.06
S. aureus[a]	2263	0.06 – 0.12	0.12 – 0.25
C. pneumoniae[b]	23	0.01 – 2.0	0.03 – 2.0
L. pneumophila	136	0.01 – 0.06	0.03 – 0.12
M. pneumoniae	90	0.001 – 0.005	0.001 – 0.005

[a] For *S. aureus* susceptible to erythromycin A or resistant to erythromycin A by an MLS_B inducible mechanism of resistance. When a constitutive MLS_B mechanism of resistance is harbored by a *S. aureus* strain, the telithromyci MIC is above 16 μg/mL.
[b] *C. pneumoniae*: MIC(μg/mL) and MCC (μg/mL)

Clinical pharmacokinetics and dose determination (see *Section 5, Clinical pharmacokinetics and dose determination*)

After oral administration, absorption of telithromycin is almost complete (90%), and the absolute bioavailability is 57% in both young and elderly subjects. The rate and extent of absorption are not influenced by food. Mean maximum concentration (C_{max}) of telithromycin in plasma is 1.9 µg/mL after a single oral dose of 800 mg, and 2.27 µg/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 µg/mL). Telithromycin has a terminal half-life (after multiple dosing) 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 µg/mL, and C_{max} in white blood cells of healthy subjects was 83 µg/mL, with a substantial concentration, 8.9 µg/mL, at 48 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 dose, and three other metabolites each represent 3% or less. None of these metabolites contribute appreciably to the clinical antibacterial activity of telithromycin.

Prior to entering the systemic circulation, about 33% of the administered telithromycin is metabolized. The absorbed telithromycin is eliminated via multiple pathways, with 7% excreted unchanged in feces by biliary and/or intestinal secretion, 13% excreted unchanged in urine by renal excretion, and 37% metabolized by the liver.

The overall metabolism of telithromycin accounts for 70% of the dose (33% presystemic, 37% systemic), and is mediated by CYP3A4- and non-CYP3A4-mediated pathways to approximately equal degrees. The multiplicity of elimination pathways for telithromycin suggests that significant impairment of a single pathway is unlikely to have a clinically relevant effect on systemic exposure to telithromycin because of the availability of compensatory pathways. This principle has been verified for a number of populations of special interest.

The observed pharmacokinetic profile in elderly patients with RTIs, in subjects with hepatic impairment, and in subjects with renal impairment was not substantially different from that of young and/or healthy subjects, as was anticipated (exposure did not exceed 2-fold in any of these populations).

Phase I studies have shown that the risk of increased telithromycin exposure due to inhibition of CYP3A4 is minimal. A potent inhibitor such as ketoconazole results in only a 1.5-fold increase in the C_{max} of telithromycin in plasma, and a 2-fold increase in AUC.

Telithromycin, like clarithromycin, has been shown to increase the plasma concentrations of drugs metabolized by CYP3A4, such as cisapride, simvastatin, and midazolam. Caution is therefore advised, as with macrolides, if telithromycin is administered concomitantly with CYP3A4 substrates that have a narrow therapeutic margin. As with clarithromycin, use of telithromycin with cisapride or pimozide is contraindicated. There were no clinically relevant interactions between telithromycin and theophylline or warfarin.

The mouse thigh infection model with *S. pneumoniae* (Craig) was used as a pharmacokinetic/ pharmacodynamic model to support selection of the telithromycin dosing regimen. Over 24 hours, the effective dose of telithromycin is independent of the dosing frequency, and the efficacy is concentration-dependent rather than time-dependent. The key parameters determining efficacy are the

AUC/MIC and C_{max}/MIC ratios. The peak concentrations in respiratory tissue are well above the MIC_{90} of the targeted pathogens, and the excellent tissue penetration and maintenance of tissue concentrations favor a prolonged effect at the site of infection. The favorable pharmacokinetic profile, combined with potent intrinsic antibacterial activity, permits once-daily dosing and a shortened treatment duration of 5 days in RTIs such as AECB, acute sinusitis, and tonsillitis/pharyngitis caused by GABHS.

Clinical efficacy (see *Section 6, Efficacy by indication*)

Thirteen Phase III clinical trials, 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, most given more than once daily (see table below). In addition, the analysis of outcomes in CAP patients with erythromycin or penicillin resistant *S. pneumoniae* includes data obtained in a Phase II dose comparison study carried out in Japan (Study 2105). As agreed with the FDA, other data from this study will not be presented.

Table ES-3. 13 Phase III telithromycin clinical trials

	Study	Telithromycin		Comparator		
Indication	**No.**	**Dose**	**Duration**	**Drug/**	**Dose**	**Duration**
CAP	3000	800 mg qd	7-10 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[a]	800 mg qd	7-10 d	TVA	200 mg qd	7-10 d
	3009OL [b]	800 mg qd	7-10 d	-	-	-
	3010	800 mg qd	7 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
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
T/P	3004	800 mg qd	5 d	PEN VK	500 mg tid	10 d
	3008	800 mg qd	5 d	CLA	250 mg bid	10 d

CAP = community-acquired pneumonia, AECB = acute exacerbation of chronic bronchitis, AS = acute sinusitis, T/P = tonsillitis/pharyngitis. AMX=amoxicillin; CLA=clarithromycin; TVA=trovafloxacin; AMC=coadministration of amoxicillin and clavulanic acid; CXM=cefuroxime axetil; PEN VK=penicillin VK

[a] 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.

[b] No subjects from Study 3009OL were enrolled in Study 3009.

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

- Safety population: All subjects who received at least one dose of study medication and had at least one safety assessment following randomization.
- mITT (modified intent-to-treat population): All subjects with disease who received at least one 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 13 Phase III trials by indication is given in the following table.

Table ES-4. Number of telithromycin-treated subjects in 13 Phase III trial populations by indication

Indication	Population			
	Safety	mITT	PPc	PPb
CAP	1415	1373	1132	344
AECB	340	342	255	64
Acute sinusitis	1083	980	731	253
Tonsillitis/pharyngitis	427	430	265	265
TOTAL	**3265**	**3125**	**2383**	**926**

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 trials, the clinical cure rates for clinically evaluable telithromycin-treated subjects (PPc, the primary analysis population) 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 prematurely discontinued due to safety concerns about trovafloxacin, the comparator.

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

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]
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]
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]
						[-8.4; 13.3] [c]
	3011	161/189	(85.2)	73/89	(82.0)	[-7.1; 13.4] [c]
T/P:	3004	109/115	(94.8)	112/119	(94.1)	[-6.1; 7.4]
	3008	139/150	(92.7)	123/135	(91.1)	[-5.5; 8.6]

Comparators = amoxicillin (Study 3001); amoxicillin/clavulanic acid (Studies 3003 and 3005); clarithromycin (Studies 3006 and 3008); cefuroxime axetil (Studies 3007 and 3011); penicillin VK (Study 3004); 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.

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 (13 Phase III studies)

Key pathogen	n/N (%) Subjects							
	CAP		AECB		Acute sinusitis		Tonsillitis/ pharyngitis	
S. pneumoniae	165/174	(94.8)	12/14	(87.5)	82/91	(90.1)	0/0	(0)
H. influenzae	95/105	(90.5)	17/25	(68.0)	57/64	(89.1)	0/0	(0)
M. catarrhalis	26/30	(86.7)	10/10	(100)	16/18	(88.9)	0/0	(0)
S. aureus	15/19	(78.9)	2/2	(100)	22/23	(95.6)	0/0	(0)
S. pyogenes	0/0	(0)	0/0	(0)	5/5	(100)	248/265	(93.6)
C. pneumoniae	32/34	(94.1)	10/11	(90.9)	0/0	(0)	0/0	(0)
M. pneumoniae	30/31	(96.8)	1/1	(100)	0/0	(0)	0/0	(0)
L. pneumophila	12/12	(100)	0/0	(0)	0/0	(0)	0/0	(0)

In CAP (*Section 6.4.1, Community-acquired pneumonia*), telithromycin administered orally 800 mg once a day for 7 to 10 days has a comparable efficacy to a broad range of active comparators administered more than once daily for 10 days (amoxicillin high dosage, 1 g three times a day; clarithromycin 500 mg twice a day), and against trovafloxacin 200 mg once a day. Particularly noteworthy results are:

- Telithromycin demonstrated efficacy in the most vulnerable patients in the community: the elderly (90.3%, 139/154 cases cured) and subjects with pneumococcal bacteremia (91.5%, 43/47 cases cured). In addition, excellent results have been obtained in subjects with a diagnosis of *S. pneumoniae* infections (94.8%, 165/174 cases cured) and *Legionella* infections (100%, 12/12 cases cured), which are the infections most frequently associated with morbidity. This is particularly important because increasing numbers of elderly patients and patients at high risk are being treated as outpatients within the community.
- High efficacy was also obtained in resistant *S. pneumoniae* isolates: For penicillin G-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 16/19 isolates. For erythromycin A-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 21/25 isolates. When only single pathogen infections are considered, 11/12 of *S. pneumoniae* resistant to penicillin G and 15/17 of *S. pneumoniae* resistant to erythromycin A were clinically cured.

Telithromycin can therefore be used effectively in the therapy of pneumonia in outpatients.

In AECB (*Section 6.4.2, Acute exacerbation of chronic bronchitis*), 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,) given 2 to 3 times daily for 10 days. Efficacy was maintained in patients more likely to require hospitalization such as the elderly and patients with COPD, even with significant obstruction (FEV_1/FVC <60%).

In acute sinusitis (*Section 6.4.3, 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 it was also demonstrated in two studies that 10 days of treatment with telithromycin was comparable to 5 days of telithromycin treatment. When only single pathogen infections are considered, 9/11 of *S. pneumoniae* resistant to penicillin G and 13/16 of *S. pneumoniae* resistant to erythromycin A were clinically cured. A 5 day regimen has the advantage of reducing the

likelihood of missing doses at the end of a prolonged treatment period, which could promote the selection of resistant pathogens.

In tonsillitis/pharyngitis (*Section 6.4.4, Tonsillitis/pharyngitis*) due to Group A beta hemolytic streptococcus in patients aged 13 years or older, telithromycin 800 mg given once daily for 5 days was equivalent in clinical and bacteriological efficacy to 10 days of penicillin VK, the standard first line therapy for this indication, and to 10 days of clarithromycin treatment, the standard therapy for subjects allergic to beta-lactams.

Clinical safety (see *Section 7, Safety*)

A total of 4937 subjects were evaluated for safety in the 13 Phase III trials (9 controlled and 4 uncontrolled): 3265 subjects received telithromycin (2045 in comparative trials) and 1672 subjects received comparator drugs. Rates for adverse events are based on these 13 trials, with emphasis on rates for the 9 controlled studies.

Telithromycin is generally well tolerated. The rates of all treatment-emergent adverse events (TEAEs), serious adverse events and discontinuations due to adverse events were comparable between telithromycin and comparators. No specific risk was associated with age group, sex, race, or indication. Safety was assessed in 372 subjects ≥65 years of age and in 95 subjects ≥13 to 18 years of age.

Frequencies of possibly related TEAEs in controlled Phase III studies are summarized in the table below.

Table ES-7. Frequency of possibly related TEAEs in controlled Phase III studies [a]

Coded Term	Number (%) of Subjects	
	Possibly related TEAEs	
	Telithromycin N=2045	Comparator N=1672
Total	**712 (34.8)**	**465 (27.8)**
Diarrhea	272 (13.3)	158 (9.4)
Nausea	166 (8.1)	64 (3.8)
Headache	45 (2.2)	51 (3.1)
Dizziness	73 (3.6)	26 (1.6)
Vomiting	57 (2.8)	24 (1.4)
Dyspepsia	39 (1.9)	20 (1.2)
Abdominal pain	32 (1.6)	19 (1.1)
Rhinitis	1 (0.05)	1 (0.1)
Taste perversion	34 (1.7)	35 (2.1)
Upper respiratory infection	1 (0.05)	3 (0.2)

[a]Based on a frequency of at least 2.0% for all TEAEs.

Because telithromycin, a ketolide, is derived from macrolide antibiotics, gastrointestinal safety, hepatic safety, effect on cardiac repolarization, and possible drug-drug interactions were potential

safety issues. Each was thoroughly examined in the clinical development program in addition to the overall adverse event profile.

Gastrointestinal safety *(*see *Section 7.2.4, TEAEs of special interest)*

The incidences of gastrointestinal drug-related TEAEs in the 9 active-controlled Phase III studies are shown below:

Table ES-8. Frequency of severe and discontinuations due to possibly related diarrhea, nausea and vomiting TEAEs in 9 controlled Phase III studies

Coded term	Number (%) of Subjects	
	Telithromycin (N=2045)	Comparator (N=1672)
Diarrhea		
Possibly related TEAEs	272 (13.3)	158 (9.4)
Severe possibly related TEAEs	18 (0.9)	5 (0.3)
Discontinuation due to TEAEs	19 (0.9)	13 (0.8)
Nausea		
Possibly related TEAEs	166 (8.1)	64 (3.8)
Severe possibly related TEAEs	13 (0.6)	4 (0.2)
Discontinuation due to TEAEs	18 (0.9)	9 (0.5)
Vomiting		
Possibly related TEAEs	57 (2.8)	24 (1.4)
Severe possibly related TEAEs	8 (0.4)	4 (0.2)
Discontinuation due to TEAEs	19 (0.9)	6 (0.4)

The incidence of possibly related treatment-emergent diarrhea in telithromycin-treated subjects was higher (13.3%) than that for pooled-comparator subjects (9.4%); this incidence was higher than that observed for clarithromycin (7.3%) but was lower than that of subjects treated with amoxicillin/clavulanic acid (18.0%). These events were generally mild or moderate in intensity. Only 2.6% of subjects treated with telithromycin in the controlled Phase III studies discontinued their treatment due to gastrointestinal related adverse events. It is noteworthy that 0.9% of subjects treated with telithromycin discontinued treatment due to diarrhea, compared with 2.4% of subjects treated with amoxicillin/clavulanic acid alone and 0.8% of subjects treated with all active comparators (including amoxicillin/clavulanic acid).

Hepatic safety *(see Section 7.4.2.2, Hepatic adverse events)*

The frequency of ALT ≥3 times the upper limit of the normal range (ULN) in the controlled Phase III studies at baseline and during treatment is summarized in the table below. Because patients with CAP are known to have a higher incidence of disease-related abnormal liver functions, data for CAP and non-CAP studies are presented.

Table ES-9. Frequency of subjects with normal and elevated ALT values (≥3x ULN) at baseline and during treatment in the 9 controlled Phase III studies

ALT status at baseline	n/N (%) Subjects with elevated ALT during treatment	
	Telithromycin	Comparator
CAP studies		
Normal	5/395 (1.3)	3/388 (0.8)
Elevated	10/101 (9.9)	13/96 (13.5)
Non-CAP studies		
Normal	3/1251 (0.2)	2/936 (0.2)
Elevated	14/182 (7.7)	12/130 (9.2)

The incidences of elevated ALT ≥3xULN were similar in the telithromycin and comparator groups. As anticipated, the frequency of patients with elevated ALT values was higher in CAP subjects than in non-CAP subjects. In the CAP and non-CAP studies, the incidence of elevated ALT values during treatment with telithromycin or comparator was higher in subjects with elevated ALT values at baseline. No subjects in either the CAP or the non-CAP studies had ALT or AST ≥3xULN together in combination with total bilirubin ≥1.5xULN.

One patient treated with telithromycin had a serious adverse event of hepatitis that was considered by the investigator to be possibly related to the study medication. However, this patient had a second episode of hepatitis nine months later, which occurred in the absence of telithromycin treatment. A full description of this patient can be found in *Appendix 19. Narratives for subjects treated with telithromycin who experienced serious hepatic events*.

Electrocardiographic QT interval *(see Section 7.5, Assessment of the effects of telithromycin administration on cardiac repolarization)*

Because telithromycin has structural similarities to erythromycin, a comprehensive assessment of the effects on cardiac repolarization was conducted. Data were obtained from 25 preclinical studies, 8 clinical pharmacology studies, and 10 Phase III studies, including almost 2200 subjects.

This extensive analysis revealed the following:

- In patients with RTIs, the mean change in electrocardiographic QTc interval (QT interval corrected for heart rate by the Bazett formula [see *Section 7.5.3.1, Electrocardiographic QT interval findings in patients receiving telithromycin*]) following treatment with telithromycin was small (~1 ms).
- A shallow relationship of telthromycin concentration to QTc interval was established across a wide range of observed plasma concentrations.
- There was no difference in the frequency of QTc outliers (≥500 ms) between telithromycin and macrolide and non-macrolide antibiotics.
- An extensive analysis of at-risk subpopulations did not reveal a propensity for enhanced effect on cardiac repolarization in such patients.
- No increase in the incidence of cardiovascular adverse events was noted when compared to macrolide and non-macrolide active comparators.

Conclusions

Telithromycin is the first in a new class of antimicrobial agents, the ketolides. It has a novel mechanism of action that results in outstanding activity against sensitive strains of *S. pneumoniae*, as well as potent activity against macrolide- resistant strains. *S. pneumoniae* is the pathogen most associated with risk of morbidity and mortality in community-acquired RTIs. Reliable activity against this pathogen is the most important feature of an antibiotic for treatment of these infections. In addition to its outstanding activity against *S. pneumoniae*, telithromycin is active against the full spectrum of respiratory pathogens, both common and atypical, including *L. pneumophila*, which is associated with mortality in pneumonia. Its activity against penicillin- and erythromycin-resistant pathogens is crucial in this age of increasing resistance. As would be expected from its mechanism of action, there is no cross resistance to beta lactams or quinolones.

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. This assures efficacy in infected tissues as well as in undetected bacteremia in outpatients. The brief, simple regimen will promote patient compliance, an important factor in reducing further pressure for development of resistance due to missed doses at the end of prolonged therapy [39].

The clinical efficacy of telithromycin was studied in 3125 patients with the following community-acquired RTIs: community acquired pneumonia (CAP, 1,373 patients), acute bacterial sinusitis (980 patients), acute exacerbation of chronic bronchitis (AECB, 342 patients), and tonsillitis/pharyngitis due to *S. pyogenes* (430 patients). Excellent efficacy was demonstrated in all patient populations and against all key pathogens in each of the clinical trials in the four proposed indications. Telithromycin was effective in treating CAP subjects with pneumococcal bacteremia, with *Legionella pneumophila*, in the elderly in both CAP and AECB, in AECB subjects with severe bronchial obstruction, and in subjects at greater risk for morbid sequelae. Telithromycin demonstrated efficacy in AECB, acute sinusitis, and tonsillitis/pharyngitis with a treatment regimen of 5 days.

Telithromycin is effective in vitro against macrolide-, beta-lactam-, and quinolone-resistant *S. pneumoniae*. Clinical efficacy in infections due to *S. pneumoniae* resistant to penicillin G or erythromycin was demonstrated with overall cure rates of 91.7% (11/12 subjects) in CAP subjects with single pathogen infections of penicillin G-resistant strains and 88.2% (15/17 subjects) for erythromycin A-resistant strains. Similarly, efficacy against penicillin G- and erythromycin A-resistant *S. pneumoniae* was also demonstrated in patients with acute sinusitis.

The safety of telithromycin was assessed in 3265 patients with RTIs. This population included a broad spectrum of patients with underlying diseases, who received a wide variety of concomitant medications as well as elderly patients with additional risk factors for morbidity and mortality. Telithromycin exhibited an excellent safety profile, comparable to that of other marketed outpatient antibiotics and in particular to that of the macrolides. The incidence of gastrointestinal adverse events, while slightly higher than that of the new macrolides, falls within the range of marketed antibiotics. There is no evidence of excess risk of hepatic adverse events. Treatment with telithromycin, which has a weak inhibitory effect on the cardiac Ikr channel, was associated with a small (approximately 1 ms) change in the electrocardiographic QT interval (corrected for heart rate). No excess in adverse cardiovascular events was observed with telithromycin administration.

Telithromycin is metabolized in part by cytochrome P450 (CYP3A4). Concomitant administration with a potent inhibitor of CYP3A4 (ketoconazole) was associated with a modest elevation in plasma concentrations in a clinical pharmacology study. No excess of adverse events was observed in telithromycin treated patients who received concomitant therapy with CYP3A4 inhibitors.

Thus, telithromycin is highly effective in the treatment of outpatient RTIs. It has excellent activity against *S. pneumoniae*, including macrolide- and penicillin G-resistant strains, and all the other major common, intracellular and atypical pathogens. Telithromycin provides an alternative to quinolones for physicians who are increasingly concerned about beta-lactam- and macrolide-resistant *S. pneumoniae* and atypical and intracellular pathogens in community respiratory infections. Telithromycin can be given in a convenient regimen and can be given to patients intolerant to beta lactams or quinolones. Few oral antibiotics fulfill all of these requirements. Telithromycin will therefore be an important addition to the outpatient antimicrobial therapeutic armamentarium.

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LIST OF ABBREVIATIONS

AECB	Acute exacerbation of chronic bronchitis
ALT	Alanine transaminase (also referred to as SGPT)
AMC	Coadministration of amoxicillin + clavulanic acid
AS	Acute sinusitis
AST	Aspartate transaminase (also referred to as SGOT)
AMX	Amoxicillin
AUC	Area under the plasma concentration *vs* time curve
AUC_{ss}	Area under the curve at steady state
BAL	Bronchial alveolar lavage
BCYEα	Buffered charcoal yeast extract
bmITT population	Bacteriologically evaluable modified intent to treat population: all mITT subjects with a bacteriological sample at pretherapy/entry containing at least one pathogen considered by the investigator to be responsible for infection
bid	Two times daily
BYE	Buffered yeast extract agar
CAP	Community-acquired pneumonia
C/E ratio	Intracellular/extracellular ratio
cfu	Colony forming units
CHO	Chinese hamster ovary
CI	Confidence interval
CLA	Clarithromycin
CL_{CR}	Creatinine clearance
CL_R	Renal clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CMI	Clinical Microbiology Institute, Inc
CNALV	Clinically noteworthy abnormal laboratory value
COPD	Chronic obstructive pulmonary disease
CXM	Cefuroxime axetil
CV	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram
ED_{50}	Median effective dose
ELISA	Enzyme-linked immunosorbent assay
ENT	Ear, nose, and throat
Ery-A	Erytthromycin A
Ery-R	Erythromycin A-resistant
Ery-S	Erythromycin A-susceptible

EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GABHS	Group A beta-hemolytic streptococcus
HDL	High density lipoprotein
HTM	*Haemophilus* test medium
IC_{50}	50% inhibitory concentration
Ig	Immunoglobulin
INR	International normalized ratio
ITT	Intent to treat (all subjects who received at least one dose of study medication)
iv	Intravenous
K_i	Inhibition equilibrium constant
LDL	Low density lipoprotein
LFT	Liver function test
LPTV	Late posttherapy visit
MCC	Minimal chlamydicidal concentration
MIC	Minimum inhibitory concentration
$MIC_{50/90}$	Minimum inhibitory concentration at 50%/90%
mITT population	Modified intent-to-treat population: all subjects with clinical signs and symptoms of the disease who received at least one dose of study medication, as treated
MLS_B	Macrolide lincosamine streptogramine-B
MSSA	Methicillin-susceptible *S. aureus*
NA	Not applicable
NCCLS	National Committee for Clinical Laboratory Standards
ND	Not determined
NDA	New drug application
NOAEL	No observed adverse effect level
OL	Open label
PAE	Postantibiotic effect
PCR	Polymerase chain reaction
PD_{50}	Protective dose at 50%
PEN	Penicillin VK (comparator in study 3004)
Pen-I	Penicillin G-intermediate resistance
Pen-R	Penicillin G-resistant
Pen-S	Penicillin G-susceptible
PMN	Polymorphonuclear neutrophils
po	Oral (per os)
PP population	Per protocol population
PPb population	Bacteriologically evaluable per protocol population: all PPc subjects who had a causative pathogen isolated at pretherapy/entry

PPc population	Clinically evaluable per protocol population: all mITT subjects excluding those with major protocol violations and/or indeterminate responses
PRSP	Penicillin G-resistant *Streptococcus pneumoniae*
qd	Once daily
QTc	QT interval corrected according to Bazett formula
QTf	QT interval corrected according to Fridericia formula
QTn	QT interval corrected according to new formula
rRNA	ribosomal ribonucleic acid
RTI	Respiratory tract infection
SD	Standard deviation
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TEL	Telithromycin
tid	Three times daily
t_{max}	Time of occurrence for maximum (peak) drug concentration
TOC	Test of cure
TVA	Trovafloxacin
UK	United Kingdom
ULN	Upper limit of normal range
US	United States
VLDL	Very low density lipoprotein
WBC	White blood cell

1. BACKGROUND AND MEDICAL NEED

Clinical background

Respiratory tract infections (RTIs) are the most common infectious diseases observed in outpatients. Treatment of community respiratory infections remains challenging in 2001 despite the availability of a variety of oral antibiotics. These infections are caused by several classes of organisms including common pathogens such as *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes* as well as the increasingly recognized atypical and intracellular microorganisms such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. It is challenging to find a single drug that is effective against all these organisms, particularly as many of them are becoming increasingly resistant to older agents.

The high level of beta lactamase production among *H. influenzae* and *M. catarrhalis* is well recognized as is the increasing prevalence of penicillin resistance among *S. pneumoniae*. These penicillin-resistant *S. pneumoniae* have been recently demonstrated to be resistant to other classes of antibiotics as well, including macrolides, sulfonamides, and tetracyclines giving rise to the concept of multi-drug-resistant pneumococci.

While penicillin resistance in *S. pneumoniae* has been acknowledged as an epidemiologic and clinical problem for at least 10 years, macrolide resistance is a more recent issue. There were few reports of in vitro macrolide resistance prior to the mid 1990's, but in 2000, CDC reported that 20.3% of US isolates of *S. pneumoniae* from sterile sites were resistant to erythromycin A [14]. Of note, a large fraction of these, 61%, were also highly penicillin resistant. There is considerable regional variation in erythromycin resistance but the temporal trend is consistent in most regions. In the Atlanta area Gay et al have reported that resistance to erythromycin A increased from 13% in 1994 to 31% in 1999 [36]. Strains of *S. pneumoniae* which are erythromycin resistant due to an efflux mechanism generally have minimum inhibitory concentrations (MICs) in the range of 2 to 16 μg/mL for erythromycin, azithromycin and clarithromycin with an increase of MIC in the past 4 years to higher levels of MICs (16 μg/mL) in some areas [36]. Those with resistance due to methylation (macrolide-lincosamine-streptogramine-B [MLS_B]) typically have MICs ≥64 μg/mL for erythromycin [36]. It is unlikely that treatment with the marketed macrolides could achieve levels exceeding these MICs in patients.

While there are numerous reports documenting the increasing prevalence of in vitro erythromycin-resistant *S. pneumonia*, it is more difficult to document the extent to which this constitutes a clinical problem. Because macrolide monotherapy is generally an outpatient regimen administered to patients without the benefit of bacteriologic documentation, there is limited literature about adverse outcomes in these patients. It is of interest that Lonks and Madeiros [52] were only able to identify 6 cases of adverse outcomes in macrolide-treated patients who had macrolide-resistant *S. pneumoniae* in their review of the literature prior to 1992. Since that time the frequency of such case reports has increased and last year, Kelley et al [48] reported that 4/41 patients hospitalized with pneumococcal bacteremia at their institution had macrolide-resistant isolates and had received prior oral macrolide therapy. Thus, recent literature supports the concept of macrolide resistance as an emerging clinical concern.

Macrolides have long been one of the mainstays of therapy for outpatient RTIs and the recent Infectious Diseases Society of America guidelines have recommended them for first-line therapy of community-acquired pneumonia (CAP) [7]. The increasing prevalence of macrolide resistance will erode the utility of these drugs. With many pneumococci resistant to erythromycin, penicillin,

cefotaxime, and other drugs, there remain few classes of oral antibiotics which can be used to treat these infections.

While seeking a broadly effective drug for treatment of these infections, the physician must remain aware of safety considerations and also attempt to identify a regimen that is simple, brief, and convenient in order to facilitate patient compliance. Failure to comply with antibiotic treatment may lead to therapeutic failure in the individual and may enhance the likelihood of emergent resistance in the community.

Rationale for development

A new antibiotic for the treatment of RTIs should cover all the major pathogens mentioned above and should also be active against strains of *S. pneumoniae* resistant to penicillin G and/or erythromycin A. Some new quinolones that are active in vitro against resistant strains of *S. pneumoniae* represent one of the answers to this medical need. However, their potential for selecting resistant gram-negative strains and *S. pneumoniae* strains, as well as questions over the safety of some recent quinolones, justify the development of other therapeutic alternatives.

Because of its spectrum of activity, telithromycin is a suitable candidate for therapy of adults with upper and lower RTIs, including those infections caused by common, atypical, and intracellular pathogens. Unlike currently marketed macrolides, telithromycin has in vitro activity against strains of *S. pneumoniae* resistant to beta-lactams, erythromycin A, and quinolones. Telithromycin has in vitro activity against *H. influenzae* similar to that of azithromycin, but has a higher plasma concentration in vivo. As a ketolide, telithromycin does not induce resistance to macrolides by an inducible MLS_B mechanism in vitro. In addition, telithromycin's spectrum of antibacterial activity is more tailored to respiratory tract pathogens than is the wider antibacterial spectrum of the new quinolones.

The pharmacokinetic profile of telithromycin demonstrates plasma exposures that reach or exceed the MICs of the target pathogens, particularly *S. pneumoniae*, the RTI pathogen most often associated with bacteremia (see *Section 2, Claimed indications*). It also demonstrates excellent tissue penetration and persistent therapeutic levels at the sites of infection in patients.

The balance of plasma and tissue levels achieved with telithromycin administration support a shortened treatment duration. Medical benefits of a shortened treatment duration include a shorter period of risk for drug-drug interactions and side effects, potentially improved compliance, and decreased induction of resistance, which could result from poor compliance with prolonged treatments (see [39], available in *Appendix 1. Relevant references*). Therefore, based on the pharmacokinetic properties of telithromycin and on the potential medical benefit of a shorter treatment duration, it was decided to test the efficacy and safety of a 5-day treatment duration in acute exacerbation of chronic bronchitis (AECB), acute sinusitis, and tonsillitis/pharyngitis caused by group A beta-hemolytic streptococci (GABHS).

Beginning in early 1998, the efficacy and safety of telithromycin administered orally have been investigated in 13 international/multicenter Phase III studies performed in subjects with CAP, AECB, acute sinusitis, or GABHS tonsillitis/pharyngitis. In addition, data from a Phase II study (Study 2105) carried out in Japan in 103 subjects with CAP have been evaluated with respect to subjects with penicillin G-resistant and erythromycin A-resistant *S. pneumoniae*.

The data and analyses contained in this Briefing Document have been provided to the FDA in the original NDA (submitted 28 February 2000), in the 4-month safety update (submitted 30 June 2000), in the NDA major amendment (submitted March 2001), or on request by the FDA during the assessment period.

2. CLAIMED INDICATIONS

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

Community-acquired pneumonia (treatment duration: 7 to 10 days) due to *S. pneumoniae*, including strains resistant to penicillin G and erythromycin A, *H. influenzae, M. catarrhalis, C. pneumoniae, L. pneumophila*, or *M. pneumoniae* in patients 18 years of age or older.

Acute bacterial exacerbation of chronic bronchitis (treatment duration: 5 days) due to *S. pneumoniae*, including strains resistant to penicillin G and erythromycin A, *H. influenzae, M. catarrhalis, 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 erythromycin A, *H. influenzae, M. catarrhalis*, or *S. aureus* in patients 18 years of age or older.

GABHS tonsillitis/pharyngitis (treatment duration: 5 days) due to *S. pyogenes* in patients 13 years of age or older.

3. MICROBIOLOGY

Telithromycin, a ketolide, is two- to four-times more active than clarithromycin against gram-positive cocci susceptible to erythromycin A, and retains activity against gram-positive cocci isolates with an underlying mechanism of resistance to erythromycin A. Telithromycin is active against other pathogens involved in RTIs, including atypical pathogens (*Mycoplasma pneumoniae*) and intracellular pathogens (*Legionella pneumophila*, *Chlamydia pneumoniae*). The dual mechanism of action on bacterial ribosomes is responsible for telithromycin activity.

The antibacterial spectrum and activity of telithromycin have been assessed by MIC determinations and experimental infections in rodents. Reported in vitro data were mainly obtained according to National Committee for Clinical Laboratory Standards (NCCLS) recommendations (North America) or national recommendations (Europe). For each bacterial species or genus, both the wild phenotype and isolates with different phenotypes of resistance to the major antibacterial agents (penicillin G, erythromycin A, fluoroquinolones) were tested. Activities were investigated against fresh clinical isolates and against stock collections of pathogens. Numerous centers were included in these studies, with most data deriving from experimental studies carried out in North America (the US and Canada), Western Europe, South Africa, Australia, and Japan.

3.1 Ketolides: A new chemical class

The need to overcome resistance, and particularly to provide activity against penicillin G- and/or erythromycin A-resistant *S. pneumoniae* clinical isolates, has driven the development of new compounds designed to overcome multidrug-resistant *S. pneumoniae*. The ketolides are a new class of drugs resulting from intensive research to discover novel antibacterials.

Ketolides are semisynthetic derivatives of erythromycin A. The word ketolide is derived from keto (3-keto group) and olide (lactone). The defining chemical characteristic of ketolides is a 3-keto function on erythronolide A instead of L-cladinose, which confers the following novel biological properties:

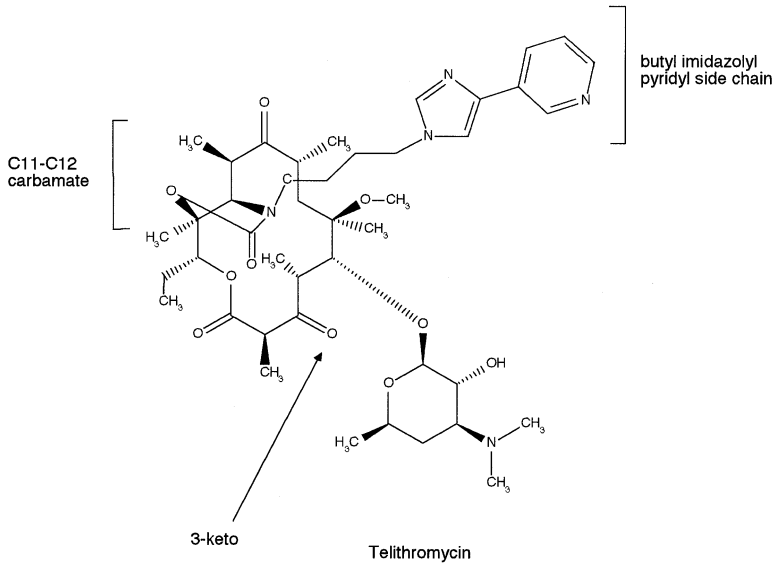
- High stability in acidic media, enhancing the ability of the drug to pass through the stomach. After 6-hours of contact in a solution of pH 1.0, more than 90% of the antibacterial activity of telithromycin remains [11].
- Inability to induce MLS_B resistance (see *Section 3.9.3, Inducible MLS_B resistance*). Ketolides also exhibit antibacterial activity against inducible *erm*-containing gram-positive cocci such as *S. aureus* and *S. pneumoniae*.

Substitution of the C_{11}-C_{12} hydroxyl groups of the erythronolide A ring by a carbamate residue results in additional beneficial properties when combined with the 3-keto function, as follows:

- The C_{11}-C_{12} carbamate residue enhances antibacterial activity when compared with erythromycin A, and confers the ability to overcome erythromycin-A resistance due to the efflux mechanism.
- The butyl imidazolyl pyridinyl side chain attached to the C_{11}-C_{12} carbamate residue is responsible for the antibacterial activities, mode of action, pharmacokinetics, intracellular uptake, accumulation, and efflux.

The chemical structure of telithromycin is shown below.

Figure 3-1. Chemical structure of telithromycin



3.2 Telithromycin mode of action

Erythromycin A, clarithromycin, and azithromycin prevent bacterial protein synthesis by binding to specific sites in the bacterial ribosome and interfering with the elongation of nascent polypeptide chains [56]. In addition, these compounds interfere with a second cellular process, the formation of the 50S ribosomal subunit [16].

Ribosomes are the functional units of translation. Bacterial ribosomes consist of ribonucleoprotein particles having a sediment coefficient of 70S. The 70S ribosome is composed of two subunits: 30S and 50S particles. The 30S subunit is made up of 16S ribosomal ribonucleic acid (rRNA) and 21 different proteins. The 50S subunit consists of 2 rRNA molecules: 23S rRNA and 5S rRNA, and 33 proteins. The main function of the 50S ribosomal subunit is to promote peptide bond formation. Six distinct structural domains have been found in the 23S rRNA, and 5S rRNA forms a structural link between domain II and domain V. Further, 5S rRNA may help in the proper juxtaposition of domain II and V in the ribosomal tertiary structure [54].

3.2.1 Dual interaction of telithromycin with domain V and domain II

Interaction with domain V

The interaction with domain V of 23S rRNA (at the peptidyl transferase loop), detected by the methodology known as footprinting, is comparable for 14- and 15-membered-ring macrolides and for

telithromycin. One specific nucleotide, adenine A-2058, is pivotal for the binding of macrolide-lincosamide and streptogramin B antibiotics at this site in domain V. The erythromolide A ring of ketolide docks into the same site of domain V of the 23S rRNA target through the dimethylamino group of the D-desosamine.

Interaction with domain II

The difference in affinity for the ribosome affects how 14- and 15-membered ring macrolides and telithromycin interact with A-752 in domain II of 23S rRNA. Telithromycin exhibits a strong interaction in the vicinity of the 752 hairpin of domain II, mainly due to the C_{11}-C_{12} carbamate side chain on the erythronolide A ring [40].

In contrast, erythromycin A cannot form a strong interaction with domain II. These differences in the interactions of erythromycin A and telithromycin with domain II are determined, at least in part, by the distance the drugs span from their domain V site. Structural activity studies demonstrated that the C_{11}-C_{12} carbamate residue in telithromycin plays an important role in the interaction at domain II.

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

In an erythromycin-A susceptible strain of *S. pneumoniae*, both erythromycin A and telithromycin are able to bind to the A2058 residue in domain V. However, because telithromycin additionally binds to the A752 residue in domain II of the pocket, telithromycin has a higher overall binding affinity compared with erythromycin A. In an *erm* -containing strain of *S. pneumoniae*, the A2058 binding site is modified by methylation, and erythromycin A can no longer bind efficiently. This results in the strain being rendered resistant to erythromycin A, and cross resistant to other available 14- and 15-membered ring macrolides. In contrast, the modification of A2058 by methylation does not render the strain resistant to telithromycin because, by virtue of its additional binding site at A 752 in domain II, telithromycin retains its affinity for the active site of the pocket. This explains why telithromycin retains activity against erythromycin A-resistant strains.

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

Erythromycin A has a second target for inhibition in susceptible cells. The assembly sequence leading to the formation of nascent 50S particles is interrupted by erythromycin A [17] and telithromycin.

Antibiotic binding at a specific receptor in the 50S precursor particle site inhibits subunit formation, and the incomplete particle is subject to degradation by cellular ribonuclease activities. This leads to the gradual depletion of functional ribosomes in the cell and to the accumulation of RNA oligonucleotides in cells. Inhibition of the assembly of the 50S ribosomal subunit is a lethal event for bacterial cells because of ribonuclease degradation of the ribosomal RNAs [16].

Telithromycin reduces formation of the smaller 30S subunit. This effect is not observed with available 14- and 15-membered ring macrolides [15]. The result is an additional mechanism for the lethal disruption of ribosomal subunit formation. It is possible that this mechanism may reinforce the bactericidal action of telithromycin, which is significantly more bactericidal than members of the macrolide class.

3.2.3 Telithromycin: affinity for bacterial ribosomes

Telithromycin binds approximately 10-fold more tightly than erythromycin A to MLS_B -sensitive ribosomes of *S. pneumoniae* and 20-fold more tightly for *S. aureus* ribosomes. The higher affinity of telithromycin for the ribosome is a function of the C_{11}-C_{12} side chain. Telithromycin binds 6-fold more tightly to ribosomes than clarithromycin and this is reflected in lower MIC values [29] . The presence of an A-2058 G mutation in the 23S rRNA (domain V) virtually eliminates binding of erythromycin a and clarithromycin to bacterial ribosomes. The binding of telithromycin is also lowered by this mutation, but to a smaller extent, and telithromycin remained active against these isolates while erythromycin A and clarithromycin did not.

3.2.4 Conclusion

Telithromycin acts on protein synthesis by a double interaction on the peptidyl transferase loop, allowing activity against erythromycin A-resistant gram-positive cocci due to A-2058-methylation. In addition, telithromycin inhibits the formation of the two subunits of the bacterial ribosome. This double interaction at two levels of the cellular machinery explains the enhanced in vitro activity of telithromycin against gram-positive cocci in comparison to clarithromycin and its capacity to overcome erythromycin A resistance due to A-2058-methylation.

3.3 Antipneumococcal activity

3.3.1 In vitro antipneumococcal activity

S. pneumoniae is one of the major pathogens responsible for community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and acute bacterial maxillary sinusitis. In recent years, the penicillin G and erythromycin A susceptibilities of *S. pneumoniae* have rapidly decreased. As previously shown, erythromycin A resistance may occur by multiple mechanisms, including MLS_B (erm^+), efflux (M phenotype: *mef* E^+ genotype), and ribosomal mutation on protein L4.

The results of in vitro studies demonstrate that telithromycin is one of the most active antibiotics against *S. pneumoniae*, irrespective of sensitivity or resistance to other antibacterial agents. Telithromycin was more active than erythromycin A, clarithromycin, and azithromycin.

Comparison with clarithromycin

In vitro studies demonstrated that telithromycin is more active than clarithromycin against *S. pneumoniae* isolates. Telithromycin was also highly active against erythromycinA-resistant strains having an MLS_B mechanism of resistance, an efflux (*mef E*) mechanism of resistance, or a mutation on ribosomal protein L4. In contrast, clarithromycin was inactive against isolates that are resistant to erythromycin A due to MLS_B, efflux mechanisms, or L4 protein mutation.

Telithromycin was tested against more than 5000 isolates collected from various countries (including the US, Canada, Europe, South Africa, and Japan), using clarithromycin as the comparator. Against fully susceptible *S. pneumoniae* isolates, MIC_{50} values for telithromycin were 0.004 to 0.06 µg/mL, and MIC_{90} values were 0.004 to 0.125 µg/mL. Telithromycin was 2 to 4 times more active than clarithromycin.

Against isolates showing intermediate susceptibility to penicillin G (MIC 0.12 to 1.0 µg/mL), telithromycin MIC_{50} values were 0.015 to 0.03 µg/mL, and MIC_{90} values were 0.03 to 0.25 µg/mL. Telithromycin was up to 10 times more active than clarithromycin.

Telithromycin MIC_{50} values for *S. pneumoniae* isolates resistant to penicillin G (MIC >1 µg/mL) were 0.015 to 0.125 µg/mL, and MIC_{90} values were 0.015 to 2.0 µg/mL. In contrast, clarithromycin and azithromycin activities delineate 2 populations of *S. pneumoniae* isolates: 1 population remaining sensitive and the second being totally resistant. This finding is mainly attributable to a combination of penicillin G- and erythromycin-A resistance.

Telithromycin was also active (MIC_{50} 0.015 to 0.06 µg/mL, MIC_{90} 0.015 to 2 µg/mL) against erythromycin A-resistant strains harboring an MLS_B mechanism of resistance (*erm B*). Against isolates resistant to erythromycin A, clarithromycin and azithromycin are inactive whether the mechanism of resistance is MLS_B efflux, or a mutation in ribosomal protein L4.

In multiple studies, telithromycin activity was investigated against 114 *S. pneumoniae* isolates of M-phenotype (erythromycin A-resistant and clindamycin-susceptible). MIC_{50} values for telithromycin ranged from 0.0015 to 0.25 µg/mL, and MIC_{90} values from 0.12 to 0.5 µg/mL. Clarithromycin exhibited a lower in vitro activity than telithromycin, with MIC_{50} values ranging from 0.5 to 8.0 µg/mL and MIC_{90} values from 4.0 to 16 µg/mL.

Comparisons with other antibacterial agents

It was demonstrated that telithromycin is more active against *S. pneumoniae* isolates (including resistant strains) than macrolides, fluoroquinolones, and other antibacterial agents tested.

In a comparative study, 400 *S. pneumoniae* isolates were tested for their susceptibility to 15 antibacterial agents, including telithromycin. Results for selected agents are summarized in the table below.

Table 3-1. In vitro activity of antibacterial agents against *S. pneumoniae* isolates

Antibacterial agent	MIC (µg/mL)	
	MIC_{50}	MIC_{90}
Telithromycin	0.015	0.12
Levofloxacin	1.0	1.0
Trovafloxacin	0.06	0.12
Sparfloxacin	0.12	0.25
Quinupristin/ dalfopristin	0.25	0.5
Linezolid	1.0	1.0

Telithromycin was more active than the fluoroquinolones tested, 16 times more active than quinupristin/dalfopristin, and 60 times more active than linezolid.

Telithromycin was active against ofloxacin-resistant *S. pneumoniae* ($MIC_{50/90}$ 0.03 µg/mL) and other fluoroquinolone-resistant strains. All the strains tested were susceptible to telithromycin, irrespective of the underlying mechanism of fluoroquinolone resistance. This included 19 multidrug-resistant strains and 3 strains containing *par C* and *par E* mutations in topoisomerase IV.

In in vitro studies, telithromycin was compared with oral cephems against *S. pneumoniae* isolates. The results showed that telithromycin was more active in vitro against *S. pneumoniae* than cefpodoxime, cefditoren, and cefdinir [43,44,58,60].

A total of 75 *S. pneumoniae* clinical isolates that were penicillinG-resistant (Pen-R) or intermediately resistant (Pen-I) were tested for their susceptibilities to various oral antibacterial agents. The results are summarized in the table below.

Table 3-2. In vitro activity of antibacterial agents against *S. pneumoniae* Pen-R or Pen-I

Antibacterial agent	MIC (µg/mL)		
	MIC_{50}	MIC_{90}	Range
Telithromycin	0.002	0.016	0.002 – 0.031
Erythromycin A	0.06	16	0.016 – 128
Clindamycin	0.03	0.06	0.016 – 128
Sparfloxacin	0.25	0.5	0.002 – 1.0
Grepafloxacin	0.12	0.25	0.008 – 1.0
Levofloxacin	0.5	1.0	0.002 – 1.0
Trovafloxacin	0.12	0.25	0.06 – 0.5
Linezolid	1.0	1.0	0.125 – 1.0
Cefprozil	8.0	16	0.12 – 16

Telithromycin showed the lowest MIC range and $MIC_{50/90}$ values of all isolates tested, and was more active than fluoroquinolones, linezolid, and cefprozil.

A total of 39 isolates of *S. pneumoniae* harboring different genes conferring erythromycin A resistance and 20 erythromycin A-susceptible isolates were tested for their susceptibility to telithromycin and 6 comparative compounds. Telithromycin was 4 times more active than clarithromycin against erythromycin A-susceptible *S. pneumoniae* isolates, and 16 times more active than clarithromycin against *S. pneumoniae* isolates harboring the *mef* E^+ gene (efflux). Telithromycin remained active against isolates harboring an *erm* B^+ gene, whereas clarithromycin was inactive. Telithromycin was 4 times more active than clarithromycin or ampicillin, and 30 times more active than cefdinir against erythromycin-A susceptible strains. These results are summarized in the table below.

Table 3-3. In vitro activity of antibacterial agents against *S. pneumoniae* Ery-S and Ery-R (*mef E*$^+$ and *erm B*$^+$)

Antibacterial agent	MIC (µg/mL)					
	Ery-S (N=20)		Ery-R *mef E*$^+$ (N=21)		Ery-R *erm B*$^+$ (N=18)	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Telithromycin	0.008	0.008	0.06	0.12	0.03	0.125
Erythromycin A	0.03	0.06	2.0	2.0	32	>128
Clarithromycin	0.016	0.03	1.0	2.0	16	>128
Azithromycin	0.12	0.125	2.0	4.0	64	>128
Ampicillin	0.03	0.25	1.0	2.0	0.03	2.0
Cefdinir	0.125	4.0	4.0	8.0	0.25	16
Levofloxacin	1.0	2.0	1.0	1.0	1.0	2.0

Note: N = number of isolates. Ery-R = erythromycin A-resistant, Ery-S = erythromycin A-susceptible.

Against 15 tetracycline-resistant *S. pneumoniae* strains, the $MIC_{50/90}$ value for telithromycin was 0.0015 µg/mL. In this same study, the MIC_{50} was 0.003 and the MIC_{90} was 0.007 µg/mL against 20 cotrimoxazole-resistant strains.

In summary, telithromycin exhibited high in vitro activity against isolates of *S. pneumoniae*. This was observed regardless of the underlying resistance of *S. pneumoniae* to penicillin G, erythromycin A, fluoroquinolones, tetracyclines, cotrimoxazole, and cefotaxime.

3.3.2 Bactericidal activity of telithromycin against *S. pneumoniae*

Telithromycin is bactericidal against *S. pneumoniae* (including strains resistant to penicillin G, erythromycin A, and cefotaxime).

Kill kinetics of telithromycin (reduction >3 log_{10} cfu/mL) were investigated at 4 x MIC against *S. pneumoniae* RYC 58956 (MIC values: penicillin G 0.008 µg/mL, erythromycin A 0.03 µg/mL, clarithromycin 0.03 µg/mL, telithromycin 0.015 µg/mL) and *S. pneumoniae* RYC 92740 (MIC values: penicillin G 2.0 µg/mL, erythromycin A 8.0 µg/mL, clarithromycin 4.0 µg/mL, telithromycin 0.01 µg/mL).

After 2 hours of exposure to telithromycin, *S. pneumoniae* RYC58956 (Pen-S, Ery-S) inoculum size was reduced by 5.2 log_{10} cfu/mL (initial inoculum size 10^7 cfu/mL) and 5.9 log_{10} cfu/mL (initial inoculum size 10^6 cfu/mL). After 2 hours, the reduction with clarithromycin was 2.8 and 3.8 log_{10} cfu/mL, and at 4 hours, the reduction was 4.0 and 4.7 log_{10} cfu/mL. Telithromycin was highly and rapidly bactericidal against this isolate. Against *S. pneumoniae* RYC 92740 (Pen-R, Ery-R), reductions with telithromycin after inoculum sizes of 10^7 and 10^6 cfu/mL were 3.1 and 3.5 log_{10} cfu/mL at 2 hours, and 3.7 and 4.0 log_{10} cfu/mL at 4 hours. Under the same conditions, clarithromycin showed poor bactericidal activity.

Against cefotaxime-resistant *S. pneumoniae* isolates, telithromycin was bactericidal at 4 x MIC and 8 x MIC. Telithromycin was rapidly bactericidal against *S. pneumoniae* strains that were resistant to erythromycin A and susceptible to clindamycin (M-phenotype : efflux mechanism), with a decrease in inoculum size of approximately 3 $\log_{10}$ cfu/mL in under 2 hours.

Against erythromycin A-resistant *S. pneumoniae* isolates (*erm B*-containing strain), the rapidity of the bactericidal activity of telithromycin was strain dependent. Bactericidal activity occurred more slowly compared with erythromycin A-susceptible strains. Regrowth occurred at 2 x MIC and 4 x MIC, but not at 8 x MIC, for some isolates.

3.3.3 In vivo activity in murine infection models

Disseminated infections in mice

In disseminated murine infections, telithromycin displayed oral in vivo activity against pneumococcal infections due to erythromycin A-resistant isolates. In contrast, clarithromycin and azithromycin were inactive (Protective $Dose_{50}$ [PD_{50}]>50 mg/kg). Telithromycin was also more active than clarithromycin against *S. pneumoniae* strains susceptible to erythromycin A.

Pneumococcal murine respiratory infections

In 2 studies in mice infected intratracheally with erythromycin A-susceptible or erythromycin A-resistant *S. pneumoniae* strains, oral telithromycin demonstrated protective effects when administered at a dosage of 25 to 100 mg/kg twice daily over 3 days.

In the first of these studies, mice were infected with *S. pneumoniae* 6254 (Ery-R, MIC >128 µg/mL). Telithromycin 25, 50, and 100 mg/kg/day, begun 6 or 18 hours after bacterial challenge, demonstrated protective effects, with survival rates from 50 to 75%. All control mice developed bacteriemic pneumonia and died within 2 to 5 days.

A second group of mice were infected with *S. pneumoniae* 4241 (Ery-S, MIC 0.06 µg/mL), and telithromycin or erythromycin was administered orally at 50 mg/kg/day. Dosing started 48 or 72 hours after bacterial challenge. Survival with erythromycin was 70% (48 hours after infection) and 67% (72 hours), whereas survival for telithromycin was 100% in both regimens.

In a second study mice were infected by intranasal instillation with *S. pneumoniae* strains TUH 39 (Pen-S, *mef* E^-/*erm* B^-), TUM 741 (Pen-R, *mef* E^+, *erm* B^-), and TOH 117 (*erm* B^+/ *mef* E^-). Telithromycin and other compounds were administered by the oral route, starting 16 hours after bacterial innoculation for *S. pneumoniae* TUH 39, and 40 hours after bacterial instillation for the other 2 *S. pneumoniae* strains. Compounds were administered for 3 days. Telithromycin was administered in the following regimens: 25, 50, or 100 mg/kg every 12 hours, and 50, 100, and 200 mg/kg once daily. Lung bacterial burden was determined 16 hours after the last administration of compounds.

The results showed that the median effective dose (ED_{50}) of telithromycin (6.5 mg/kg once daily) was comparable with that of azithromycin (6.9 mg/kg once daily) for *S. pneumoniae* TUH 39 (susceptible). Cefdinir (ED_{50} 46.4 mg/kg once daily) and clarithromycin (ED_{50} 15.9 mg/kg once daily) were less active than telithromycin.

Against *S. pneumoniae* TUM 741 (Pen-R, *mef* E^+/*erm* B^-), a 3 $\log_{10}$ cfu/g reduction of lung burden was recorded after administration telithromycin at 50 mg/kg twice a day, compared with control, and a >6 $\log_{10}$ cfu/g reduction was recorded for 100 mg/kg telithromycin given twice a day. Results were statistically comparable for telithromycin administered at 100 mg/kg every 12 hours and at 200 mg/kg once daily. The bacterial clearance of the lung was markedly greater for telithromycin compared with clarithromycin, azithromycin, or cefdinir.

When telithromycin was administered every 12 hours at a dosage of 50 mg/kg/day against *S. pneumoniae* TOH 117 (Pen-R, *mef* E^-/*erm* B^+), reduction in *S. pneumoniae* burden was approximately 2.5 $\log_{10}$ cfu/g. Reduction was >6 $\log_{10}$ cfu/g when telithromycin was administered at 100 mg/kg every 12 hours.

In summary, telithromycin exhibits a good efficacy in murine models of pneumococcal pneumonia. Efficacy remained in murine pneumonia induced with *S. pneumoniae* strains resistant to erythromycin A and/or penicillin G. In these models, the in vivo efficacy of telithromycin was greater than that of clarithromycin, azithromycin, or cefdinir.

3.3.4 Intracellular antipneumococcal activity

The intracellular antipneumococcal activity of telithromycin was evaluated after polymorphonuclear neutrophil (PMN) phagocytosis of *S. pneumoniae*. Telithromycin was very active intracellularly against *S. pneumoniae*, irrespective of susceptibility to penicillin G or erythromycin A. Telithromycin at 4 x MIC reduced intracellular growth by 1.8 to 3.0 $\log_{10}$ cfu at 24 hours, irrespective of the strain [46].

It has been shown that *S. pneumoniae* can enter and survive within human lung alveolar carcinoma cells (Type 2 pneumocytes, A I49 cells) [73]. *S. pneumoniae* isolates may persist in tissue, despite exposure to adequate antibacterial concentrations. Telithromycin killing activity was compared with that of azithromycin and 3 fluoroquinolones in human lung alveolar carcinoma cells against *S. pneumoniae* 14.8 and *S. pneumoniae* ATCC 49619 (MIC 0.002 µg/mL). It was found that moxifloxacin, trovafloxacin, and telithromycin were most active, but only telithromycin killed all intracellular pneumococci. This finding appears to be related, at least in part, to a high intracellular accumulation of telithromycin in addition to its potent bactericidal activity against *S. pneumoniae*.

3.4 Activity against other pathogens involved in lower respiratory tract infections

3.4.1 Activity against other common pathogens

Haemophilus influenzae

H. influenzae is involved in RTIs such as community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, and acute bacterial maxillary sinusitis. In recent years, there has been an increase in the incidence of ampicillin-resistant *H. influenzae* isolates due to beta-lactamase production. Nonenzymatic resistance to beta-lactams is a second mechanism of resistance, with a lower incidence than beta-lactamase production.

In vitro, telithromycin is slowly bactericidal against *H. influenzae*.

In vitro activity against Haemophilus influenzae

MIC values against *H. influenzae* are strongly influenced by the experimental medium. In the US, NCCLS recommends use of the microbroth dilution technique in the Haemophilus Test Medium (HTM). The HTM medium tends to give higher MIC values than those used in other parts of the world. MIC values can also vary with incubation atmosphere, with high values occurring in 6% CO_2.

A total of 1603 *H. influenzae* isolates were tested in the USA using NCCLS methodology with HTM. The MIC_{50} value for telithromycin ranged from 1.0 to 2.0 µg/mL, and the MIC_{90} value from 2.0 to 4.0 µg/mL.

The in vitro activity of telithromycin was tested against 2300 isolates collected worldwide. Irrespective of the resistance profile to ampicillin, MIC_{50} or MIC_{90} values were consistent for each given investigator. The MIC_{50} values for telithromycin ranged from 0.25 to 2.0 µg/mL, and MIC_{90} values from 0.5 to 4.0 µg/mL.

Telithromycin was shown to be slowly bactericidal against *H. influenzae*. A reduction of 2.9 (2 x MIC), 3.2 (4 x MIC), and 3.9 (8 x MIC) log_{10} cfu/mL occurred after 24 hours of contact. Results are summarized in the table below.

Table 3-4. Telithromycin bactericidal activity (kill kinetics) against *H. influenzae*

Concentration Tested	Mean (range) log_{10} cfu change	
	at 6 hours	at 24 hours
1 x MIC	–1.1 (0.0 to –3.6)	–2.0 (+0.9 to –4.9)
2 x MIC	–1.1 (–0.1 to –2.5)	–2.9 (–0.5 to –4.8)
4 x MIC	–1.3 (–0.1 to –3.0)	–3.2 (–1.1 to –5.1)
8 x MIC	–1.5 (–0.3 to –3.0)	–3.9 (–2.0 to –4.9)
Control	+1.8 (+1.2 to +2.3)	+2.6 (+2.2 to +3.2)

MIC of telithromycin against *H. influenzae* in this study: 1 or 2 µg/mL.

The in vitro bactericidal activity of telithromycin against *H. influenzae* has been assessed by kill kinetics using the HTM medium, and was shown to be strain- and inoculum size-dependent. For some isolates, with 10^7 cfu/mL as a starting inoculum, bacteriostatic activity was recorded (e.g., strain CI012). Telithromycin appeared to be less bactericidal against ampicillin-resistant *H. influenzae* type b, but variations were observed for ampicillin-resistant *H. influenzae* isolates producing beta-lactamase and also for non–beta-lactamase producing strains.

Activity in Haemophilus influenzae murine lung infections

In a first study in mice, animals were infected intratracheally with ~10^7 cfu of *H. influenzae* 87169. The animals developed inflammatory bronchopulmonary disease that resolved spontaneously. Kinetics of bacterial killing were recorded over a 24-hour period following a single oral dose of antibacterial agents administered 16 hours after bacterial challenge. The MIC values were 1.0 µg/mL for telithromycin, 0.25 µg/mL for azithromycin, and 2.0 µg/mL for erythromycin A. Results for kill kinetics are summarized in the table below.

Table 3-5. Efficacy of telithromycin in *H. influenzae* lung infections in mice at 9 and 24 hours postdosing

Treatment	N	Dosage (mg/kg)	log_{10} cfu/lungs at 9 hours (mean ± std dev.)	log_{10} cfu/ reduction at 9 hours	log_{10} cfu/lungs at 24 hours (mean ± std dev.)	log_{10} cfu/ reduction at 24 hours
Control (saline)	5	–	7.25 ± 0.49	0.0	6.52 ± 0.25	0.0
Erythromycin A	5	100	6.80 ± 0.25	–0.45	5.83 ± 0.60	–0.69
Telithromycin	5	50	4.45 ± 0.21*	–2.80	3.65 ± 0.38*	–2.87
	5	100	3.97 ± 0.25*	–3.28	3.42 ± 0.35*	–3.10
Azithromycin	5	50	5.15 ± 0.25*	–2.10	3.92 ± 0.15*	–2.60
	5	100	4.26 ± 0.18*	–2.99	3.88 ± 0.22*	–2.64

N = number of mice
*p ≤0.05 compared with control or erythromycin A.

At 24 hours, telithromycin 50 mg/kg showed comparable lung bacterial clearance compared with azithromycin 100 mg/kg, and greater clearance compared with erythromycin A. Assays at 3 hours demonstrated greater activity for telithromycin (50 mg/kg) compared with azithromycin (100 mg/kg), with a lung burden of 5.96 ± 0.45 log_{10} cfu/lungs for telithromycin and 6.71 ± 0.39 log_{10} cfu/lungs for azithromycin.

Studies in mouse models of experimental murine pneumonia due to *H. influenzae* showed that telithromycin 50 mg/kg had a faster onset of activity against *H. influenzae* than azithromycin 100 mg/kg. Lung bacterial clearance was comparable for the 2 compounds at 24 hours.

In a second study, mice were infected intratracheally with 10^8 cfu of *H. influenzae* type b. The lung clearance of *H. influenzae* was analyzed after oral therapy with telithromycin (50 mg/kg), azithromycin (100 mg/kg), amoxicillin (25 mg/kg), pristinamycin (100 mg/kg), clarithromycin (100 mg/kg), and erythromycin (100 mg/kg). Therapy started 4 hours after bacterial challenge and was subsequently administered every 6 hours for a total of 4 doses. The lungs were removed for analysis 6 hours after the last dose. Results are summarized below:

Table 3-6. Lung clearance of *H. influenzae* in murine lung tissues after therapy with telithromycin and other antibacterial agents

Treatment	Dosage (mg/kg/day)	MIC (µg/mL)	Plasma levels (µg/mL)		Sterile/ total	log_{10} cfu/g lung	
			$C_{30\ min}$	$C_{90\ min}$		Median	Range
Control	–	–	–	–	0/35	9.1	8.7 – 9.6
Telithromycin	50	1.0	3.2	3.9	3/12	4.3	2.1 – 5.1
Azithromycin	100	1.0	0.8	1.8	5/18	3.9	1.7 – 4.2
Erythromycin A	100	8.0	6.1	3.6	0/12	5.4	5.1 – 5.7
Clarithromycin	100	8.0	3.2	2.8	0/12	5.7	5.6 – 6.0
Pristinamycin	100	1.0	2.2	0.8	0/14	7.4	6.5 – 8.4
Amoxicillin	25	8.0	12	1.3	0/15	8.6	7.3 – 9.7

Telithromycin 50 mg/kg showed activity comparable with that of azithromycin 100 mg/kg in this model, and greater activity than other compounds tested.

Moraxella catarrhalis

Telithromycin was tested against 1108 isolates of *M. catarrhalis*, against which it displayed in vitro activity comparable with clarithromycin. The MIC_{50} values for telithromycin ranged from 0.02 to 0.25 µg/mL, and MIC_{90} values from 0.03 to 0.5 µg/mL. The MIC_{50} values for clarithromycin ranged from 0.03 to 0.25 µg/mL, and MIC_{90} values from 0.06 to 0.25 µg/mL.

There are difficulties in performing kill kinetics experiments with *M. catarrhalis*, probably associated with aggregation of the organism in the test tube, particularly for high inoculum size explaining discrepancies between the different investigations.

Telithromycin, like 14- and 15-membered ring macrolides, is slowly bactericidal against *M. catarrhalis*. At 8 x MIC, a reduction of 3 $\log_{10}$ cfu/mL was observed at 12 and 24 hours.. Another study demonstrated a reduction of approximately 4 $\log_{10}$ cfu/mL after 12 hours of contact between *M. catarrhalis* and telithromycin.

3.4.2 *Bordetella* species

Bordetella pertussis and *B. parapertussis* are the etiologic agents of whooping cough, and 14- and 15-membered ring macrolides are reference antibacterial agents for this infection. The in vitro activity of telithromycin was investigated against 133 isolates of *B. pertussis*. Results showed that MIC_{50} values for telithromycin were 0.01 to 0.03 µg/mL, and MIC_{90} values were 0.01 to 0.06 µg/mL. The MIC_{50} values for clarithromycin were 0.01 to 0.06 µg/mL, and MIC_{90} values were 0.03 to 0.06 µg/mL.

The MIC_{50} and MIC_{90} values for telithromycin against 31 *B. parapertussis* isolates were 0.12 µg/mL, and 0.25 µg/mL respectively.

3.5 Activity against beta-hemolytic streptococci (*Streptococcus pyogenes* and other streptococci)

S. pyogenes (Lancefield Group A streptococci) and Lancefield Group C and G streptococci are responsible for tonsillitis. In vitro and in vivo activities of telithromycin against *S. pyogenes* were investigated.

3.5.1 In vitro studies with beta-hemolytic streptococci

Telithromycin displayed good in vitro activity against β-hemolytic Lancefield Group A (N=1445), B (N=464), C and G (N=251), and F (N=41) streptococci isolates. For telithromycin, MIC_{50} values were ≤0.008 to 0.03 µg/mL and MIC_{90} values were 0.015 to 0.06 µg/mL against erythromycin A-susceptible strains. Telithromycin showed comparable in vitro activity to clarithromycin.

When an efflux mechanism of resistance to erythromycin A was present, $MIC_{50/90}$ values for telithromycin rose to 2.0 µg/mL. Against the few isolates in which an *erm B* gene was the underlying mechanism of resistance to erythromycin A, MIC values for telithromycin reached >16 µg/mL. For *erm TR*-containing *S. pyogenes*, MIC values ranged from 0.03 to 0.25 µg/mL; however, for one isolate, an MIC of 64 µg/mL was recorded.

Telithromycin showed bactericidal activity at 4 x MIC and at 6 hours against *S. pyogenes* erythromycin A-susceptible isolates and against erythromycin A-resistant (M-phenotype) isolates. Against *erm B*-containing *S. pyogenes* isolates, telithromycin was bacteriostatic. Telithromycin was highly active against other β-hemolytic streptococci (Group C, G, and F) ($MIC_{50/90}$ ≤0.015 to 0.06 µg/mL). In studies conducted at several centers, the MIC_{50} range against Lancefield Group B streptococci was 0.008 to 0.06 µg/mL and the MIC_{90} range was 0.015 to 0.12 µg/mL.

3.5.2 In vivo studies of activity against beta-hemolytic streptococci

The efficacy of telithromycin in a murine model of Group A streptococcal necrotizing fasciitis/myonecrosis was compared with that of clindamycin (the reference therapy in this model) and penicillin G. Female mice were inoculated in the thigh with *S. pyogenes* ATCC 12384 with an inoculum size of 10^7 to 10^9 cfu/100 µL. The infection was 100% lethal in untreated animals. Clindamycin provided complete protection, irrespective of inoculum size. Telithromycin provided significantly greater protection compared with penicillin G for all inocula sizes.

3.6 Activity against atypical and intracellular micro-organisms

3.6.1 Intracellular concentration of telithromycin

Telithromycin (like the macrolides, fluoroquinolones, tetracycline, and clindamycin) concentrates in various types of cells. Telithromycin also exhibits a phase of steady efflux from the cells, which results in maintenance of inhibitory extracellular levels.

Polymorphonuclear neutrophils (PMN)

The in vitro uptake of [^{3}H]-telithromycin was investigated using a velocity gradient centrifugation technique. Telithromycin (extracellular concentration of 2.5 µg/mL) was gradually concentrated by PMN with an intracellular/extracellular concentration ratio reaching 27.0 ± 8.1 at 5 minutes and 348 ± 27.1 at 180 minutes.

Telithromycin was located mainly in the granule fraction of PMN (56 ± 10.9%). Telithromycin was gradually released from drug-loaded PMN placed in a drug-free medium. In the first 5 minutes, approximately 20% of telithromycin was effluxed from the cell; after 5 minutes, the efflux slope was slower, with approximately 60% telithromycin remaining in the cell at 1 hour. The uptake of telithromycin was temperature dependent [50].

Macrophages

Uptake by peritoneal macrophages was rapid, with an intracellular/extracellular (C/E) ratio of 65 (extracellular concentration of 2 µg/mL) after 60 minutes. The intracellular penetration of telithromycin was not saturable (extracellular concentrations 2.0 to 25 µg/mL).

Epithelial cells

After 20 minutes of incubation (extracellular concentration 2.0 µg/mL), the C/E ratio of telithromycin was 7 in McCoy cells and 11 in HEp-2 cells. The kinetics of telithromycin efflux were rapid. After

60 minutes of incubation in an antibacterial-free medium, the amount of cell-associated telithromycin was 10% in McCoy cells and 32% in HEp-2-cells.

3.6.2 Activity against atypical or intracellular pathogens involved in lower respiratory tract infections

Three intracellular or atypical pathogens are commonly associated with infections known as atypical parenchymal lower RTIs: *Chlamydia (Chlamydophila) pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*. Other intracellular pathogens are also responsible for lung parenchymal infections, but to a lower extent : *Chlamydia psittaci* and *Coxiella burnetii*.

3.6.2.1 *Chlamydia pneumoniae*

C. pneumoniae is an obligate intracellular pathogen. Different cell lines were used to test the in vitro activity of telithromycin against *C. pneumoniae*, and the results are summarized in the table below.

Table 3-7. In vitro activity of telithromycin against *C. pneumoniae*

C. pneumoniae	N	MIC (µg/mL)	MCC (µg/mL)	Medium
Clinical isolates	5	0.12 – 0.25	–	McCoy cells
Clinical isolates	15	0.03 – 2.0	0.03 – 2.0	HEp-2 cells
TW 183	1	0.06	0.12	McCoy cells
ATCC VR1310	1	0.0156	2.5	HEp-2 cells
G954	1	0.0156	0.312	HEp-2 cells

MCC: minimum chlamydicidal concentration.

Telithromycin exhibits a good in vitro and bactericidal activity against *C. pneumoniae*.

3.6.2.2 Legionella pneumophila

In vitro, telithromycin was active against various strains of *L. pneumophila* as well as against other *Legionella* species. Therapeutic efficacy of telithromycin was demonstrated in animal models of *L. pneumophila* infection.

In vitro *activity against Legionella pneumophila*

- Telithromycin was tested against approximately 140 strains of *L. pneumophila*. The resulting $MIC_{50/90}$ values were 0.015 to 0.06 µg/mL and 0.03 to 0.12 µg/mL, respectively, in buffered yeast extract agar (BYE). However, in buffered charcoal yeast extract (BCYE α), $MIC_{50/90}$ values increased to 2 µg/mL. The presence of charcoal in BCYE α is known to impair the in vitro activity of several antibacterial agents.
- The postantibiotic effect (PAE) of telithromycin on *L. pneumophila* was 4.6 hours, recorded at 2 x MIC, compared with a PAE of 1.0 hours with erythromycin A.
- Using broth dilution techniques, bactericidal synergy of telithromycin was shown in combination with rifampin. Telithromycin was active against intracellular *L. pneumophila* F2111 and F889 (guinea pig alveolar macrophages).

- The bactericidal activity of telithromycin was assessed against *L. pneumophila* serogroup 1 (strain CB 81-13) within monocyte-derived macrophages, and the results are summarized in the table below.

Table 3-8. Intracellular bioactivity of telithromycin against *L. pneumophila*

Treatment	Extracellular conc. (µg/mL)	Telithromycin cfu	Erythromycin Group cfu
Control	–	7.0 ± 0.85	7.0 ± 0.85
Telithromycin or Erythromycin A	0.0125	7.15 ± 0.28	7.65 ± 0.27
	0.025	6.15 ± 0.45	6.60 ± 0.28
	0.05	5.36 ± 0.25	5.65 ± 0.50
	0.10	4.25 ± 0.59	4.16 ± 0.35

- For a low extracellular concentration (0.05 µg/mL) of telithromycin, an inhibition of intracellular multiplication of *L. pneumophila* has been demonstrated.
- The antibacterial activity of telithromycin alone or in combination with rifampin has been determined against *L. pneumophila* L-1033 serogroup 1 within human monocytes. Telithromycin antibacterial activity was observed at 0.25 x MIC and increased with 2.5 x MIC and 10 x MIC. Combination of telithromycin with rifampin at 10 x MIC produced activity that was comparable with that of telithromycin alone.
- There is a prolonged intracellular activity of telithromycin.

In vivo activity in animal models of Legionella pneumophila infection

In vivo efficacy of telithromycin against *L. pneumophila* was investigated in Dunkin-Hartley strain male guinea pig models of infections.

In the first study, 16 male guinea pigs per group were infected with *L. pneumophila* serogroup 1 (strain F889) by the intratracheal route. Animals were completely protected by oral or intraperitoneal telithromycin 10 mg/kg administered once daily for 5 days, begun on day 1 after infection. All animals that received placebo died.

In the second study, 16 male guinea pigs per group were infected with *L. pneumophila* serogroup 1 (strain Paris CB81-13) by the intraperitoneal route. At 48 hours after infection, animals received 2 daily oral doses of telithromycin, erythromycin A, or placebo for 2 days. Survival rates are summarized in the table below.

Table 3-9. Survival of guinea pigs infected with *L. pneumophila*

Treatment	Survival rate (%)		
	15 mg/kg	30 mg/kg	60 mg/kg
Control	6	0	10
Telithromycin	86	89	90
Erythromycin A	14	60	67

At all dosages, telithromycin was more effective than erythromycin A.

Mycoplasma pneumoniae

In vitro activities of telithromycin against *M. pneumoniae* were studied by 4 investigators. Methods are not yet standardized, yielding variations in results from different laboratories.

Telithromycin was very active against *M. pneumoniae.* Against 90 isolates, $MIC_{50/90}$ values ranged from 0.001 to 0.005 µg/mL.

In a separate study, the comparative in vitro activity of telithromycin and 7 other antibacterial agents was investigated against *M. pneumoniae*. Telithromycin was more active than the 14- and 16-membered-ring macrolides tested, and was more active than minocycline and levofloxacin, as shown in the table below.

Table 3-10. In vitro activity of antibacterial agents against *M. pneumoniae* (N = 41)

Antibacterial agent	MIC (µg/mL)		
	MIC_{50}	MIC_{90}	Range
Telithromycin	0.00097	0.00097	0.00024 – 0.0019
Erythromycin A	0.0039	0.0078	0.0019 – 0.0078
Clarithromycin	0.0019	0.0019	0.00048 – 0.0039
Roxithromycin	0.0039	0.0078	0.0019 – 0.0078
Azithromycin	0.00024	0.00048	0.00006 – 0.00048
Josamycin	0.0078	0.0156	0.0019 – 0.0313
Minocycline	0.125	0.25	0.062 – 0.25
Levofloxacin	0.25	0.25	0.125 – 0.5

Chlamydia psittaci

Telithromycin displays in vitro activity against *Chlamydia psittaci* 4521UC1 strain (MIC and MCC values: 0.006 µg/mL) and against *C. psittaci* 1058 strain (MIC 0.25 µg/mL and MCC 0.5 µg/mL) [9].

Coxiella burnetii

The bacteriostatic activity of telithromycin was determined against 3 strains of *C. burnetii:* the Nine Mile strain (reference strain in acute infections), Q-212 strain, and the Priscilla strain (reference strains in chronic infections). Assays were conducted using human fibroblasts (HEL).

Table 3-11. Susceptibility of *C. burnetii* to telithromycin and erythromycin A

Strain	MIC (µg/mL)	
	Telithromycin	Erythromycin A
Nine Mile	1.0	>8.0
Priscilla	1.0	>8.0
Q-212	1.0	>8.0

Telithromycin exhibited in vitro activity against *C. burnetii*, while erythromycin A was inactive. Telithromycin, like other antibacterials, did not exhibit bactericidal activity against the 3 strains of *C. burnetii* tested.

3.7 In vitro activity against other pathogens

3.7.1 *Staphylococcus aureus*

Telithromycin demonstrated activity against 2263 *S. aureus* isolates with different patterns of resistance to methicillin and erythromycin A. The MIC_{50} values ranged from 0.06 to 0.12 µg/mL, and MIC_{90} values ranged from 0.12 to 0.25 µg/mL, irrespective of susceptibility to oxacillin (methicillin). For an *S. aureus* isolate harboring an inducible MLS_B mechanism of resistance, MIC_{50} and MIC_{90} values remained in the range 0.06 to 0.25 µg/mL. However, when an isolate of *S. aureus* harbored a constitutive MLS_B mechanism of resistance, MIC_{50} values were above 16 µg/mL.

Irrespective of the species of coagulase-negative staphylococci, telithromycin $MIC_{50/90}$ values were 0.03 to 0.25 µg/mL with isolates susceptible to erythromycin A. When a constitutive MLS_B mechanism of resistance was present, the telithromycin $MIC_{50/90}$ value was above 16 µg/mL. In contrast, when an inducible MLS_B mechanism of resistance was present, $MIC_{50/90}$ values were of the same magnitude as those observed for erythromycin A-susceptible strains.

3.7.2 *Enterococcus* species

Telithromycin exhibits in vitro activity against enterococci in the absence of underlying mechanisms of resistance (vancomycin, gentamicin, ampicillin). Telithromycin was active against *E. faecalis* (MIC_{50} 0.12 to 1.0 µg/mL and MIC_{90} 2.0 to 8.0 µg/mL) and *Enterococcus* species ($MIC_{50/90}$ ≤0.03 to 0.06/0.06 to 8.0 µg/mL), with a bimodal population distribution. Telithromycin also exhibited bimodal in vitro activity against *E. faecium* ($MIC_{50/90}$ ≤0.03/4.0 µg/mL).

3.7.3 Anaerobes

Telithromycin has been tested against numerous genera and species of anaerobic bacteria.

Telithromycin was active against gram-positive cocci and bacilli. Against various *Propionobacterium* spp (N=66), MIC_{50} was 0.015 µg/mL; against *Peptostreptococcus* spp (N=232), MIC_{50} was 0.004 to 0.12 µg/mL; and against *Clostridium difficile* (N=169), MIC_{50} was 0.06 to 1.0 µg/mL. Against *C. difficile*, which is a major cause of nosocomial antibiotic-associated diarrhea and pseudomembranous colitis, telithromycin showed a bimodal distribution of activity.

The activity of telithromycin against gram-negative anaerobes was shown to be more species variable than against gram-positive species. Telithromycin was active against *Prevotella* spp (N=753) (MIC_{50} ≤0.008 to 0.25 µg/mL) and *Porphyromonas* spp (N=188) (MIC_{50} 0.008 to 0.06 µg/mL). However, activity was lower against *B. fragilis* (N=244) (MIC_{50} 4.0µg/mL) and *Fusobacterium* spp (N=261) (MIC_{50} 1.0 to >32 µg/mL).

3.7.4 Other bacterial species

Telithromycin showed in vitro activity against a variety of other pathogens. These results are summarized in the table below.

Table 3-12. Summary of telithromycin in vitro activity against various other pathogens

Species/group studied		MIC (µg/mL)		
	N	Range	MIC_{50} range	MIC_{90} range
Viridans group streptococci	1141	–	≤ 0.003 - 0.25	≤ 0.003 – 0.5
Corynebacterium diphtheriae	442	–	0.004	0.008
Listeria spp.	181	–	0.03 - 0.12	0.03 - 0.25
Lactobacillus spp.	124	–	0.007 - 0.03	0.03 - 0.12
Pediococcus spp.	40	–	0.007 - 0.03	≤ 0.03
Leuconostoc spp.	91	–	≤ 0.03	≤ 0.03 - 0.25
Erysipelothrix rhusopathiae	10	≤ 0.015 - 0.03	–	–
Micrococcus spp.	191	–	≤ 0.03	≤ 0.03
Stomatococcus spp.	63	–	≤ 0.03	≤ 0.03
Rhodococcus equi	31	≤0.015 - 0.25	–	–
Neisseria meningitidis	448	–	0.015 - 0.12	0.03 - 0.25
Saprophytic *Neisseria* spp.	50	–	0.06 - 0.12	0.25 - 4.0

Telithromycin was very active against gram-positive bacilli and the other species listed above. Additionally, against *Mycoplasma hominis*, MIC_{50} values for telithromycin were 2 to 32 µg/mL, and MIC_{90} values were 4 to 32 µg/mL. The corresponding MIC_{50} and MIC_{90} values for clarithromycin were >32 to >64 µg/mL. Telithromycin exhibited bimodal activity against *Corynebacterium jeikeium* and *C. urealyticum* and good activity against other coryneforms.

Telithromycin was inactive against *Enterobacteriaceae* and nonfermentative gram-negative bacilli (e.g., *Pseudomonas aeruginosa* [MIC range 32 to >128 µg/mL], *Acinetobacter baumannii* [MIC range 2 to >128 µg/mL]).

3.8 Postantibiotic effect of telithromycin

A postantibiotic effect (PAE) is the suppression of bacterial growth that persists after short exposure to an antibacterial agent.

3.8.1 Postantibiotic effect in vitro

Several laboratories have investigated the PAE of telithromycin. Although methodology varied between laboratories (a factor that may influence the precise quantitative measurement of PAE), all studies clearly demonstrated a PAE for telithromycin. Telithromycin exhibited a PAE against *S. pneumoniae* of 1.5 to 3.8 hours, and a PAE of 0.3 to 2.4 hours against *S. aureus* and 0.4 to 2.7 hours against *S. pyogenes*.

Telithromycin exhibited a significant PAE against other species involved in RTIs, including *H. influenzae* (2.2 to 6.2 hours) and *M. catarrhalis* (2.5 to 5.0 hours).

3.8.2 Postantibiotic effect in vivo

Studies with *S. pneumoniae* ATCC10813 in mice demonstrated that telithromycin exhibits concentration-dependent killing with a prolonged in vivo PAE. These results are shown in the table below.

Table 3-13. In vivo postantibiotic effect of telithromycin against *S. pneumoniae* in mice

Telithromycin	Time to grow one log_{10} cfu/thigh (h)		
dosage (mg/kg)	Control	Treated	PAE
0.29	2.81	3.69	0.88
1.17	2.81	3.44	0.63
4.69	2.81	6.05	3.24
18.8	3.03	8.82	5.79

At low dosages, the PAE was approximately 1 hour, but at higher doses, the PAE was from 3.2 to 5.8 hours.

3.9 Resistance

3.9.1 Mechanisms of resistance to erythromycin A

All 14- and 15-membered ring macrolides derived from erythromycin A share the same mechanism of resistance. The mechanisms of resistance to erythromycin A are complex and can be divided into three main patterns:

- Housekeeping
- Defensive
- Preventive.

Each of these mechanisms is described in the sections that follow.

3.9.1.1 "Housekeeping"

3.9.1.1.1 Efflux mechanism of resistance

In gram-positive cocci, efflux pumps for erythromycin A have been described for *S. aureus* (*msr*A), coagulase-negative staphylococci (*msr*A, *msr*B), *S. pyogenes* (*mef*A], *S. pneumoniae* (*mef*E), *S. agalactiae*(*mef*A and E, *mre*A), and viridans group streptococci (*mef*E and *mef*A). These pump proteins bind to erythromycin A and pump molecules out of the bacterial cells, resulting in reduced intracellular concentrations of erythromycin A.

3.9.1.1.1.1 The *mef* mechanism of efflux

The *mef* gene has been found in various gram-positive bacteria: *Streptococcus* spp, *Micrococcus* spp, *Corynebacterium* spp, and *Enterococcus* spp. Strains harboring a *mef* mechanism of resistance are also known as M-phenotype.

In streptococci, two genes encode for efflux pump proteins: *mef* for all streptococci and *mre*A for *S. agalactiae* [21]. The most important *mef* gene with respect to *S. pneumoniae*, and therefore telithromycin, is *mef*E. Telithromycin MIC_{50} values are greater against *S. pneumoniae* isolates carrying a *mef*E gene than others, but remain within the likely therapeutic range. Against *S. mitis*/*S. oralis* isolates harboring a *mef*E^+ gene, telithromycin MICs were 0.06 to 1.0 µg/mL and against 18 isolates of *S. agalactiae* with the M-phenotype (*mef*A^+ or *mef*E^+), telithromycin MICs ranged from 0.1 to 0.2 µg/mL, in comparison with MICs of 0.02 µg/mL for erythromycin A-susceptible isolates.

The *mef*A gene has been described in a variety of bacterial species, including *S. pyogenes*, *S. agalactiae*, viridans group streptococci (*S. mitis*, *S. milleri*), Lancefield group C, F, and G streptococci, *Micrococcus* spp, *Listeria* spp, *Corynebacterium jeikeium*, and *Enterococcus faecium*. The *mef A* gene appears to be inducible by 14- and 15-membered ring macrolides but not by 16-membered ring macrolides. Further, 16-membered ring macrolides are not good substrates for Mef A protein.

For telithromycin, an analogous effect to the pneumococcal Mef E pump was shown for *mef*A in *S. pyogenes*. Strains expressing this gene exhibited higher telithromycin MICs compared with strains without the gene, nevertheless, the MICs remained within the therapeutic range.

3.9.1.1.1.2 Mre A mechanism of efflux

A putative efflux pump Mre A from a S*treptococcus agalactiae* strain conferred resistance to 14-, 15-, and 16-membered ring macrolides. Telithromycin retained good activity against *S. agalactiae* harboring the *mre*A gene. $MIC_{50/90}$ values for telithromycin were ≤0.015 µg/mL in comparison with clarithromycin, for which MIC values ranged from 0.5 to 4.0 µg/mL [84].

3.9.1.1.1.3 The Msr A mechanism of efflux

Msr A protein is a member of the ABC superfamily of efflux pumps, and is specific to 14- and 15-membered ring macrolides and streptogramin B. The *msr*A gene has been sequenced from *S. epidermidis* and *S. aureus*. The 14- and 15-membered ring macrolides and telithromycin (but not 16-membered ring macrolides) act as inducers of *msr* genes [30,66]. However, the ketolides are poor substrates for Msr pumps.

3.9.1.1.2 Bottle brush

Erythromycin A resistance can be conferred by short pentapeptides with specific amino acid sequences. The synthesis of pentapeptides is due to translation of minigene sequences within 23S rRNA [74]. This mechanism of resistance is also known as bottle brush.

In bottle brush resistance, the newly synthesized pentapeptide actively displaces the macrolides or ketolides from the ribosome. After the macrolide is removed, the ribosome can either initiate synthesis of new polypeptides or can bind another molecule of macrolide or ketolide.

3.9.1.2 Defensive mechanism of resistance

The second mechanism of resistance for bacterial cells to xenobiotics is to render the ribosomal targets (the peptidyl transferase site) inaccessible. Two main mechanisms have been described: blockade of the binding site of erythromycin A by mono- or dimethylation (*erm* gene system) or transformation of the binding site by in situ mutation or indirectly by mutation on certain ribosomal proteins that modify the stereochemistry of the peptidyltransferase site.

3.9.1.2.1 Mono- or dimethylated ribosome: the erm *gene system*

MLS_B resistance is the consequence of induction of the synthesis of 23S rRNA methylase activity. This adds 1 or 2 methyl groups to a single adenosinyl residue (A-2058) on the N^6 amino group of adenine, or to one of the adjacent residues A-2057 or A-2059 in the peptidyltransferase loop of domain V of the 23S rRNA. This prevents access of erythromycin A to its binding site on the ribosome [28,81].

MLS_B resistance may be constitutively expressed or induced by subinhibitory MIC concentrations of 14- and 15-membered ring macrolides [80]. MLS_B resistance is due to *erm* (**e**rythromycin **r**esistance **m**ethylase) genes.

A total of 20 different *erm* genes have been described [65]. *S. pneumoniae* isolates resistant to erythromycin A by an MLS_B mechanism of resistance harbor the *erm*B gene. *S. pyogenes* isolates resistant to erythromycin A harbor *ermB* or *ermTR* genes. The *erm*A and *erm*C genes are found in *S. aureus* and coagulase-negative staphylococci. The *erm*C gene is found mainly in animal staphylococci. Many *erm* genes are often associated with other antibiotic-resistant genes, especially tetracycline-resistant genes. The *erm*F gene is often linked with the *tet*Q gene.

Telithromycin retains activity against *S. aureus* resistant isolates when an inducible mechanism of resistance is involved ($MIC_{50/90}$ 0.12 and 0.25 µg/mL), but not when MLS_B resistance is constitutively expressed (MIC >128 µg/mL).

Against *S. pneumoniae*, telithromycin retains good in vitro and in vivo activity, as demonstrated in animal models (lung infections) and clinical trials. There is no correlation between MIC values for telithromycin (from 0.002 to 1.0 µg/mL) and the expression of the *erm* gene in bacterial cells. Numerous studies investigated the influence of an underlying mechanism of resistance to erythromycin A on telithromycin antipneumococcal activity. Results, including epidemiological surveys, showed that *S. pneumoniae* isolates for which telithromycin exhibited MICs >2 µg/mL are rare, with an incidence of approximately 0.001%.

For *S. pyogenes*, two *erm* genes are involved: *erm*B and ermTR. The in vitro activity of telithromycin differs according to the gene that is expressed. For *erm*TR-containing *S. pyogenes*, MIC values for

telithromycin ranged from 0.03 to 0.25 µg/mL (except for 1 strain MIC 64 µg/mL), and for *erm*B-containing strains, MIC values for telithromycin ranged from 0.5 to 64 µg/mL.

3.9.1.2.2 Mutations

Resistance to erythromycin A can be achieved by mutation affecting 23S rRNA sequences or the amino acid sequences of at least two ribosomal proteins, L4 and L22 [17].

3.9.1.2.2.1 Mutations on 23S rRNA

A-2058→G mutation on 23S rRNA has been described in some bacterial species, rendering them resistant to erythromycin A and its derivatives. These mutations have been described in *Helicobacter pylori* [42], *Mycoplasma pneumoniae* [82], *Treponema pallidum* [69], *Propionibacterium acnes* [67], and *Mycobacterium avium* complex [82].

The ribosomal affinities of both erythromycin A and clarithromycin are lowered 10^4-fold by A-2058→G mutation. The binding affinity of telithromycin is also lowered by the A-2058→G mutation, but to a lesser extent. Telithromycin activity remains at least 20- to 60-fold greater than that of erythromycin A and clarithromycin [29].

3.9.1.2.2.2 Mutations on protein ribosomal L4 and L22

Clinical isolates of *S. pneumoniae* isolates containing ribosomal mutations in proteins have been reported in Bulgaria, Slovakia, and Poland [71]. Against 19 *S. pneumoniae* isolates resistant to erythromycin A (MIC >64 µg/mL) but susceptible to clindamycin and streptogramin B, a mutation on protein L4 at $_{69}$GTG $_{71}$→$_{69}$ TPS$_{71}$ was reported. Footprinting experiments in ribosomes from the *E. coli* L4 mutants revealed that the conformation of 23S rRNA in domain II (A-789, G-799 and U-1255) and domain V (A-2572) is altered relative to the wild type strain. Telithromycin retained activity against these isolates.

3.9.1.3 Preventive mechanism of resistance

The degradative enzymes produced by micro-organisms that are known to inactivate macrolide antibiotics are the glycosylases and phosphorylases. However, this mechanism is limited to bacterial species such as *Nocardia* spp [57]. These enzymes fix a glucose moiety or a phosphate on the 2′OH substituent of the D-desosamine moiety, an amino sugar at position 5 of the erythronolide A ring. By this mechanism, erythromycin A, its derivatives, and telithromycin are inactivated to various degrees. The same enzymes also render *Nocardia* spp resistant to telithromycin. Although of interest scientifically, these are of little relevance to the potential clinical use of telithromycin.

The erythronolide A ring may be hydrolyzed by esterases I or II from *E coli*, but this enzymatic activity is not known for telithromycin.

3.9.2 Resistance to telithromycin

Telithromycin is inactive against *S. aureus* isolates harboring an *erm* gene of constitutive type. MIC values for telithromycin are above 32 µg/mL. Within *S. pyogenes* isolates resistant to erythromycin A and harboring an *erm*B gene, telithromycin MIC values for some isolates are >16 µg/mL.

Other potential mechanisms of resistance have been reported from mutants obtained in the laboratory: L4 protein and L22 ribosomal mutants, 23S rRNA mutants, and K-peptide.

3.9.2.1 L4 mutants

Two types of L4 mutations have been observed. For a mutation at $_{69}$GTG$_{71}$ leading to $_{69}$TPS$_{71}$, 8-fold increases in telithromycin MIC values have been recorded in *S. pneumoniae* (MIC 0.03 to 0.1 µg/mL *vs* MIC 0.006 µg/mL for wild type). In type II mutants ($_{63}$KPW RQK GTG *REK GTC* RAR$_{74}$), increases in telithromycin MIC values up to 500-fold have been recorded (MIC 1.56 to 3.13 µg/mL *vs* MIC 0.006 µg/mL for the wild type) [72].

3.9.2.2 L22 mutants

A mutation in ribosomal protein L22 produces an increase in telithromycin MIC values of about 10-fold. However, the activity of telithromycin remains within the therapeutic range [12].

3.9.2.3 Mutations on 23S rRNA

Mutations of the 23S rRNA, which may increase MICs for telithromycin, have been artificially created by mutation selection in the laboratory. Summarized below are the mutations characterized to date. At this time, these remain laboratory curiosities and their likelihood of arising in the clinic is not known.

- Mutations at U 2609

  A novel mutation at U 2609→C has been described, which confers resistance to telithromycin but increases bacterial cell susceptibility to erythromycin A. This mutation appears to be located within the compound binding site and may directly affect interaction of the telithromycin molecule with the ribosome.

- Mutations on domain II: A-752

  One mutant selected by clarithromycin, resistant to 14- and 15-membered ring macrolides (MIC >32 µg/mL), and with decreased susceptibility to telithromycin (MIC 4 µg/mL) had a single base deletion (A-752) in domain II [12].

- Mutation at C-2611

  The C-2611→U mutation confers mild macrolide-ketolide resistance that does not extend to other members of the MLS group. This has been characterized in laboratory studies [77,78].

- Mutation on domain V

  In laboratory studies, mutations at A-2058/2059 of domain V of 23S rRNA yielded 3 different mutations: A-2058→T, A-2059→G, A-2058→G. Telithromycin in vitro activity decreased in comparison with wild type [12].

- Mutation U 754

  Mutation in the hairpin 35 at U 754→A renders bacterial cells resistant to low concentrations of erythromycin A and telithromycin [85].

3.9.2.4 K-peptide

K-peptide, a specific pentapeptide acting as a bottle brush, which cleans the ribosome from the bound antibiotic, confers resistance to the ketolides.

3.9.3 Inducible MLS_B resistance

It has been shown that ketolides, which lack L-cladinose at position 3 of the erythronolide A ring, are unable to induce MLS_B resistance. The ability to induce MLS_B resistance was investigated for telithromycin and its L-cladinose counterpart (RU 69874), and 14-membered ring macrolides with and without L-cladinose. Erythromycin A, azithromycin, clarithromycin, and RU 69874 (all bearing a 3–α-L-cladinose moiety) were strong inducers of MLS_B resistance in erythromycin A-inducible resistance strains. In contrast, telithromycin (with no L-cladinose moiety) was unable to induce resistance to erythromycin A [55].

Induced bacterial cultures containing subinhibitory concentrations of erythromycin A, telithromycin, or an uninduced control were challenged with 50 µg/mL of erythromycin A. Bacterial growth was lowest for telithromycin throughout much of the assessment time.

3.9.4 Selection of resistant mutants

3.9.4.1 Serial passage experiments

Appelbaum, Davies *et al* examined the ability of sequential subcultures in subinhibitory concentrations of telithromycin, azithromycin, roxithromycin, clindamycin, and pristinamycin to select for resistance. The study was performed in five erythromycin A-susceptible and six erythromycin A-resistant strains of *S. pneumoniae*. The latter group consisted of 3 strains containing *mef*E genes and 3 strains containing *erm*B genes. The findings can be summarized as follows:

- Overall, 54 mutants were derived with increased MICs to at least one of the antibiotics. Only three of these mutants exhibited telithromycin MICs of >1 µg/mL, compared with 34 and 28 mutants exhibiting MICs of >1 µg/mL to azithromycin and clarithromycin, respectively.
- In three of the five erythromycin A-susceptible *S. pneumoniae* strains tested, no mutants were selected, even after 50 passages with telithromycin. In contrast, passage in erythromycin A resulted in mutants for all 5 strains, and clarithromycin and azithromycin selected for 4 mutants.
- While exposure to telithromycin did select for pneumococcal mutants with increased MICs, most remained within the proposed susceptibility range and, furthermore, telithromycin selected mutations in the least number of strains, compared to the other MLS agents.

In summary, telithromycin was shown to have good in vitro activity against strains containing *mef*E and *erm*B genes and against in vitro-selected mutants resistant to the 14- and 15-membered ring macrolides, clindamycin, and pristinamycin [24,51].

3.9.4.2 Spontaneous mutation experiments

Plating of high populations of *S. pneumoniae* strains onto agar containing telithromycin showed that the spontaneous mutation frequency (i.e., recovering colonies that grew at telithromycin concentrations higher than the MIC) was less than $1x10^{-8}$, which is considered to be low.

3.10 Microbiology summary

- Telithromycin is a new medicinal chemical entity belonging to the ketolide class, with a unique chemical structure.
- Telithromycin exhibits a new mode of action, inhibiting protein synthesis by a double interaction at the 23S rRNA of bacterial ribosomes and in the formation of both ribosomal subunits.
- These properties result in superior antibacterial activity of telithromycin against the main respiratory pathogens when compared with currently available 14- and 15-membered ring macrolides, with telithromycin being two- to four-times more active than clarithromycin against *S. pneumoniae* and exhibiting a comparable activity to clarithromycin and azithromycin against *S. pyogenes* and *H. influenzae*, respectively.
- Telithromycin exhibits potent antibacterial activity against *S. pneumoniae* isolates susceptible to erythromycin A and penicillin G. In addition, telithromycin exhibits high bactericidal activity against *S. pneumoniae*.
- Telithromycin retains activity against penicillin G-resistant isolates of *S. pneumoniae* and erythromycin A-resistant isolates harboring either an MLS_B or an efflux mechanism of resistance, or protein L4 ribosomal mutation.
- Telithromycin exhibits in vitro activity against *S. pneumoniae* isolates resistant to fluoroquinolones, cefotaxime-ceftriaxone, cotrimoxazole and tetracycline.
- Telithromycin selects mutants of *S. pneumoniae* at low frequency.
- Telithromycin is active against *S. pyogenes*, *H. influenzae*, *M. catarrhalis*, and *S. aureus*.
- Telithromycin is highly concentrated in phagocytes with a moderate efflux which leads to balanced intracellular and extracellular concentrations.
- Telithromycin is active against intracellular pathogens such as *Chlamydia pneumoniae* and *Legionella pneumophila.*
- Telithromycin is highly effective against atypical microorganisms such as *Mycoplasma pneumoniae*.

4. NONCLINICAL TOXICOLOGY, PHARMACOKINETICS AND PHARMACOLOGY

4.1 Toxicology

Repeated-dose oral toxicity studies of up to 6 months in duration were carried out in the rat, dog, and monkey, as summarized in the table below.

Table 4-1. Repeated-dose oral toxicity studies with telithromycin

Species	Route	Duration of dosing	Recovery period	Dose levels (mg/kg/day)
Rat	Oral	15 days	-	0, 100, 200, 400
		30 days[a]	28 days	0, 50, 150, 300
		13 weeks[a]	-	0, 20, 50, 150
		6 months[a]	-	0, 150
		6 months[a]	28 days	0, 20, 50, 150
Dog	Oral	15 days[a]	-	0, 100, 400, 1000
		30 days[a]	-	0, 50, 150, 300
		13 weeks[a]	12 weeks	0, 20, 50, 150
Monkey	Oral	14 days	-	100, 200, 300
		28 days[a]	-	0, 30, 60, 120

[a] Studies with toxicokinetic support

In these studies, effects typical of macrolide antibiotics, as reported, for example, for erythromycin, azithromycin, and clarithromycin, were observed. Raised levels of transaminases, some increases in liver weights, and histological correlates of foci of hepatocellular necrosis were seen at higher doses in some but not all studies. Slight phospholipidosis was evident in some rat and dog tissues, with limited distribution and intensity.

The No Observed Adverse Effect Level (NOAEL) in the rat and dog studies was 50 mg/kg/day, whatever the duration of the study. All findings were reversible. Relative to exposure levels in man, these NOAELs gave ratios of 1.6 and 14 for rat and dog, respectively, based on free fractions of drugs and levels achieved in young adult humans. Based on literature data, comparative ratios for azithromycin are 4.5 and 24, respectively [32,37,53,62,68], while for clarithromycin they are 0.5 and 1.6, respectively [1,2,20,23,49].

The NOAEL of 60 mg/kg/day in the monkey corresponded to an exposure 3.4 times that in man at the therapeutic dose, again based on levels of free drug in young adult humans.

Reproductive toxicity studies were carried out in the rat and rabbit, as summarized in the following table.

Table 4-2. Reproduction toxicity studies with telithromycin

Study type	Species	Dosing period[a]	Dose levels (mg/kg/day)
Fertility	Rat	M – Day 29 pm to Day 27 pc[c] F – Day 15 pm to Day 7 pc	0, 50, 150, 300
Embryotoxicity	Rat	Days 6 to 17 pc[b]	0, 50, 150, 300
		Days 6 to 17 pc[c]	0, 50, 150, 300
	Rabbit	Days 6 to 18 pc[b]	0, 30, 100, 300
		Days 6 to 18 pc[c]	0, 20, 60, 180
		Days 6 to 18 pc[c]	0, 20, 60, 180
Pre/post natal	Rat	Day 6 pc to Day 21 pp[c]	0, 50, 125, 200

[a] pm = premating; pc = post coitum; pp = post partum
[b] Preliminary studies
[c] Studies with toxicokinetic support

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 malformations in rats at a maternally toxic dose of 300 mg/kg/day. No evidence of a direct teratogenic effect was observed. In the fertility study, fertility indices were slightly reduced at parentally 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.

Telithromycin was not genotoxic in a standard battery of tests.

4.2 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 to 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.

4.3 Safety pharmacology

Telithromycin has been subjected to a range of tests designed to evaluate its general pharmacological effect on body systems. In vivo tests were carried out by both the oral (doses up to 300 mg/kg) and intravenous routes (doses up to 15 mg/kg), while in vitro studies used concentrations of 0.1 to 500 µM. A concentration of 100 µM corresponds to 81.2 µg/mL. Few effects were observed apart from isolated findings at high doses.

Telithromycin was slightly emetic in the dog with a potency similar to that of clarithromycin but the effect was less pronounced than that of azithromycin or erythromycin. Telithromycin, unlike azithromycin or erythromycin, did not induce diarrhea in these animals. A delay in gastric emptying was seen in rats after oral doses of 100 and 300 mg/kg, but there was no action on intestinal transit and only a slight effect in reducing acidity of gastric contents. Telithromycin showed very weak binding to the human motilin receptor (23% at 100 µM) as compared to erythromycin (60% at 3 µM).

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. These data are reported and discussed in the context of clinical safety (see *Section 7.5, Assessment of the effects of telithromycin administration on cardiac repolarization*).

5. CLINICAL PHARMACOKINETICS AND DOSE DETERMINATION

The clinical pharmacology of telithromycin was investigated in an extensive program involving 847 subjects. Twenty-three studies investigated pharmacokinetics, bioavailability and metabolism. Thirteen studies investigated interactions, 7 studies investigated special populations (30 subjects with renal impairment, 12 subjects with hepatic impairment, 58 elderly subjects ≥65 years, 18 adolescents with RTIs, 24 subjects with cardiovascular disease).

The clinical pharmacokinetics of telithromycin were 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.

5.1 Absorption, distribution, metabolism, and elimination

5.1.1 Absorption/Bioavailability

The absorption of telithromycin in humans is estimated to be almost complete (90%). Prior to entering the systemic circulation, telithromycin undergoes first-pass due to 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.

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. 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 (25%), with minor contributions from acid α1-glycoprotein (11%) and the lipoproteins LDL, VLDL, and HDL (10% each). Binding was not saturable across the range of concentrations that arise from the therapeutic dose of telithromycin. This moderate level of binding, and the absence of significant saturation at therapeutic levels, mean that clinically relevant interactions by protein-binding displacement of telithromycin are unlikely.

Tissue distribution

The volume of distribution of telithromycin after intravenous infusion was high (2.9 L/kg), and extensive tissue distribution was confirmed in various biological tissues after multiple dosing, as summarized in the table below.

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

Tissue		Subjects	Mean concentration (µg/mL)				
			2-3h	6-8h	12h	24h	48h
Epithelial lining fluid		Healthy	5.4[a]	4.2[d]	–	1.17	0.30
		RTI patients	14.9[a]	–	3.27	0.84	–
Alveolar macrophages		Healthy	65[a]	100[d]	–	41	2.15
		RTI patients	69[a]	–	318	162	–
Bronchial tissue [e]		Healthy	0.68[a]	2.2[d]	–	3.5	LOQ
		RTI patients	3.88[a]	–	1.41	0.78	–
Tonsils [e]		Tonsillitis	3.95[b]	–	0.88	0.72	–
White blood cells	(Day 5)	Healthy[f]	64.6[a]	72.1[c]	39.4	14.1	–
	(Day 10)	Healthy[f]	83[a]	60.9[c]	40.6	20.9	8.9

[a] 2h, [b] 3h, [c] 6h, [d] 8h, [e] concentrations in µg/g.
[f] 600 mg once a day; all other studies used 800 mg once a day.
LOQ = Below the lower limit of quantification; NC = not calculated; – = No data collected

The concentrations of telithromycin observed in tissues are high compared to the MIC values for telithromycin against the main pathogens encountered in RTIs. High concentrations in epithelial lining fluid and alveolar macrophages persisted for up to 48 hours after dosing.

In the case of epithelial lining fluid, the difference in concentrations measured 2 to 3 hours after dosing in the 2 studies can be attributed to differences between RTI patients and healthy subjects. In addition, small differences in sampling times at around the time of peak concentrations may have resulted in differences. The higher peak concentration measured in the RTI patients is considered more representative, and samples were obtained closer to the expected C_{max}. It is also relevant to note that the study in RTI patients was conducted in the unit of Prof. Wise at the Birmingham Chest Clinic, UK, with the same methodology used for other compounds, thereby enabling direct comparisons to be made.

At the dose of 800 mg telithromycin, the maximum concentration of telithromycin in saliva (3.1 µg/mL on days 1 and 10 of dosing) was higher than in plasma, and the concentrations were above the MIC_{50} for group A, C, and G beta-hemolytic streptococci (0.008 to ≤0.06 µg/mL). The same was also true for concentrations of telithromycin in the tonsils.

5.1.3 Metabolites of telithromycin

In plasma, the main circulating compound after administration of an 800 mg radiolabelled dose was telithromycin, representing 56.7% of the total AUC of radioactivity. 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 (see table below). The antibacterial activities of the metabolites have been studied and are also summarized in the table below.

Table 5-2. Antibacterial activity of telithromycin and its main metabolites

Analyte	AUC metabolite / AUC telithromycin (%)	*S. pneumoniae* (Ery-R)		*S. pyogenes* (Ery-R)	
		MIC_{50} (µg/mL)	AUC/ MIC_{50}	MIC_{50} (µg/mL)	AUC/ MIC_{50}
Telithromycin	–	0.03	247	0.06	123
RU 72365	2.97	0.03	7.4	0.5	0.44
RU 76584	2.03	0.12	1.2	1.0	0.15
RU 76363	12.6	0.12	7.3	1.0	0.87
RU 78849	2.22	>16	<0.01	>16	<0.01

The AUC/MIC ratios for all metabolites indicate that they contribute little to the antibiotic activity of telithromycin.

5.1.4 Pathways of elimination

The 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 mainly by the liver, but also to some extent by 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 by renal excretion
  - 37% is metabolized by the liver.
- Overall metabolism accounts for approximately 70% of the dose (33% pre-systemic and 37% systemic). About half of this 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 any one pathway is impaired.

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 were assessed in young healthy subjects (18 to 29 years) in a crossover study. The mean pharmacokinetic parameters for the 800 mg doses of telithromycin (the therapeutic dose) in this study are summarized in the table below.

Table 5-3. Pharmacokinetic parameters of telithromycin in young subjects after single and multiple (qd) oral 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)
$t_{1/2,\lambda 1}$ (h) [c]	2.43 (41)	2.87 (50)
$t_{1/2,\lambda z}$ (h) [c]	7.16 (19)	9.81 (20)

SD = single dose, MD_7 = 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 seven days of dosing. AUC and C24h increased upon multiple dosing, and steady state (based on C24h) was achieved by the 2nd or 3rd 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.

5.3 Pharmacokinetics in RTI patients from clinical trials

Two hundred and twenty patients with CAP (mean age 42.6 years) in Study 3000 (Phase III) were included in the investigation of pharmacokinetics in patients from clinical trials. At the on-therapy visit (Day 3 to 5 of dosing), blood samples were taken before dosing and at 1, 2, 4, 6, and 8 hours after dosing for analysis of telithromycin concentrations in plasma. The C_{max} and AUC values in these patients were 2.89 µg/mL and 13.9 µg·h/mL, respectively, compared to values of 2.27 µg/mL and 12.5 µg·h/mL in healthy subjects (see *Section 5.2, Pharmacokinetic characteristics of telithromycin 800 mg (single and multiple dose)*).

A multiple-dose (800 mg qd) pharmacokinetic study was conducted in adolescent patients with bacterial RTIs, which confirmed that the pharmacokinetics of telithromycin in these patients were similar to those in healthy adults.

5.4 Pharmacokinetics in populations of special interest

5.4.1 Elderly subjects

The pharmacokinetics of telithromycin after multiple dosing with telithromycin 800 mg have been investigated in elderly healthy subjects and elderly patients with CAP, as summarized in the table below.

Table 5-4. Comparison of pharmacokinetics between elderly and young subjects (healthy and patients with CAP) after multiple oral dosing with telithromycin (800 mg qd)

Parameter	Mean (CV%)			
	Healthy subjects [a]		Patients 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)	3.53 (63)	2.80 (50)
AUC(0-24h) (µg.h/mL)	17.2 (32)	8.5 (31)	25.9 (70)	18.1 (63)

[a] Treatment for 10 days
[b] Treatment for 7 to 10 days
[c] N=16

The pharmacokinetics in elderly patients (≥65 years) with CAP compared to young subjects (<65 years) indicate that there is a 1.3-fold increase in C_{max} and a 1.4-fold increase in AUC in the elderly patients at the therapeutic dose of telithromycin (800 mg qd). A similar magnitude of change was also observed in healthy elderly subjects.

The unbound fraction of telithromycin is similar between elderly and young patients.

5.4.2 Subjects with renal impairment

The pharmacokinetics of a single oral dose of 800 mg telithromycin were examined in subjects with various degrees of renal impairment or end-stage renal failure (N = 30), and in control subjects with normal renal function (N = 10). The results are summarized in the table below.

Table 5-5. Comparison of pharmacokinetics between subjects with differing degrees of renal function after a single oral dose of 800 mg telithromycin

Parameter	Renal function group			
Creatinine clearance (mL/min)	>80 N=10	41 to 80 N=10	11 to 40 N=10	≤10 N=10
C_{max} (µg/mL)	2.25	3.00	3.25	2.13
AUC(0-∞) (µg·h/mL)	10.09	14.31	16.00	10.79
$t_{½,\lambda z}$ (h)	10.66	11.41	12.58	14.64

Plasma concentrations of telithromycin in subjects with mild to severe impairment were 1.4-fold higher for C_{max}, and 1.4 to 1.5-fold higher for AUC, than those of control subjects. When telithromycin was given to subjects with end-stage renal failure (CL_{CR} ≤10 mL/min) 2 hours after dialysis, C_{max} and AUC were similar to the control group. Pharmacokinetic parameters of telithromycin were similar between the subgroups of subjects with renal impairment, despite a significant linear relationship between creatinine clearance and renal clearance of telithromycin. The elimination half-life of telithromycin did not increase markedly in subjects with renal impairment or end-stage renal failure compared to the control subjects. The results in the end-stage renal failure group could be explained by the short interval of time between dialysis and administration of telithromycin.

Overall, these changes are consistent with the limited role played by renal excretion in the elimination of telithromycin. Renal excretion may play a more important role because it may serve as a compensatory elimination pathway in those patients whose metabolism of telithromycin is impaired.

5.4.3 Subjects with hepatic impairment

The pharmacokinetics of a single oral dose of 800 mg telithromycin were examined in subjects with hepatic impairment (median Child Pugh score of 9, range 5 to 12) in a study that was pair-matched to control healthy subjects in terms of demographic characteristics. The results are summarized in the table below.

Table 5-6. 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]
C24h (μg/mL)	0.088 (61)	0.039 (39)
AUC(0-∞) (μg·h/mL)	11.1 (38)	10.10 (30)
$t_{1/2,\lambda 1}$ (h)	2.60 (53)	2.00 (25)
$t_{1/2,\lambda z}$ (h)	14.16 (14)	10.33 (27)
CL_R (L/h)	17.3 (43)	10.78 (16)

[a] Median value

C_{max} and AUC were similar between subjects with hepatic impairment and healthy control subjects. 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. There was a slight increase in the terminal half-life in the subjects with hepatic impairment (1.2- to 1.4-fold). Given the minor contribution of the terminal half-life to the overall AUC of telithromycin, this increase observed after the single dose is not expected to result in further accumulation after multiple dosing.

All the available data support the view that, despite the important contribution of metabolism to the elimination of telithromycin, hepatic impairment without severe renal impairment has only a moderate effect on the pharmacokinetics of telithromycin. The conclusion that there is no

accumulation after multiple dosing has been preliminarily confirmed in mild-to-moderate hepatically impaired subjects by the initial results of an ongoing multiple-dose study. Data available for 3 subjects (Child Pugh scores of 5 to 7) indicate that the exposure to telithromycin after multiple dosing is similar to the exposure in healthy subjects.

In addition, the unbound plasma fraction of telithromycin is similar in subjects with and without hepatic impairment.

5.4.4 Subjects with multiple impairment

Telithromycin is cleared from the body by multiple routes, including excretion of unchanged drug in urine and feces, and metabolic pathways.

Based on the metabolic pathways identified and on the data obtained in subjects with renal and hepatic impairment, renal excretion may serve as a compensatory elimination pathway in situations where metabolic clearance is impaired. In patients with severe renal impairment, this compensatory pathway is not available and a dose adjustment may be required.

5.5 Drug interactions

The metabolism of telithromycin is mediated in approximately equal amounts by CYP3A4 and non-CYP3A4 pathways. In vitro, using human hepatic microsomes, telithromycin is a competitive inhibitor of CYP3A4 (Ki = 58 μM) and of CYP2D6 (Ki = 46 μM).

Based on these results, specific metabolic drug interaction studies were performed in humans to assess the effect of CYP3A4 inhibitors (itraconazole, ketoconazole, grapefruit juice) on the pharmacokinetics of telithromycin, and to assess the effect of telithromycin on CYP3A4 substrates (cisapride, simvastatin, midazolam), CYP2D6 substrates (paroxetine), and on other cytochrome P450 subfamily substrates (theophylline, warfarin and oral contraceptives). These interaction studies were all multiple-dose studies performed under clinical conditions (i.e., multiple therapeutic doses) for both drugs except for the warfarin interaction study, which had a single-dose design using a well-validated model.

5.5.1 CYP3A4 inhibitors

Itraconazole, ketoconazole

An increase in telithromycin plasma concentrations was seen on coadministration with itraconazole or ketoconazole. $AUC_{(0\text{-}24)ss}$ increased ~1.5-fold following itraconazole co-administration and 2-fold following ketoconazole co-administration, and $C_{max,ss}$ increased 1.2- and 1.5-fold, respectively. This moderate increase in AUC and $C_{max,}$, even with a potent inhibitor of CYP3A4 such as ketoconazole, is in agreement with expectations from the elimination pathways of telithromycin and from the 57% absolute bioavailability of telithromycin.

Grapefruit juice

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

5.5.2 CYP3A4 substrates

Cisapride

An increase in exposure to cisapride (a drug known to prolong the QT interval) was seen on co-administration with telithromycin, as demonstrated by increases of 2.4-fold in AUC and 2.0-fold in C_{max} at steady state. The same type of interaction has been reported with clarithromycin [76]. Inhibition of metabolic first pass could account for this interaction. Due to potential QTc prolongation related to high cisapride concentrations, coadministration of telithromycin with cisapride is contraindicated.

Simvastatin

A marked increase in simvastatin exposure was seen on co-administration with telithromycin. While the elimination half-life of simvastatin was not changed, telithromycin greatly increased the bioavailability of simvastatin. C_{max} and AUC values for simvastatin were increased 5.3- and 8.9-fold, respectively, while values for simvastatin acid were increased 15- and 12-fold. The same type of interaction has been reported with erythromycin [47]. Caution should be used if telithromycin is administered in combination with HMG-CoA reductase inhibitors that are metabolized by CYP3A4, such as simvastatin, atorvastatin, and lovastatin, and dosage adjustment of these HMG-CoA reductase inhibitors are recommended. For statins that are not metabolized by CYP3A4 (pravastatin, fluvastatin), clinically relevant interactions are unlikely.

Midazolam

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, both at the intestinal and hepatic levels. Caution is advised when midazolam is administered concomitantly with telithromycin because of the potential for inducing prolonged sedation. The dosage of orally administered midazolam should be adjusted as necessary to avoid such prolonged sedation. The same precautions should also apply to another benzodiazepine triazolam, which is highly metabolized by CYP3A4 and undergoes a high CYP3A4-dependent first-pass metabolism, and to the other benzodiazepines (or similar drugs) that are mainly metabolized by CYP3A4 pathways (alprazolam, diazepam, zolpidem). For those benzodiazepines that are only slightly or not metabolized by CYP3A4 (temazepam, nitrazepam, lorazepam), clinically relevant interaction with telithromycin is unlikely.

5.5.3 CYP2D6 substrates

Paroxetine

Co-administration of telithromycin with paroxetine did not alter the pharmacokinetics of paroxetine. A clinically significant interaction with paroxetine or other CYP2D6 drug substrates is therefore unlikely when co-administered with telithromycin.

5.5.4 Other drugs

Theophylline

$AUC_{(0-12)ss}$ and $C_{max,ss}$ values of theophylline increased by approximately 16% after co-administration of telithromycin . This level of interaction is not considered to be clinically significant. However, in a few subjects, severe nausea and vomiting were observed when the drugs were given simultaneously, but this did not recur when the theophylline dose was given 1 hour before administration of telithromycin. Thus, theophylline and telithromycin should be administered at least 1 hour apart.

Warfarin

There was no pharmacokinetic or pharmacodynamic interaction between telithromycin and racemic warfarin.

Digoxin

The AUC of digoxin increased by 36%, and the trough plasma concentrations by 20%, on coadministration with telithromycin. 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. This interaction is due to a decrease in sotalol absorption in the presence of telithromycin. The concomitant administration of the two agents did not result in a synergistic effect on cardiac repolarization.

Oral contraceptives

A multiple-dose study of the interaction between telithromycin and low-dose triphasic oral contraceptives showed that telithromycin did not affect anti-ovulatory action.

Intra-gastric pH-altering agents

Co-administration of intra-gastric pH-altering agents (Maalox® or Zantac®) did not alter the pharmacokinetics of telithromycin.

5.6 Dose regimen determination

The potential activity of an antibiotic in patients can be extrapolated from the relationship between its concentrations in healthy subjects and the MIC values of the pathogens isolated in the targeted indications. Dose-ranging studies have not generally been useful for showing differences between dosages of antibiotics. The relationship between telithromycin plasma, tissue and white blood cell concentrations was considered a more accurate basis for prediction of efficacy than a classical dose comparison study.

The telithromycin dose of 800 mg once daily selected for clinical trials was chosen based on the pharmacokinetic/pharmacodynamic profile data obtained in preclinical in vitro and animal studies, and in studies in healthy subjects.

The mouse thigh infection model (Craig model) was used to determine which PK/PD parameter is the major determinant of *in vivo* efficacy for telithromycin. In this model, neutropenic mice were infected with $10^{6.6}$ cfu/thigh of *S. pneumoniae* ATCC 10813 and treated subcutaneously for 24 hours with 2.34 to 150 mg/kg telithromycin divided in doses administered every 3, 6, 12 and 24 hours, starting 2 hours after infection. An E_{max} dose-response model was used to calculate the dose (static dose) producing a net bacteriostatic effect over 24 hours of therapy Overall the static dose was not altered by the dosing interval, as shown in the table below.

Table 5-7. Static dose of telithromycin in the mouse thigh infection model

Dosing frequency (hours)	Static dose Mean ± std dev. (mg/kg/24hours)
3	21.0 ± 3.2
6	18.5 ± 2.8
12	18.0 ± 1.7
24	29.1 ± 4.8

The corresponding pharmacokinetic parameters were calculated from the relationship between AUC and C_{max} (total and free) and the dose. These data were obtained after single subcutaneous administration of doses ranging from 4.69 to 75 mg/kg. Finally the PK/PD relationships were based on these single-dose pharmacokinetic parameters and showed that unbound AUC(0-24h)/MIC was the parameter that best correlated with efficacy (R^2 = 90% *vs* 70% for unbound peak/MIC and 46% for time above MIC). Additional studies performed in the same laboratory have demonstrated concentration-dependent killing with telithromycin, in contrast to azithromycin [22]. Further details on these PK/PD relationships are available in *Appendix 2. Dose response*. All these results demonstrate that the efficacy of telithromycin is concentration-dependent, and not time-dependent, as with erythromycin and clarithromycin, and justify the once-daily dosing regimen.

Based on the results of this PK/PD model, the dose of telithromycin in humans was selected that yielded free AUC/MIC values that were similar to, or higher than, AUC/MIC values at the static dose in mice. The 800 mg dose administered once daily fulfilled these criteria.

In contrast to the situation with *S. pneumoniae*, there is no well-validated model for lower RTI with *H. influenzae* that can be used to predict the therapeutic dose for this pathogen. Nontypable *H. influenzae* has only rarely been isolated in the bloodstream in infected patients. Hence, the levels of drug in respiratory tissue are more important than the blood levels in the treatment of infections caused by this pathogen. After once-daily dosing with 800 mg telithromycin, the concentrations in epithelial lining fluid of up to 14.9 µg/mL (see *Section 5.1.2, Distribution*) exceed the MIC values for *H. influenzae*. In addition, plasma and tissues concentrations for telithromycin are higher than those for azithromycin, which is known to be one of the most efficacious macrolides against *H. influenzae* RTIs.

At a dose of 800 mg once daily, the tolerance of telithromycin in young and elderly subjects in clinical pharmacology studies was considered adequate to initiate larger studies in patients with that dose regimen.

There is a current trend to reduce treatment duration from the traditional 7 to 10 days to a shorter 5-day duration for most upper RTIs [63]. The rationale for shortening treatment duration is based on the fact that subjects tend to stop taking their medication once symptoms have resolved. Medical benefits of a shortened treatment duration include a shorter period of risk for drug-drug interactions and side effects, potentially improved compliance, and decreased induction of resistance, which could result from poor compliance with prolonged treatments (see [39], available in *Appendix 1. Relevant references*).

The effectiveness of a shortened treatment duration depends both on the intrinsic properties of the compound (antibacterial activity, pharmacokinetic profile, and high tissue diffusion) and on the use of an adequate dose. Plasma concentrations obtained with the dose of 800 mg once daily ensured a good coverage of the causative pathogens for RTIs. High concentrations were observed in epithelial lining fluid and alveolar macrophages, and these concentrations were still substantial at 24 hours after dosing (see *Tissue distribution* in *Section 5.1.2, Distribution*). These high concentrations in tissues suggest both rapid killing (concentration-dependent antibiotic) and a long-lasting antibacterial effect of telithromycin at the site of infection.

A 5-day duration of treatment in adequate well–controlled comparative studies for registration was performed in acute sinusitis, AECB, and GABHS tonsillitis/pharyngitis in adults. The effectiveness of a shorter treatment duration is not as well documented in CAP, which could have a more severe outcome than other pathologies; therefore, a treatment duration of 7 to 10 days was used in this indication.

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), acute sinusitis, and tonsillitis/pharyngitis due to group A β-hemolytic *Streptococcus* (GABHS).

6.1.2 Studies performed

Thirteen Phase III studies were conducted by the sponsor's US and European operational sites to support the claim for the four target indications. In addition, one study in CAP (Study 2105) was conducted in Japan. Efficacy data from Study 2105 were not submitted 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 by the sponsor's US and European operational sites) and the Japanese Study 2105.

The study design and dosing regimen of the 13 Phase III studies and Study 2105 used to support the claim are summarized in the table below.

Table 6-1. Studies performed to support the claim

Study No.	Study design	Duration	Treatment Regimen	
CAP (Western studies)				
3000	Open label	7-10 d	TEL	800 mg qd
3001	Double-blind, randomized, active controlled, 2-arm, parallel group	10 d 10 d	TEL AMX	800 mg qd 1000 mg tid
3006	Double-blind, randomized, active controlled, 2-arm, parallel group	10 d 10 d	TEL CLA	800 mg qd 500 mg bid
3009	Double-blind, randomized, active controlled, 2-arm, parallel group	7-10 d 7-10 d	TEL TVA	800 mg qd 200 mg qd
3009OL	Open label	7-10 d	TEL	800 mg qd
3010	Open label	7 d	TEL	800 mg qd
CAP (Japanese study)[a]				
2105	Double-blind, randomized, 2-arm, parallel group	7 d	TEL TEL	600 mg qd 800 mg qd
AECB				
3003	Double-blind, randomized, active controlled, 2-arm, parallel group	5 d 10 d	TEL AMC	800 mg qd 500 mg/125 mg tid
3007	Double-blind, randomized, active controlled, 2-arm, parallel group	5 d 10 d	TEL CXM	800 mg qd 500 mg bid
Acute sinusitis				
3002	Double-blind, randomized, 2-arm, parallel group	5 d 10 d	TEL TEL	800 mg qd 800 mg qd
3005	Double-blind, randomized, active controlled, 3-arm, parallel group	5 d 10 d 10 d	TEL TEL AMC	800 mg qd 800 mg qd 500 mg/125 mg tid
3011	Double-blind, randomized, active controlled, 2-arm, parallel group	5 d 10 d	TEL CXM	800 mg qd 250 mg bid
Tonsillitis/Pharyngitis				
3004	Double-blind, randomized, active controlled, 2-arm, parallel group	5 d 10 d	TEL PEN	800 mg qd 500 mg tid
3008	Double-blind, randomized, active controlled, 2-arm, parallel group	5 d 10 d	TEL CLA	800 mg qd 250 mg bid

TEL = telithromycin; AMX = amoxicillin; CLA = clarithromycin; TVA = trovafloxacin; AMC = amoxicillin+clavulanic acid (Augmentin®); CXM = cefuroxime axetil; PEN = penicillin VK.

[a] Efficacy data not submitted in NDA. In agreement with the FDA, only data from subjects with resistant *S. pneumoniae* isolates are used to support the claim, and are integrated with the data from Western studies.

Across the four indications for which approval is being sought, nine actively controlled studies are used to support the claim. In addition, there are four uncontrolled studies (three open-label Western studies in CAP and one double-blind comparative study of two durations of treatment with telithromycin in acute sinusitis) which are also used to support the claim for the appropriate indication.

6.1.3 Number of subjects and enrollment

A total of 5926 subjects were enrolled and 4998 subjects were randomized (or assigned, as in open-label studies 3000, 3009OL and 3010) to telithromycin (3298 subjects) or comparator drugs (1700

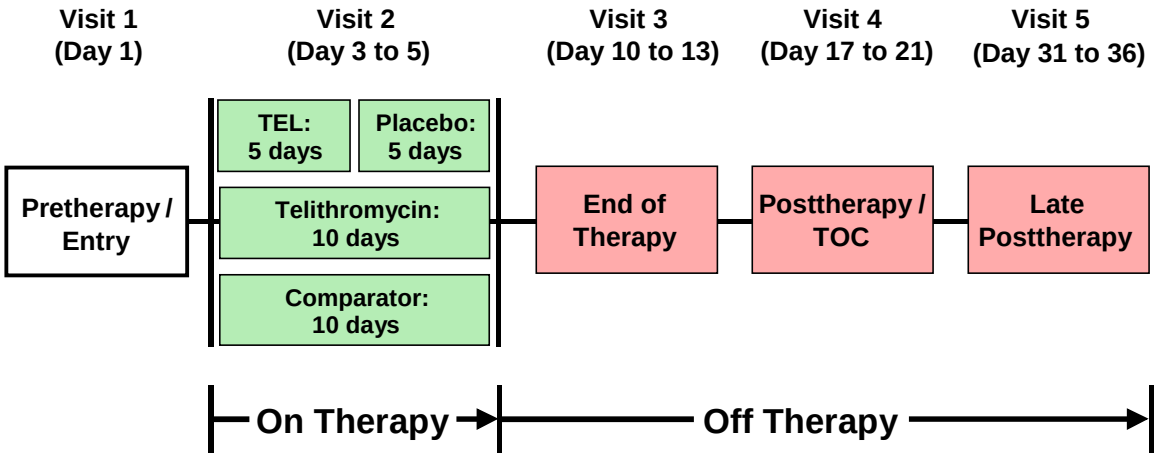
subjects) in the Phase III clinical program (Western studies): 3290 were treated with telithromycin and 1695 with a comparator antibiotic. Thirteen subjects were randomized but did not receive treatment.

Adult subjects (≥18 years of age) were to be included in CAP, AECB, and acute sinusitis studies. Adult subjects and adolescents (≥13 and <18 years of age) were to be included in the tonsillitis/pharyngitis studies.

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 Study 2105, the main end point was performed at the end of treatment (7 days) 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 28 days after commencing treatment, which approximated 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. Efficacy assessments are summarized in *Appendix 3. Schedule of efficacy assessments.*

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: 7 days only (Study 3010), 7-10 days (Studies 3000, 3009, and 3009OL), or 10 days (Studies 3001 and 3006)
- AECB: 5 days (Studies 3003 and 3007)
- Acute sinusitis: 5 days only (Study 3011), or 5 or 10 days (Studies 3002 and 3005)
- Tonsillitis/pharyngitis: 5 days (Studies 3004 and 3008)

When the telithromycin dosing regimen called for fewer days of active medication than in the comparative treatment group, a regimen of placebo treatment followed up until the maximum number of days of treatment (10 days) 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 (Study 3006), and trovafloxacin 200 mg once daily for 7 to 10 days (Study 3009). There was no active comparator in the Japanese Study 2105, which compared two 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) and cefuroxime axetil 500 mg bid for 10 days (Study 3007).
- 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 two 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.
- In the tonsillitis/pharyngitis studies, comparator regimens were penicillin VK 500 mg tid for 10 days (Study 3004) and clarithromycin 250 mg bid for 10 days (Study 3008).

6.2.3 Standardization of processes

6.2.3.1 Clinical evaluation

Time windows for assessment of outcome (Western studies)

There were five visits in each study: pretherapy/entry, on-therapy, end-of-therapy, posttherapy/TOC and late posttherapy. Efficacy was analyzed at the posttherapy/TOC and late posttherapy visits. Similar time windows were used for these visits in the studies for the four 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 17-24 (Days 16-23 in tonsillitis/pharyngitis) was used for the assessment of efficacy at TOC. A time window of Days 31-45 was used for the efficacy analyses at late posttherapy. This extended window was used to accommodate the more erratic visit timing at late posttherapy compared to posttherapy/TOC, and to ensure that relapses occurring later would be included in the per protocol analysis performed at late posttherapy.

In the studies comparing a 5-day and 10-day treatment period (3003 and 3007 in AECB, 3002 and 3005 in acute sinusitis, and 3004 and 3008 in tonsillitis/pharyngitis), 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 posttherapy/TOC and late posttherapy 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 posttherapy/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.

6.2.3.2 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.

In the tonsillitis/pharyngitis studies, throat swab specimens were obtained for a rapid streptococcal antigen test to determine subject eligibility for inclusion and to perform a bacteriological culture. Streptococcal A antigen was detected using test kits (Abbott Signify Strep A Kit).

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 two 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) and susceptibility to erythromycin was analyzed at CMI.

Pathogens were classified as follows according to provisional breakpoints:

Table 6-2. Provisional breakpoints for telithromycin

	Streptococci, including *S. pneumoniae*		*H. influenzae*		Staphylococci and Enterococci	
	MIC (µg/mL)	Zone diameter (mm)	MIC (µg/mL)	Zone diameter (mm)	MIC (µg/mL)	Zone diameter (mm)
Susceptible	≤ 1.0	≥ 19	≤ 2.0	≥ 16	≤ 1.0	≥ 22
Intermediate	2.0	16-18	4.0	14-15	2.0	20-21
Resistant	≥ 4.0	≤ 15	≥ 8.0	≤ 13	≥ 4.0	≤ 19

Source: NCCLS minutes, 1999

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.

Serotyping

In the tonsillitis/pharyngitis studies (3004 and 3008), GABHS isolates from pretherapy/entry cultures were saved. If GABHS was subsequently isolated from on-therapy, posttherapy/TOC or late posttherapy cultures, the paired isolates were sent for serotyping to determine if a positive culture in the follow-up period was from the same serotype or from a new serotype of GABHS.

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 posttherapy/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 posttherapy/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 posttherapy/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 posttherapy/TOC as satisfactory (eradication, eradication with colonization, presumed eradication) or unsatisfactory (all other categories) based on the by-pathogen bacteriological response at posttherapy/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 (posttherapy/TOC or late posttherapy visit) serology by a microimmunofluorescence method; sputum samples tested by PCR (Studies 3006 and 3009).
- *Mycoplasma pneumoniae* – Acute and convalescent serology by an enzyme-linked immunosorbant assay (ELISA) method; sputum samples tested by PCR (Studies 3006 and 3009).
- *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, four-fold increase in microimmuno-fluorescence IgG (polyclonal) titers of paired samples, or a single IgM titer ≥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 ≥1:16 by microimmunofluorescence in combination with a positive PCR for *M. pneumoniae.*

- *Legionella pneumophila* – Positive culture when available, four-fold increase in paired serum of IgG or IgM titers, or a positive urine antigen for *L. pneumophila* serogroup I.

6.3 Statistical methods

6.3.1 Definition and analysis of study populations

6.3.1.1 Analysis populations

Analyses presented in this briefing document are based on clinical and bacteriological outcome data assessed at posttherapy/TOC and late posttherapy in the individual studies. These analyses were performed for four populations:

Table 6-3. 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 infection.
PPb[b]	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*
[b]PP in Studies 3004 and 3008 where bacteriological outcome was the primary analysis of efficacy

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

The difference between the ITT and mITT populations was minimal in most studies and largely explained by subjects in whom an X-ray overread by a radiologist did not confirm the disease studied. As shown in *Appendix 4. ITT analyses*, the efficacy results for the two populations were consistent based on the primary analyses.

6.3.1.2 Evaluability criteria

Subjects were excluded from the PPc population if they met one or more of the major protocol violation criteria 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 posttherapy/TOC
- Treatment discontinued a posteriori because of laboratory exclusion criteria at pretherapy/entry.

Indeterminate response criteria were as follows:

- Missing appropriate posttreatment information or inability to determine outcome at posttherapy/TOC: for subjects with a missing posttherapy/TOC assessment, clinical failure or unsatisfactory bacteriological response before the planned assessment was carried forward to posttherapy/TOC
- If the late posttherapy assessment was missing, failure before the planned assessment was carried forward to late posttherapy
- 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 following:

- CAP, AECB, and acute sinusitis: Clinical outcome at posttherapy/TOC in the PPc population
- Tonsillitis/pharyngitis: Bacteriological outcome at posttherapy/TOC in the per-protocol (PP) population. In studies 3004 and 3008, the PPb and PPc populations were identical and therefore identified only as the PP population.

6.3.2.2 Secondary efficacy analyses

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

- CAP, AECB and acute sinusitis: Analyses included
  - clinical outcome at posttherapy/TOC in the mITT population,
  - clinical outcome at late posttherapy in the PPc and mITT populations, and
  - bacteriological outcome at posttherapy/TOC and late posttherapy in the PPb and bmITT populations.

- Tonsillitis/pharyngitis: Analyses included
  - clinical outcome at posttherapy/TOC and late posttherapy in the PP and mITT populations,
  - bacteriological outcome at late posttherapy in the PP 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 two 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 two study drugs. A lower limit greater than or equal to –10% would have been required if the efficacy rate was above 90%.

6.4 Clinical studies

The number of subjects in telithromycin-treated populations are summarized below and by study in *Appendix 5. Number of telithromycin-treated subjects in populations by study*. A chart describing the number of subjects excluded from each population is provided in *Appendix 6. Flow chart of Phase III subject disposition*.

Table 6-4. Number of telithromycin-treated subjects in Phase III populations by indication

Indication	Population					
	Randomized	Treated	mITT	PPc	bmITT	PPb
CAP (Western studies)	1427	1427	1373	1132	562	344
AECB	346	343	342	255	82	64
Acute sinusitis	1095	1090	980	731	345	253
Tonsillitis/pharyngitis	430	430	430	265	325	265
TOTAL	3298	3290	3125	2383	1314	926

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 7-10 days in the treatment of community-acquired pneumonia (CAP) in adults was evaluated in three double-blind, comparative studies (Studies 3001, 3006, and 3009) and in three uncontrolled studies (Studies 3000, 3009OL and 3010). In addition, one double-blind study was conducted in Japan (Study 2105) to compare two different doses of telithromycin in Japanese subjects. For Study 2105, 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 6-5. CAP: Studies conducted

Study No.	Treatment regimen			No. in mITT
Western studies				
3001	TEL	10 d	800 mg qd	199
	AMX	10 d	1000 mg tid	205
3006	TEL	10 d	800 mg qd	204
	CLA	10 d	500 mg bid	212
3009	TEL	7 - 10 d	800 mg qd	100
	TVA	7 - 10 d	200 mg qd	104
3000	TEL	7 - 10 d	800 mg qd	240
3009OL	TEL	7 - 10 d	800 mg qd	212
3010	TEL	7 d	800 mg qd	418
Total CAP	TEL			1373
	Comparators			521
Japanese study				
2105	TEL	7 d	600 mg qd	46
	TEL	7 d	800 mg qd	50

AMX = amoxicillin; CLA = clarithromycin; TVA = trovafloxacin

Controlled studies

In Study 3001, amoxicillin 1000 mg tid was chosen as the comparator because in countries where the prevalence of penicillin G-resistant *S. pneumoniae* is high, the recommendation of the medical community is to increase the dose of the beta-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 ([75], available in *Appendix 1. Relevant references*).

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 and atypical pathogens and has excellent activity against *S. pneumoniae* resistant to penicillin G and erythromycin A. Trovafloxacin was approved in the US at this dosage for the treatment of CAP, and was chosen as an alternative to high-dose amoxicillin for the treatment of resistant strains of *S. pneumoniae*. 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. It was decided that recruitment would continue as an open-label study (Study 3009OL, conducted in South Africa). None of the subjects enrolled in Study 3009 were subsequently enrolled in Study 3009OL.

Uncontrolled studies

Study 3000 was a multicenter, uncontrolled study of the safety and efficacy of telithromycin and included population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses.

Study 3009 OL was a multicenter, uncontrolled study of the safety and efficacy of telithromycin that aimed to increase the likelihood of enrolling subjects with *S. pneumoniae*, and to obtain additional experience with *S. pneumoniae* resistant to penicillin G and/or erythromycin A.

Study 3010 was a multicenter, uncontrolled study aimed at increasing the number of strains of *S. pneumoniae* resistant to penicillin G and/or erythromycin A.

In Studies 3001, 3009OL, and 3010, 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/mm^3, or a Gram stain showing gram-positive diplococci. In addition, in Study 3009OL, subjects had to have consolidation on their chest X-ray at pretherapy/entry.

The criteria for exclusion of severe cases of pneumonia differed between the Western studies and Study 2105. In the Western studies, subjects requiring intravenous treatment according to American Thoracic Society or British Thoracic Society criteria (see *Appendix 7. Key inclusion/exclusion criteria*) were excluded, whereas in Study 2105 cases were to be included if two or more of the following symptoms were present: body temperature <38.6°C (101.2°F); low total peripheral white blood cell count <20,000/mm^3; chest X-ray score <6 points; C-reactive protein <20 mg/dL.

The subject disposition within each population in the Western studies is shown below.

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

Population	Telithromycin	Comparators	Total
Randomized	1427	542	1969
Treated	1427	541	1968
mITT	1373	521	1894
PPc	1132	394	1526
bmITT[a]	562	142	704
PPb[a]	344	90	434

[a]Does not include subjects with a diagnosis of atypical infections.

In the mITT population, the mean duration of treatment with telithromycin was 8.7 days (median 10.0, ranging from 1 to 15 days) for all CAP studies. The mean number of doses of active treatment was 8.5 (median 10.0, ranging from 0 to 10 doses). In Study 3010 the treatment duration was limited to 7 days. Hence in all CAP studies (mITT population), 449 subjects were treated for 7 days, compared with 26 subjects treated for 8 days, 29 subjects for 9 days, 598 subjects for 10 days, 153 subjects for 11 days, and 23 subjects for >11 days.

The key demographic characteristics across the three controlled studies and across all CAP studies are summarized in the table below.

Table 6-7. CAP (Western studies): Key demographic characteristics – mITT population

Characteristic	All controlled studies		All CAP studies	
	Telithromycin	Comparators	Telithromycin	Comparators
Total Treated	503	521	1373	521
Sex				
Male	266 (52.9)	263 (50.5)	779 (56.7)	263 (50.5)
Female	237 (47.1)	258 (49.5)	594 (43.3)	258 (49.5)
Age				
Mean (years)	44.8	45.5	44.6	45.5
13 to 18 years	13 (2.6)	18 (3.5)	34 (2.5)	18 (3.5)
>18 to <65 years	407 (80.9)	416 (79.8)	1143 (83.2)	416 (79.8)
≥65 years	83 (16.5)	87 (16.7)	196 (14.3)	87 (16.7)
Race				
White	408 (81.1)	422 (81.0)	986 (71.8)	422 (81.0)
Black	75 (14.9)	76 (14.6)	286 (20.8)	76 (14.6)
Asian	3 (0.6)	5 (1.0)	23 (1.7)	5 (1.0)
Other	17 (3.4)	18 (3.5)	78 (5.7)	18 (3.5)
Smoker	164 (32.6)	209 (40.1)	475 (34.6)	209 (40.1)

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

Table 6-8. CAP (Western studies): Key pretherapy/entry characteristics – mITT population

Characteristic	All CAP Studies	
	Telithromycin	Comparators
Total Treated	1373	521
At least 1 risk factor for morbidity[a]	410 (29.9)	176 (33.8)
Fever >39°C	626 (45.6)	230 (44.1)
WBC >10^3/mm^3	658 (47.9)	248 (47.6)
Documented pneumococcal bacteremia	56 (4.1)	18 (3.5)
Severity, moderate[b]	954 (69.5)	378 (72.6)
Fine score		
Class I	685 (49.9)	244 (46.8)
Class II	468 (34.1)	172 (33.0)
Class ≥III	220 (16.0)	105 (20.2)

[a] COPD, asthma, interstitial lung disease, respiratory insufficiency, congestive heart failure, coronary artery disease, atrial fibrillation, cerebrovascular disease, diabetes mellitus, renal disease, liver disease, cancer/neoplastic disease, sickle cell disease, alcoholism.
[b] As assessed by the investigator.

The severity of infection was generally assessed as moderate by the investigator (69.5% of subjects) for the mITT population in all six Western CAP studies. Most subjects treated with telithromycin had a Fine score of I (49.9%) or II (34.1%); 220 (16.0%) subjects had a Fine score ≥III. A relatively high number of subjects had documented pneumococcal bacteremia (56 cases treated with telithromycin in the bmITT population, 47 of whom were evaluable in the PPb population), which is another indication of the severity of infection in the overall population of subjects with CAP recruited in the program testing an oral antibiotic. Of note, in Study 3009OL, 81/212 (38.6%) subjects had bilateral pneumonia.

6.4.1.1 Clinical outcome (Western studies)

The primary efficacy analysis in CAP (Western studies) was the analysis of clinical outcome at posttherapy/TOC (Days 17 to 21) in the per protocol population of subjects (PPc). Clinical outcomes at posttherapy/TOC for the PPc and mITT populations are summarized in the table below.

Table 6-9. CAP (Western studies): Clinical cure rate by study for telithromycin and comparator(s) at posttherapy/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 3000	197	183	(92.9)				
Study 3009OL	187	175	(93.6)				
Study 3010	357	332	(93.0)				
All controlled studies[b]	391	356	(91.0)	394	356	(90.4)	[-3.6; 5.0]
All CAP studies	1132	1046	(92.4)	394	356	(90.4)	
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 3000	240	191	(79.60				
Study 3009OL	212	182	(85.8)				
Study 3010	418	357	(85.4)				
All controlled studies[b]	503	414	(82.3)	521	421	(80.8)	[-3.4; 6.4]
All CAP studies	1373	1144	(83.3)	521	421	(80.8)	

[a] 95% confidence interval of the difference in cure rates between the treatment groups.
[b] Studies 3001, 3006, 3009

The two controlled studies at posttherapy/TOC in the PPc population (primary efficacy endpoint) were completed with the planned number of subjects (Study 3001 *vs* amoxicillin; Study 3006 *vs* clarithromycin). Studies 3001 and 3006 had clinical cure rates for the telithromycin treatments of 94.6% and 88.3%, respectively. In both studies the clinical cure rates for the 10-day telithromycin treatment and the 10-day comparator treatment were equivalent.

Study 3009 was stopped prematurely before the planned sample size was reached, after the FDA restricted the use of trovafloxacin to inpatient use for severe infections as a result of safety concerns that arose during postmarketing surveillance. The clinical cure rate for telithromycin in this study is comparable to that observed in the other 2 controlled studies.

As shown in the table above, the results of clinical efficacy obtained in the mITT population confirmed the results obtained in the PPc population showing equivalence with the active comparators. Clinical cure rates in the mITT population were lower than those in the PPc population because subjects with indeterminate responses (such as missing information for assessment of clinical status) were counted as failures in the mITT analysis, but were similar for telithromycin and active comparators in the controlled studies (82.3% *vs* 80.8%; 95% confidence interval [–3.4; 6.4]).

For the three controlled studies, clinical cure rates based on the PPb population were similar for telithromycin and comparator (89.0% [73/82 subjects] *vs* 92.2% [83/90 subjects]). Clinical cure rates in the open-label studies were similar to those in the controlled studies (92.7% [243/262 subjects]) for the PPb population and for the PPc population (93.1% [690/741 subjects]).

Cure rates in subjects (PPc population) treated with 7 days of telithromycin (373/398, 93.7%) were similar to those obtained with 10 days of treatment (620/649, 95.5%).

6.4.1.2 In vitro susceptibility of causative pathogens at pretherapy/entry

In all the Western CAP studies, bacteriological documentation was derived mainly from sputum or respiratory aspiration cultures as well as from blood cultures at all centers.

The number and percent of telithromycin-resistant strains (tested by MIC at the central laboratory) isolated at pretherapy/entry for key pathogens causative for CAP in outpatients are summarized in the table below.

Table 6-10. CAP (Western studies): Number and percent of key targeted pathogens[a] resistant to telithromycin at pretherapy/entry according to provisional breakpoints – bmITT population (MIC[b] – Central Laboratory)

Pathogens	All CAP studies		
	N[c]	n	(%)
S. pneumoniae	250	0	(0.0)
Pen-I[d]	19	0	(0.0)
Pen-R[d]	23	0	(0.0)
Ery-R[d]	23	0	(0.0)
H. influenzae	195	11	(5.6)
M. catarrhalis	45	0	(0.0)
S. aureus	39	0	(0.0)

Pen-I = penicillin G-intermediate (MIC ≥0.1 µg/mL and ≤1.0 µg/mL);
Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL);
Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL).
[a] Key pathogens causative for CAP in outpatients across all treatment groups.
[b] Not all the pathogens isolated in the bmITT population had an MIC determination.
[c] Total excludes isolates that were not tested by MIC.
[d] Subjects with *S. pneumoniae* isolates intermediate/resistant to both penicillin G and erythromycin A are displayed in the Pen-I, Pen-R, and Ery-R rows.

Very few of the key pathogens isolated from respiratory aspiration or blood cultures at pretherapy/entry were resistant to telithromycin by MIC testing at central laboratories. None of the penicillin G-resistant, penicillin G-intermediate, or erythromycin A-resistant *S. pneumoniae* isolates were also resistant to telithromycin. For telithromycin-treated subjects, the MIC for telithromycin is displayed for these pathogens in *Section 6.4.1.4, Bacteriological eradication and clinical cure rate by pathogen (Western studies)*.

6.4.1.3 Bacteriological outcome by subject

The bacteriological outcome was similar between telithromycin and active comparators for the PPb and bmITT populations, as shown in the table below.

Table 6-11. CAP (Western studies): Subjects with satisfactory[a] bacteriological outcome at posttherapy/TOC

	Telithromycin			Comparator		
	N	n	(%)	N	n	(%)
PPb population						
Study 3001	40	36	(90.0)	40	35	(87.5)
Study 3006	28	25	(89.3)	28	27	(96.4)
Study 3009	14	13	(92.9)	22	22	(100.0)
Study 3000	45	40	(88.9)			
Study 3009OL	68	61	(89.7)			
Study 3010	149	137	(91.9)			
All controlled studies[a]	82	74	(90.2)	90	84	(93.3)
All CAP studies	344	312	(90.7)	90	84	(93.3)
bmITT population						
Study 3001	56	49	(87.5)	54	46	(85.2)
Study 3006	40	36	(90.0)	39	37	(94.9)
Study 3009	29	27	(93.1)	32	30	(93.8)
Study 3000	54	49	(90.7)			
Study 3009OL	88	80	(90.9)			
Study 3010	239	215	(90.0)			
All controlled studies[a]	125	112	(89.6)	125	113	(90.4)
All CAP studies	506	456	(90.1)	125	113	(90.4)

[a] Satisfactory = eradication, eradication with colonization, or presumed eradication
[b] Studies 3001, 3006, 3009

6.4.1.4 Bacteriological eradication and clinical cure rate by pathogen (Western studies)

The bacteriological eradication rate (documented and presumed eradication) and clinical cure rate at posttherapy/TOC for the PPb population in Western studies are presented below for select common causative pathogens. The overall eradication rate was 90.5% with the highest rate observed in *S. pneumoniae* isolates. Atypical pathogens are discussed in *Section 6.4.1.6, Clinical outcome of infections caused by atypical pathogens (Western studies)*.

Table 6-12. CAP (Western studies): Bacteriological eradication and clinical cure rates by pathogen in telithromycin-treated subjects – PPb population

Causative pathogen	Bacteriological eradication			Clinical cure		
	N	n	(%)	N	n	(%)
S. pneumoniae	174	166	(95.4)	174	165	(94.8)
H. influenzae	105	94	(89.5)	105	95	(90.5)
M. catarrhalis	30	27	(90.0)	30	26	(86.7)
S. aureus	19	15	(78.9)	19	15	(78.9)
Other	114	98	(86.0)	114	102	(89.5)
Total (all pathogens)	442	400	(90.5)	442	403	(91.2)

6.4.1.4.1 S. pneumoniae isolates resistant to penicillin G and/or erythromycin A (Western studies and Japanese Study 2105)

In the following sets of tables displaying data for *S. pneumoniae* resistant to penicillin G and/or erythromycin A, the term "single pathogen" indicates that no other causative pathogen was isolated in that subject. Data from single pathogen infections are presented before the data from single and mixed pathogen infections.

Data obtained in the Western studies and in the Japanese study (Study 2105) are first presented separately, and are then integrated. For the purpose of this briefing document, only the data obtained from Study 2105 at posttherapy/ TOC with *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A (600 and 800 mg treatment groups) are pooled with the corresponding data from the Western studies.

Single pathogen infections

Clinical cure rates at posttherapy/TOC for resistant *S. pneumoniae* isolates from single pathogen infections in telithromycin-treated subjects (PPb population) are summarized in the table below for the Western studies, for the Japanese Study 2105, and for all CAP studies combined. Bacterial eradication rates (not reported in the table) were identical to the clinical cure rate.

Table 6-13. CAP (All studies): Clinical cure rates at posttherapy/TOC for resistant *S. pneumoniae* isolates[a] from single pathogen infections in telithromycin-treated subjects – PPb population

Causative pathogen	Western Studies			Study 2105 (Japan)			All Studies		
	N	n	(%)	N	n	(%)	N	n	(%)
All *S. pneumoniae*	127	122	(96.1)	16	15	(93.8)	143	137	(95.8)
Pen-R	9	8	(88.9)	3	3	(100.0)	12	11	(91.7)
Ery-R	9	8	(88.9)	8	7	(87.5)	17	15	(88.2)
Pen-R or Ery-R	14	13	(92.9)	8	7	(87.5)	22	20	(90.9)

Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL).
[a] Subjects with *S. pneumoniae* isolates resistant to both penicillin G and erythromycin A are displayed in both subcategories.

When only single pathogen infections are considered, 11/12 of *S. pneumoniae* resistant to penicillin G and 15/17 of *S. pneumoniae* resistant to erythromycin A were clinically cured. Two subjects (3009OL/0369/105 and 2105/15/15-1) with *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A were classified as clinical failures. Narratives for these subjects are supplied in *Appendix 8. Narratives for subjects with S. pneumoniae from single or mixed pathogen infections at entry who failed therapy*).

Single and mixed pathogen infections

Clinical cure rates at posttherapy/TOC for resistant *S. pneumoniae* isolates from single and mixed pathogen infections in telithromycin-treated subjects (PPb population) are summarized in the table below for the Western studies, for the Japanese Study 2105, and for all CAP studies combined.

Table 6-14. CAP (All studies): Clinical cure rates at posttherapy/TOC for resistant *S. pneumoniae* isolates[a] from single and mixed pathogen infections in telithromycin-treated subjects – PPb population

Causative pathogen	Western Studies			Study 2105 (Japan)			All Studies		
	N	n	(%)	N	n	(%)	N	n	(%)
All *S. pneumoniae*	174	165	(94.8)	17	16	(94.1)	191	181	(94.8)
Pen-R	16	13	(81.3)	3	3	(100.0)	19	16	(84.2)
Ery-R	16	13	(81.3)	9	8	(88.9)	25	21	(84.0)
Pen-R or Ery-R	23	20	(87.0)	9	8	(88.9)	32	28	(87.5)

Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL).
[a] Subjects with *S. pneumoniae* isolates resistant to both penicillin G and erythromycin A are displayed in both subcategories.

For penicillin G-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 16/19 isolates. For erythromycin A-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 21/25 isolates. When both single and mixed pathogen infections are considered, 4 subjects were classified as clinical failures, one each in Studies 3000, 3001, 3009OL, and 2105. Narratives for these subjects are presented in *Appendix 8. Narratives for subjects with S. pneumoniae from single or mixed pathogen infections at entry who failed therapy*.

Detailed subject listings

The listing below provides details (demographics, susceptibility, genotype and outcome) on the subjects with single *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A.

Additional data on efficacy against *S. pneumoniae* resistant to erythromycin A or resistant or intermediate resistant to penicillin G obtained with telithromycin are given in *Appendix 9. Listing of subjects with resistant S. pneumoniae – bmITT not PPb population* and with active comparators in *Appendix 10. Listing of subjects with resistant S. pneumoniae treated with active comparators – PPb and bmITT not PPb populations*.

Table 6-15. CAP (All studies): Subjects with *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A from single pathogen infections – PPb population at posttherapy/TOC

Subject (Study/Center/ Subject No.)	Age/ Fine Score	Isolate Source	MIC Susceptibility μg/mL			Geno-type	Bacteriological Outcome	Clinical Outcome
			TEL	Pen G	Ery A			
Western studies								
3000/0603/1081	55/II	Blood	0.015 (S)	2.000 (R)	0.030 (S)	NA	Eradication	Cure
3000/0610/1110	23/I	Sputum	0.015 (S)	2.000 (R)	0.030 (S)	NA	Pres erad	Cure
3001/1101/005	67/IV	Blood	0.030 (S)	0.008 (S)	32.000 (R)	*erm*B	Pres erad	Cure
3006/0008/031	46/I	Blood	0.060 (S)	2.000 (R)	0.060 (S)	NA	Eradication	Cure
3006/0008/039	33/I	Sputum	0.060 (S)	2.000 (R)	4.000 (R)	*mef*E	Pres erad	Cure
3006/0425/008	24/I	Sputum	0.060 (S)	0.500 (I)	8.000 (R)	Neg[a]	Pres erad	Cure
3009OL/0355/104	52/II	Blood[b]	0.060 (S)	2.000 (R)	4.000 (R)	*mef*E	Pres erad	Cure
3009OL/0355/154	58/II	Sputum	0.030 (S)	0.250 (I)	32.000 (R)	*erm*B	Pres erad	Cure
3009OL/0355/157	40/I	Sputum	1.000 (S)	0.030 (S)	32.000 (R)	*mef*E	Pres erad	Cure
3009OL/0368/105	46/I	Blood	0.030 (S)	2.000 (R)	0.060 (S)	NA	Pres erad	Cure
3009OL/0369/105	37/II	Blood[b]	0.120 (S)	2.000 (R)	4.000 (R)	*mef*E	Persistence	Failure
3010/0523/001	45/I	Sputum	0.030 (S)	0.030 (S)	8.000 (R)	*erm*B	Eradication	Cure
3010/0526/001	61/II	Sputum	0.030 (S)	2.000 (R)	0.250 (S)	NA	Pres erad	Cure
3010/0533/007	25/I	Sputum	0.500 (S)	2.000 (R)	8.000 (R)	*erm*B/ *mef*E	Pres erad	Cure
Study 2105 (Japan)								
2105/13/13-2[c]	27/NA	Sputum	0.030 (S)	2.000 (R)	4.000 (R)	*erm*B	Pres erad	Cure
2105/15/15-1[c]	68/NA	Sputum	0.120 (S)	0.250 (I)	>64 (R)	*erm*B	Eradication	Failure
2105/30/30-2[c]	45/NA	Sputum	0.015 (S)	1.000 (I)	32.000 (R)	*erm*B	Pres erad	Cure
2105/17/17-1	40/NA	Sputum	0.030 (S)	0.120 (I)	>64 (R)	*erm*B	Pres erad	Cure
2105/30/30-4	75/NA	Sputum	0.015 (S)	0.500 (I)	8.000 (R)	*erm*B	Eradication	Cure
2105/32/32-1	60/NA	Sputum	0.120 (S)	4.000 (R)	4.000 (R)	*mef*E	Pres erad	Cure
2105/46/46-1	29/NA	Sputum	0.250 (S)	2.000 (R)	>64 (R)	*erm*B	Eradication	Cure
2105/56/56-1	41/NA	Sputum	0.060 (S)	0.120 (I)	>64 (R)	*erm*B	Eradication	Cure

Tel = telithromycin, Pen G = penicillin G, Ery A = erythromycin A. Susceptibility: S = susceptible, I = intermediate, R = resistant. Fine score: NA = Not applicable, because the protocol did not capture all the criteria necessary for the Fine score. Bacteriological outcome: Pres erad = presumed eradication, Pres persist = presumed persistence. Genotype for erythromycin A-resistant isolates: NA = not applicable.

[a]Strain resistant to clindamycin, i.e., M-phenotype negative.

[b]*S. pneumoniae* was isolated in both blood and sputum, with similar MIC. The genotype was obtained from the *S. pneumoniae* isolated from the sputum.

[c]Treated with 600 mg (Study 2105).

The listing below provides details (demographics, susceptibility, genotype and outcome) on the subjects with mixed *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A.

Table 6-16. CAP (All studies): Subjects with *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A from mixed pathogen infections– PPb population at posttherapy/TOC

Subject (Study/Center/ Subject No.)	Age/ Fine Score	Isolate Source	MIC Susceptibility μg/mL			Geno-type	Bacteriological Outcome	Clinical Outcome
			TEL	Pen G	Ery A			
Western studies								
3000/0605/1091	78/III	Blood[a]	0.030 (S)	2.000 (R)	32.000 (R)	*erm*B	Pres persist	Failure
3001/1002/027	71/IV	Sputum	0.030 (S)	2.000 (R)	32.000 (R)	*erm*B	Pres persist	Failure
3006/0012/019	42/I	Sputum	0.060 (S)	2.000 (R)	0.060 (S)	NA	Pres erad	Cure
3010/0483/008	40/I	Sputum	0.060 (S)	2.000 (R)	4.000 (R)	*mef*E	Pres erad	Cure
3010/0494/036	72/III	Sputum	0.250 (S)	2.000 (R)	8.000 (R)	*erm*B	Pres erad	Cure
3010/0503/001	59/II	Sputum	0.030 (S)	2.000 (R)	0.060 (S)	NA	Pres erad	Cure
3010/0534/059	40/I	Sputum	0.500 (S)	2.000 (R)	8.000 (R)	*erm*B/ *mef*E	Pres erad	Cure
3010/0536/014	42/I	Blood	1.000 (S)	0.250 (I)	8.000 (R)	*mef*E	Pres erad	Cure
3010/0536/031	35/I	Blood	1.000 (S)	0..500 (I)	8.000 (R)	*mef*E	Pres erad	Cure
Study 2105 (Japan)								
2105/17/17-2	32/NA	Sputum	0.008 (S)	0.030 (S)	2.000 (R)	*erm*B	Pres erad	Cure

Tel = telithromycin, Pen G = penicillin G, Ery A = erythromycin A. Susceptibility: S = susceptible, I = intermediate, R = resistant. Fine score: NA = Not applicable, because the protocol did not capture all the criteria necessary for the Fine score. Bacteriological outcome: Pres erad = presumed eradication, Pres persist = presumed persistence. Genotype for erythromycin A-resistant isolates: NA = not applicable.
[a] *S. pneumoniae* was isolated in both blood and bronchial alveolar lavage with similar MIC. The genotype was obtained on the *S. pneumoniae* isolated from the bronchial alveolar lavage.

Of note, 9 subjects had *S. pneumoniae* isolates resistant to penicillin G or erythromycin A cultured from their blood. Of the 25 erythromycin A-resistant strains, 9 expressed the *mef*E gene or the M phenotype, 14 expressed the *erm*B gene, and 2 were both *mef*E and *erm*B. The cure rate by genotype was 8/9 (88.9%) for pathogens expressing the *mef*E gene or the M phenotype, 11/14 (78.6%) for pathogens expressing *erm*B, and 2/2 (100.0%) when both *mef*E and *erm*B were expressed. No significant difference in the susceptibility to telithromycin was observed in erythromycin A-resistant *S. pneumoniae* expressing either the *mef*E or *erm*B gene.

6.4.1.4.2 S. pneumoniae isolates with intermediate resistance to penicillin G

Fourteen of the 15 subjects (9 from Western studies, 6 from Study 2105) in the PPb population with *S. pneumoniae* infections with intermediate resistance to penicillin G (MIC ≥0.1 μg/mL to ≤1.0 μg/mL) were clinically cured with bacterial eradication.

A listing of the 15 subjects with single and mixed pathogen infections including *S. pneumoniae* isolates of intermediate resistance to penicillin G in the PPb population at posttherapy/TOC is shown in the table below. Nine of these subjects are also listed in the tables above presenting erythromycin A-resistant *S. pneumoniae* isolates.

Table 6-17. CAP (All studies): Subjects with single and mixed *S. pneumoniae* isolates of intermediate[a] resistance to penicillin G – PPb population at posttherapy/TOC

Subject (Study/Center/ Subject No.)	Age/ Fine Score	Isolate Source	MIC Susceptibility μg/mL			Geno-type	Bacterio-logical outcome	Clinical outcome
			TEL	Pen G[a]	Ery A[a]			
Western studies, single pathogen infections								
3001/1005/014	24/I	Blood	0.015 (S)	0.500 (I)	0.060 (S)	NA	Pres erad	Cure
3006/0386/004	25/I	Sputum	0.060 (S)	0.250 (I)	0.060 (S)	NA	Pres erad	Cure
3006/0425/008[b]	24/I	Sputum	0.060 (S)	0.500 (I)	8.000 (R)	Neg[c]	Pres erad	Cure
3009OL/0365/111	33/I	Sputum	0.016 (S)	0.500 (I)	0.060 (S)	NA	Pres erad	Cure
3009OL/0365/114	26/I	Sputum	0.016 (S)	0.250 (I)	0.060 (S)	NA	Pres erad	Cure
3009OL/0355/154	58/II	Sputum	0.030 (S)	0.250 (I)	32.000 (R)	*erm*B	Pres erad	Cure
Study 2105 (Japan), single pathogen infections								
2105/15/15-1[d]	68/NA	Sputum	0.120 (S)	0.250 (I)	>64 (R)	*erm*B	Eradication	Failure
2105/30/30-2[d]	45/NA	Sputum	0.015 (S)	1.000 (I)	32.000 (R)	*erm*B	Pres erad	Cure
2105/16/16-2	73/NA	Sputum	0.008 (S)	0.120 (I)	0.030 (S)	NA	Eradication	Cure
2105/17/17-1	40/NA	Sputum	0.030 (S)	0.120 (I)	>64 (R)	*erm*B	Pres erad	Cure
2105/30/30-4	75/NA	Sputum	0.015 (S)	0.500 (I)	8.000 (R)	*erm*B	Eradication	Cure
2105/56/56-1	41/NA	Sputum	0.060 (S)	0.120 (I)	>64 (R)	*erm*B	Eradication	Cure
Western studies, mixed pathogen infections								
3006/0012/015	67/IV	BAL	0.060 (S)	1.000 (I)	0.060 (S)	NA	Pres erad	Cure
3010/0536/014	42/I	Blood	1.000 (S)	0.250 (I)	8.000 (R)	*mef*E	Pres erad	Cure
3010/0536/031	35/I	Blood	1.000 (S)	0.500 (I)	8.000 (R)	*mef*E	Pres erad	Cure

Tel = telithromycin, Pen G = penicillin G, Ery A = erythromycin A. Isolate source: BAL = bronchial alveolar lavage. Susceptibility: S = susceptible, I = intermediate, R = resistant. Bacteriological outcome: Pres erad = presumed eradication, Pres persist = presumed persistence. Genotype for erythromycin A-resistant isolates: NA = not applicable.

[a] *S. pneumoniae* that had intermediate resistance to penicillin G and were resistant to erythromycin A are also presented in the table of resistant isolates above.

[b] Subject had an infection with *S. pneumoniae* that had intermediate resistance to penicillin G and was resistant to erythromycin A and is described in the previous listing.

[c] Strains resistant to clindamycin, i.e., M-phenotype negative.

[d] Treated with 600 mg (Study 2105).

6.4.1.4.3 S. pneumoniae isolated by blood culture

Clinical cure rates for *S. pneumoniae* infections, including infections due to resistant pathogens, isolated from blood cultures in studies performed in Western countries are summarized in the table below for single and mixed pathogen infections. No blood cultures were obtained in Study 2105 (conducted in Japan).

Table 6-18. CAP (Western studies): Clinical cure rates for single and mixed *S. pneumoniae* isolated[a] from blood cultures in telithromycin-treated subjects at posttherapy/TOC – PPb population

Causative pathogen	Single infections		Mixed infections		Single and mixed infections	
	N	n	N	n	N	n
All *S. pneumoniae*	40	38	7	5	47	43
Pen-R	5	4	1	0	6	4
Ery-R	3	2	3	2	6	4
Pen-R or Ery-R	6	5	3	2	9	7

Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL).
[a] Subjects with *S. pneumoniae* isolates resistant to both penicillin G and erythromycin A are displayed in both subcategories.

The table above displays only the 47 PPb subjects with documented pneumococcal bacteremia. The clinical cure rate in subjects with pneumococcal bacteremia was high with 38/40 (95.0%) of subjects with single pathogen infections cured and 43/47 (91.5%) of subjects with mixed pathogen infections cured. Efficacy is also demonstrated in subjects with erythromycin A- or penicillin G-resistant strains of *S. pneumoniae*. Of note, where 4/6 subjects were clinically cured, one subject's *S. pneumoniae* (resistant to both erythromycin A and penicillin G) was eradicated (a repeat blood culture was negative), but the subject was categorized as a clinical failure because of treatment with another antibiotic for *S. aureus* in the urine at the end of therapy. Therefore, 5/6 erythromycin A-resistant isolates of *S. pneumoniae* and 5/6 penicillin G-resistant isolates of *S. pneumoniae* were eradicated.

Four of the 47 subjects with pneumococcal bacteremia at entry (PPb population) were assessed as clinical failures at posttherapy/TOC. In two subjects (3000/701/1450 and 3000/1201/1245) the blood culture was not repeated before the switch to another antibiotic. In two other subjects (3000/605/1091 and 3009OL/0369/105) the blood cultures were repeated and one was negative, i.e., the *S. pneumoniae* was eradicated (this subject was categorized as a clinical failure because of treatment with another antibiotic for *S. aureus* in the urine); Subject 3009OL/0369/105 had a positive blood culture. None of these four subjects died and all were cured with subsequent treatment. Narratives for these 4 subjects are supplied in

Appendix 11. Narratives for subjects with S. pneumoniae positive blood cultures who failed therapy. Nine subjects were not evaluable for the PPb population. A listing of the reasons and outcomes for the nonevaluable subjects is supplied in *Appendix 12. Listing of subjects with pneumococcal bacteremia – bmITT but not PPb population* .

The clinical cure rate of 91.5% in subjects with pneumococcal bacteremia provides additional evidence that telithromycin is highly effective in the treatment of CAP including those outpatients at greatest risk for morbid sequelae.

6.4.1.5 Efficacy according to MIC (Western studies)

The overall bacteriological eradication and clinical cure rates at posttherapy/TOC according to MIC values for all pathogens in telithromycin-treated subjects are shown in the table below for the PPb population in all CAP studies conducted in Western countries.

Table 6-19. CAP (Western studies): Bacteriological eradication and clinical cure rates at posttherapy/TOC for all pathogens according to MIC in telithromycin-treated subjects – PPb population

MIC (µg/mL)	Bacteriological Eradication			Clinical Cure		
	N	n	(%)	N	n	(%)
All pathogens						
0.001	1	1	(100.0)	1	1	(100.0)
0.002	1	1	(100.0)	1	1	(100.0)
0.004	2	2	(100.0)	2	2	(100.0)
0.008	38	38	(100.0)	38	38	(100.0)
0.016[a]	81	79	(97.5)	81	78	(96.3)
0.03	23	21	(91.3)	23	21	(91.3)
0.06	18	15	(83.3)	18	14	(77.8)
0.12	32	29	(90.6)	32	29	(90.6)
0.25	6	5	(83.3)	6	5	(83.3)
0.5	3	3	(100.0)	3	3	(100.0)
1	26	22	(84.6)	26	22	(84.6)
2	46	41	(89.1)	46	43	(93.5)
4	56	50	(89.3)	56	51	(91.1)
8	53	46	(86.8)	53	48	(90.6)
16	3	0	(0.0)	3	1	(33.3)
Not done	2	2	(100.0)	2	2	(100.0)
Total	391	355	(90.8)	391	359	(91.8)

All pathogens tested by MIC are presented in this table.
[a] Data for MIC values of 0.015 and 0.016 have been pooled.

Because there were relatively few pathogens at higher MICs it is difficult to identify a cut off for efficacy. However, no bacteriological eradication occurred in the few strains with MICs >8 µg/mL.

The bacteriological eradication and clinical cure rates at posttherapy/TOC according to MIC values for *S. pneumoniae* and *H. influenzae* in telithromycin-treated subjects are displayed below for the PPb population in all CAP studies performed in Western countries. Because there were relatively few pathogens at higher MICs for *S. pneumoniae* and *H. influenzae* it is difficult to identify a cut off for efficacy in these two pathogens.

Table 6-20. CAP (Western studies): Bacteriological eradication and clinical cure rates at posttherapy/TOC for *S. pneumoniae* and *H. influenzae* according to MIC in telithromycin-treated subjects – PPb population

MIC (µg/mL)	Bacteriological Eradication			Clinical Cure		
	N	n	(%)	N	n	(%)
S. pneumoniae						
0.004	2	2	(100.0)	2	2	(100.0)
0.008	38	38	(100.0)	38	38	(100.0)
0.016[a]	81	79	(97.5)	81	78	(96.3)
0.03	21	19	(90.5)	21	19	(90.5)
0.06	3	3	(100.0)	3	3	(100.0)
0.12	2	1	(50.0)	2	1	(50.0)
0.25	1	1	(100.0)	1	1	(100.0)
0.5	2	2	(100.0)	2	2	(100.0)
1	3	3	(100.0)	3	3	(100.0)
Total	153	148	(96.7)	153	147	(96.1)
H. influenzae						
0.002	1	1	(100.0)	1	1	(100.0)
0.12	1	1	(100.0)	1	1	(100.0)
0.25	1	1	(100.0)	1	1	(100.0)
0.5	1	1	(100.0)	1	1	(100.0)
1	21	17	(81.0)	21	17	(81.0)
2	38	34	(89.5)	38	35	(92.1)
4	29	27	(93.1)	29	28	(96.6)
8	5	5	(100.0)	5	5	(100.0)
Total	97	87	(89.7)	97	89	(91.8)

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

6.4.1.6 Clinical outcome of infections caused by atypical pathogens (Western studies)

Using highly specific criteria based on FDA recommendations (see *Section 6.2.3.2, Bacteriological evaluation*), the clinical cure rate at posttherapy/TOC in telithromycin subjects was analyzed and is presented in the table below for posttherapy/TOC.

Table 6-21. CAP (Western studies): Clinical outcome at posttherapy/TOC in atypical pathogen isolates in the PPc population using highly specific criteria[a]

Pathogen	Telithromycin			Comparator		
	N	n	(%)	N	n	(%)
Chlamydia pneumoniae	34	32	(94.1)	18	17	(94.4)
Mycoplasma pneumoniae	31	30	(96.8)	19	18	(94.7)
Legionella pneumophila	12	12	(100.0)	3	2	(66.7)

[a]Diagnostic criteria are described in *Section 6.2.3.2, Bacteriological evaluation*

Telithromycin was highly effective against *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila.* Of note, *L. pneumophila* isolates were obtained in 12 subjects, all of whom were cured. The latter finding is important as *Legionella* and *S. pneumoniae* are the two pathogens most frequently associated with the greatest risk of mortality in CAP.

6.4.1.7 Efficacy in subgroups of special interest (Western studies)

Clinical cure rate in subgroups of special interest in telithromycin-treated subjects are summarized for the PPc population at posttherapy/TOC in the six combined Western CAP studies in the table below.

Table 6-22. CAP (Western studies): Clinical cure rate in subgroups of special interest in telithromycin-treated subjects at posttherapy/TOC – PPc population

Subgroup	Clinical cure		
	N	n	(%)
Per protocol (overall)	1132	1046	(92.4)
Age (years)			
<65	978	907	(92.7)
≥65	154	139	(90.3)
Pneumococcal bacteremia[a]	47	43	(91.5)
Fine score			
Class I	554	517	(93.3)
Class II	403	368	(91.3)
Class ≥III	175	161	(92.0)

[a]PPb population: Two subjects (3000/101/1364 and 3006/012/0007) were excluded from the PPb population. They were considered failures due to a switch to another antibiotic because of an adverse event, in the PPc population of subjects with pneumococcal bacteremia.

Telithromycin was highly effective in the treatment of subjects who were at increased risk of morbidity and mortality. Clinical outcome was comparable in subjects ≥65 years (clinical cure = 90.3%) with those <65 years of age (clinical cure = 92.7%). In subjects with more severe disease (Fine score ≥III, pneumococcal bacteremia), the clinical cure rate was also >90.0%.

6.4.1.8 Overall conclusions on the efficacy of telithromycin for CAP

Telithromycin 800 mg administered orally once daily for 7-10 days was studied in 1427 subjects with CAP in 6 clinical trials. Overall the clinical cure rate was 92.4% in the PPc population. Telithromycin given orally at 800 mg once daily for 10 days was equivalent in clinical efficacy at posttherapy/TOC to clarithromycin given orally at 500 mg bid for 10 days (Study 3006) and

amoxicillin given orally 1000 mg tid for 10 days (Study 3001) in the treatment of adult subjects with CAP. In Study 3009, clinical cure rates were >90% for both telithromycin (800 mg orally once a day for 7-10 days) and trovafloxacin (200 mg orally once daily for 7-10 days). In all studies, results in the mITT population were consistent with the results observed in the PPc population.

Telithromycin's excellent efficacy was also demonstrated in subgroups of interest with cure rates of over 90% in subjects with an increased risk of morbidity, such as subjects ≥65 years of age, Fine score ≥III, and subjects with documented pneumococcal bacteremia (43/47 subjects), or a diagnosis of *Legionella* infection (12/12 subjects).

When analyzed by pathogen, telithromycin was highly effective in treating CAP due to *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, the atypical pathogen, *M. pneumoniae*, and the intracellular pathogens, *C. pneumoniae* and *L. pneumophila*. It was also highly effective in treating resistant *S. pneumoniae* isolates. For penicillin G-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 16/19 isolates. For erythromycin A-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 21/25 isolates. When only single pathogen infections are considered, 11/12 of *S. pneumoniae* resistant to penicillin G and 15/17 of *S. pneumoniae* resistant to erythromycin A were clinically cured.

6.4.2 Acute exacerbation of chronic bronchitis

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

Table 6-23. AECB: Studies conducted

Study No.	Treatment regimen			No. in mITT
3003	TEL	5 d	800 mg qd	160
	AMC	10 d	500 mg/125 mg tid	160
3007	TEL	5 d	800 mg qd	182
	CXM	10 d	500 mg bid	191
All AECB	TEL	5 d		342
	Comparators	10 d		351

TEL = telithromycin
AMC = amoxicillin/clavulanic acid (Augmentin®)
CXM = cefuroxime axetil

Study 3003 focused on clinical efficacy in subjects with documented associated chronic obstructive pulmonary disease (COPD) and used amoxicillin/clavulanic acid at 500/125 mg tid as the comparator. Study 3007 was aimed to provide clinical and bacteriological efficacy data for a broad population of subjects with AECB and used cefuroxime axetil at 500 mg bid as the comparator. Both active comparators were chosen because of their excellent in vitro activity against the main pathogens associated with AECB (*H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*).

Table 6-24. AECB: Subject disposition

Population	Telithromycin	Comparators	Total
Randomized	346	354	700
Treated	343	352	695
mITT population	342	351	693
PPc population	255	254	509
bmITT	82	79	161
PPb population	64	58	122

Pretherapy/entry characteristics, including smoking status, clinical findings, characteristics of the current AECB episode, and medical history, were generally similar among subjects who received telithromycin or comparator within each study and for the pooled analysis across the mITT, PPc, and PPb populations. However, Study 3003, performed in subjects with associated COPD, enrolled more subjects with a higher risk of morbidity (subjects ≥65 years old, FEV_1/FCV <60%) than Study 3007.

Table 6-25. AECB: Key demographic and pretherapy/entry characteristics for telithromycin-treated subjects – mITT population

Subgroup	Study 3003		Study 3007		Combined	
Total	160		182		342	
Sex:						
Male	93	(58.1)	85	(46.7)	178	(52.0)
Female	67	(41.9)	97	(53.3)	164	(48.0)
Age (yrs)						
Mean	61.3		51.9		56.3	
13 to 18	1	(0.6)	0	(0.0)	1	(0.3)
>18 to <65	89	(55.6)	138	(75.8)	227	(66.4)
≥65	70	(43.8)	44	(24.2)	114	(33.3)
Race						
White	148	(92.5)	160	(87.9)	308	(90.1)
Black	4	(2.5)	20	(11.0)	24	(7.0)
Asian	4	(2.5)	0	(0.0)	4	(1.2)
Other	4	(2.5)	2	(1.1)	6	(1.8)
History of COPD[a]	157	(98.1)	90	(49.5)	247	(72.2)
FEV_1/FVC <60%	69	(43.1)	13	(7.1)	82	(24.0)

[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. However, these subjects did have documented obstruction in lung function tests.

In the mITT population, the mean duration of treatment with telithromycin was 4.9 days (median 5.0, ranging from 1 to 5 days) for all AECB studies. The mean number of doses of active treatment was 4.9 (median 5.0, ranging from 1 to 5 doses).

6.4.2.1 Clinical outcome

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

Table 6-26. AECB: Clinical cure rate by study for telithromycin and comparator(s) at posttherapy/TOC

	Telithromycin			Comparator			95% CI
	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]
All AECB	255	220	(86.3)	254	210	(82.7)	[-3.1; 10.3]
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]
All AECB	342	272	(79.5)	351	263	(74.9)	[-1.9; 11.1]

The clinical outcome at posttherapy/TOC in the PPc population (primary efficacy endpoint) indicates equivalence for the 5-day telithromycin treatment *vs* the 10-day amoxicillin/clavulanic acid treatment (Study 3003), and for the 5-day telithromycin treatment *vs* the 10-day cefuroxime axetil treatment (Study 3007).

In both studies, the results of clinical efficacy obtained in the mITT population confirmed the results obtained in the PPc population.

For the two studies combined, clinical cure rates at posttherapy/TOC based on the PPb population were similar for telithromycin and comparator (78.1% [50/64 subjects] *vs* 81.0% [47/58 subjects]).

Clinical outcome evaluated at the late posttherapy visit (Days 31-45) was a secondary efficacy variable, and in both studies the analysis of clinical outcome at late posttherapy reinforces the conclusion of the primary analysis by demonstrating equivalence between telithromycin and the active comparators for the mITT and PPc populations.

Table 6-27. AECB: Clinical cure rate by study for telithromycin and comparator(s) at LPTV

	Telithromycin			Comparator			95% CI
	N	n	(%)	N	n	(%)	
PPc population							
Study 3003	105	82	(78.1)	108	81	(75.0)	[-9.2;15.4]
Study 3007	131	103	(78.6)	136	104	(76.5)	[-8.6; 12.9]
All AECB	236	185	(78.4)	244	185	(75.8)	[-5.4; 10.5]
mITT population							
Study 3003	160	118	(73.8)	160	114	(71.3)	[-7.9;12.9]
Study 3007	182	125	(68.7)	191	124	(64.9)	[-6.3; 13.8]
All AECB	342	243	(71.1)	351	238	(67.8)	[-3.9; 10.4]

Relapse/reinfection at the late posttherapy visit was similar for telithromycin given for 5 days and active comparators given for 10 days: of subjects classified as cured at posttherapy/TOC and evaluable at late posttherapy in the PPc population across the two AECB studies, a total of 16/201 (8.0%) subjects in the telithromycin group and 15/200 (7.5%) subjects in the comparator group were designated as relapse/reinfection. Therefore, the shorter duration of treatment with telithromycin was not associated with a higher rate of relapse.

6.4.2.2 Bacteriological outcome by subject

As shown in the table below, the bacteriological outcome was similar between telithromycin and the active comparators.

Table 6-28. AECB: Subjects with bacteriological outcome "satisfactory"[a] by study

Study	Telithromycin			Comparator		
	N	n	(%)	N	n	(%)
PPb population						
Study 3003	39	27	(69.2)	30	21	(70.0)
Study 3007	25	19	(76.0)	28	22	(78.6)
All AECB	64	46	(71.9)	58	43	(74.1)

[a] Satisfactory = eradication, eradication with colonization, or presumed eradication

In Study 3003, satisfactory bacteriological outcome was lower in both the telithromycin group and the amoxicillin/clavulanic acid group than in Study 3007. This can be explained by the greater severity of disease in Study 3003 in which all subjects had documented bronchial obstruction.

6.4.2.3 Bacteriological eradication and clinical cure rate by pathogen

Bacteriological eradication and clinical cure rates for select causative pathogens in telithromycin-treated subjects are presented in the tables below for the PPb population.

Table 6-29. AECB: Bacteriological eradication by pathogen – PPb population

Causative pathogen	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
S. pneumoniae	14	13	(92.9)	12	9	(75.0)
Pen-R	0			2	1	(50.0)
Ery-R	0			3	2	(66.7)
H. influenzae	25	15	(60.0)	17	15	(88.2)
M. catarrhalis	10	10	(100.0)	16	14	(87.5)
S. aureus	2	2	(100.0)	3	2	(66.7)
Other	19	14	(73.7)	20	13	(65.0)
Total (all pathogens)	70	54	(77.1)	68	53	(77.9)

Pen-R = penicillin G-resistant. Ery-R = erythromycin A-resistant.

Table 6-30. AECB: Clinical cure rates by pathogen – PPb population

Causative pathogen	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
S. pneumoniae	14	12	(85.7)	12	8	(66.7)
Pen-R	0			2	0	(0.0)
Ery-R	0			3	1	(33.3)
H. influenzae	25	17	(68.0)	17	13	(76.5)
M. catarrhalis	10	10	(100.0)	16	14	(87.5)
S. aureus	2	2	(100.0)	3	3	(100.0)
Other	19	14	(73.7)	20	16	(80.0)
Total (all pathogens)	70	55	(78.6)	68	54	(79.4)

Pen-R = penicillin G-resistant. Ery-R = erythromycin A-resistant.

For *S. pneumoniae*, the eradication and clinical cure rates were 92.9% and 85.7% respectively.

In Study 3003 in which all subjects had documented bronchial obstruction, efficacy against *H. influenzae* (bacteriological eradication was 50.0% [7/14] and clinical cure was 57.1% [8/14]) was lower than for other pathogens. The eradication rate for telithromycin was higher in Study 3007 (72.7% with a 81.8% clinical cure rate) and higher than that for cefuroxime axetil (60.0% with a 60% clinical cure rate).

In Study 3003, a higher efficacy rate was observed in subjects with *H. influenzae* infections in the amoxicillin/clavulanic acid group than in the telithromycin group. Part of the difference between the treatment groups can be explained by the greater severity of disease in telithromycin-treated subjects with *H. influenzae* as shown in the table below.

Table 6-31. Key background characteristics of all subjects with *H. influenzae* – Study 3003, PPb population

	Telithromycin N = 14		Amoxicillin/clavulanic acid N = 12	
	n	(%)	n	(%)
Systemic steroids	11	(78.6)	6	(50.0)
FEV1/FVC<60%	9	(64.3)	4	(33.3)
Smoker	7	(50.0)	5	(41.7)
>4 episodes last year	2	(14.3)	1	(8.3)
Severity of infection				
Mild	0	–	2	(16.7)
Moderate	11	(78.6)	8	(66.7)
Severe	3	(21.4)	2	(16.7)

Analysis of efficacy according to MIC in the PPb population does not lead to any obvious conclusions. This is expected in a disease where the underlying risk factors and severity of infection could have more impact than the pathogen isolated at entry.

6.4.2.4 Clinical outcome of infections caused by atypical pathogens

Using highly specific criteria based on FDA recommendations, the clinical cure rate at posttherapy/TOC was 10/11 (90.9%) in subjects with *C. pneumoniae* infection and 1/1 in the subject with *M. pneumoniae.*

6.4.2.5 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 6-32. AECB: Clinical cure at posttherapy/TOC by demographic subgroup for telithromycin-treated subjects – PPc population

Subgroup	Clinical cure		
	N	n	(%)
Per protocol (overall)	255	220	(86.3)
Age (yrs)			
<65	165	141	(85.5)
≥65	90	79	(87.8)
Risk factors[a] for morbidity			
At least 1	148	128	(86.5)
At least 2	70	59	(84.3)
FEV1/FVC <60%	68	56	(82.4)

[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)

The efficacy of telithromycin was consistent across subgroups of subjects at increased risk for morbid sequelae.

6.4.2.6 Overall conclusions on the efficacy of telithromycin for AECB

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 in subjects with AECB. Telithromycin's efficacy was consistent across all subgroups of subjects, including those with increased risk for morbidity, such as subjects ≥65 years of age (87.8%) and subjects with severe bronchial obstruction defined by FEV_1/FVC <60% (82.4%).

Bacteriological eradication and clinical cure rates by pathogen were high in telithromycin-treated subjects for *S. pneumoniae, M. catarrhalis, S. aureus,* and *C. pneumoniae*. Against *H. influenzae*, eradication and clinical cure for telithromycin in Study 3007 (72.7% and 81.8%, respectively), and tended to be higher than with cefuroxime axetil (60% and 60.0%, respectively). Eradication and clinical cure for telithromycin were lower in Study 3003 performed in subjects with COPD and more severe obstruction (50.0% and 57.1%, respectively) and lower than amoxicillin/clavulanic acid (100.0% and 83.3%, respectively).

6.4.3 Acute sinusitis

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 three 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 of telithromycin 800 mg qd for 5 days *vs* 10 days 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.

Study 3005 was an active-controlled, three-arm study comparing the efficacy and safety of oral telithromycin 800 mg qd for 5 days *vs* oral telithromycin 800 mg qd for 10 days *vs* oral amoxicillin/clavulanic acid 500/125 mg administered tid for 10 days. The primary aim of the study 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 for its excellent coverage of the three main pathogens involved in acute sinusitis: *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

Study 3011 was a double-blind study comparing 5 days of telithromycin treatment (800 mg qd) with 10 days of treatment with cefuroxime axetil (250 mg bid) using a 2:1 randomization scheme (telithromycin:cefuroxime axetil). In addition to studying the clinical efficacy, the aim of the study was to increase the experience with *S. pneumoniae* resistant to penicillin G and/or erythromycin A using telithromycin given for 5 days. Bacterial documentation was obtained by sinus puncture at the US sites and by sinus endoscopy with a thin catheter at all non-US sites.

Table 6-33. Acute sinusitis: Studies conducted

Study No.	Treatment regimen			No. in mITT
3002	TEL	5 d	800 mg qd	167
	TEL	10 d	800 mg qd	168
3005	TEL	5 d	800 mg qd	201
	TEL	10 d	800 mg qd	204
	AMC	10 d	500/125 mg tid	202
3011	TEL	5 d	800 mg qd	240
	CXM	10 d	250 mg bid	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 three acute sinusitis studies is summarized in the table below.

Table 6-34. Acute sinusitis: Subject disposition

Population	Telithromycin		Comparator	Total
	5-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.

Across all studies, 582 subjects were treated with telithromycin for 5 days (mean days of treatment = 4.8) and 224 subjects were treated with telithromycin for 10 days (mean days of treatment = 10.1). There were 157 subjects treated with active comparators (mean days of treatment = 10.0).

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

Table 6-35. Acute sinusitis: Key demographic characteristics for telithromycin-treated subjects – mITT population

Subgroup	5-day		10-day	
Total	608		372	
Sex				
Male	275	(45.2)	167	(44.9)
Female	333	(54.8)	205	(55.1)
Age (yrs)				
Mean	39.2		40.3	
13 to 18	13	(2.1)	4	(1.1)
>18 to <65	563	(92.6)	352	(94.6)
≥65	32	(5.3)	16	(4.3)
Race				
White	556	(91.4)	349	(93.8)
Black	24	(3.9)	13	(3.5)
Asian/Oriental	20	(3.3)	7	(1.9)
Other	8	(1.3)	3	(0.8)

Table 6-36. Acute sinusitis: Key pretherapy/entry characteristics of telithromycin-treated subjects – 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.

In Study 3002, all the subjects had total opacity or air fluid level findings on X-ray. Compared with Studies 3005 and 3011, fewer telithromycin subjects in Study 3002 had prior episodes of allergic rhinitis in the last 30 days, a history of asthma, or prior ENT-related surgery.

6.4.3.1 Clinical outcome

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

Table 6-37. Acute sinusitis: Clinical cure rate by study at posttherapy/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.

The clinical outcome at posttherapy/TOC in the PPc population (primary efficacy endpoint) in Study 3005 indicates equivalence for the 5-day telithromycin treatment and the 10-day amoxicillin/ clavulanic acid treatment. Equivalence between the 10-day telithromycin treatment and the 10-day amoxicillin/clavulanic acid treatment was also observed.

The 5-day and 10-day telithromycin treatment regimens demonstrated equivalent efficacy in Studies 3002 and 3005.

In Study 3011, equivalent efficacy was observed between the 5-day telithromycin treatment and the 10-day cefuroxime axetil treatment.

Clinical efficacy data obtained in the mITT population confirmed the results obtained in the PPc population.

For Studies 3002 and 3005 combined, clinical cure rates based on the PPb population were similar for 5-day telithromycin and 10-day telithromycin regimens (92.2% [71/77 subjects] and 90.8% [69/76 subjects]).

In all three studies, clinical outcome results at late posttherapy reinforced the conclusion of equivalence between the (5- and 10-day) telithromycin treatment regimens and the 10-day

amoxicillin/ clavulanic acid or cefuroxime axetil treatments based on clinical cure rates at posttherapy/TOC. Thus, the shorter 5-day duration of treatment was not associated with a higher rate of relapse at the late posttherapy evaluation. These data are summarized in the table below.

Table 6-38. Acute sinusitis: Clinical cure rate by study at LPTV

Study	Telithromycin						Comparators			95% CI
	5 days			10 days			10 days			
	N	n	(%)	N	n	(%)	N	n	(%)	
PPc population										
Study 3002	108	96	(88.9)	120	107	(89.2)	NA			[-9.3; 8.7][a]
Study 3005	136	95	(69.9)	133	90	(67.7)	130	92	(70.8)	[-12.7; 10.8] [b]
										[-15.0; 8.8] [c]
										[-9.6; 14.0] [a]
Study 3011	174	139	(79.9)	NA			82	64	(78.0)	[-9.8; 13.5][b]
All AS Studies	418	330	(78.9)	253	197	(77.9)	212	156	(73.6)	[-2.1; 12.8][b]
										[-4.0; 12.5][c]
										[-5.7; 7.8][a]
mITT population										
Study 3002	167	135	(80.8)	168	145	(89.3)	NA			[-14.0; 3.0] [a]
Study 3005	201	132	(65.7)	204	132	(64.7)	202	132	(65.3)	[-9.5; 10.1] [b]
										[-10.4; 9.1] [c]
										[-8.8; 10.7] [a]
Study 3011	240	178	(74.2)	NA			116	77	(65.4)	[-3.1; 18.7][b]
All AS Studies	608	445	(73.2)	372	277	(74.5)	318	209	(65.7)	[0.9; 14.0][b]
										[1.6; 15.9][c]
										[-7.1; 4.6][a]

LPTV = Late posttherapy visit. 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.

Although clinical cure rates in Study 3005 were lower than in Study 3002, the difference was observed across all treatment groups, i.e., the same cure rate was observed for both 5-day and 10-day telithromycin treatment and for the amoxicillin/clavulanic acid treatment, which is a widely used agent for treating acute sinusitis. Equivalence was also confirmed in Study 3011 between 5 days of telithromycin treatment and 10 days of treatment with cefuroxime axetil. Although several factors could have influenced the observed cure rates in these studies (sinus puncture, underlying allergic disease, season when the study was performed), no clear explanation is apparent at this time.

6.4.3.2 In vitro susceptibility of causative pathogens at pretherapy/entry

The number and percent of telithromycin-resistant strains (tested by MIC at the central laboratory) isolated at pretherapy/entry for key pathogens causative for acute sinusitis are summarized in the table below.

Table 6-39. Acute sinusitis: Number and percent of key targeted pathogens[a] resistant to telithromycin at pretherapy/entry according to provisional breakpoints – bmITT population (MIC[b] – Central Laboratory)

Pathogen	All AS Studies		
	N[c]	n	(%)
S. pneumoniae	116	0	(0.0)
Pen-R[d]	22	0	(0.0)
Ery-R[d]	32	0	(0.0)
H. influenzae	88	3	(3.4)
M. catarrhalis	30	0	(0.0)
S. aureus	45	2	(4.4)

AS = acute sinusitis. Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL).
[a]Key pathogens causative for acute sinusitis across all treatment groups.
[b]Not all the pathogens isolated in the bmITT population also had an MIC determination.
[c]Total excludes isolates that were not tested.
[d]Subjects with *S. pneumoniae* isolates resistant to penicillin G and resistant to erythromycin A are displayed in both the Pen-R and Ery-R rows.

Nine of the 290 (3.1%) key pathogens isolated at pretherapy/entry across all treatment groups were resistant to telithromycin by MIC testing at the central laboratory. None of the 22 penicillin G-resistant or 32 erythromycin A-resistant *S. pneumoniae* isolates were resistant to telithromycin.

6.4.3.3 Bacteriological outcome by subject

As shown in the table below, satisfactory bacteriological outcome tended to be higher for telithromycin than for the active comparators.

Table 6-40. Acute sinusitis: Subjects with bacteriological outcome "satisfactory"[a] by study

Study	Telithromycin						Comparators		
	5 days			10 days			10 days		
	N	n	(%)	N	n	(%)	N	n	(%)
PPb population									
Study 3002	70	65	(92.9)	69	62	(89.9)	NA		
Study 3005	7	6	(85.7)	7	6	(85.7)	8	6	(75.0)
Study 3011	100	84	(84.0)	NA			49	39	(79.6)
All AS Studies	177	155	(87.6)	76	68	(89.5)	57	45	(78.9)

NA = not applicable. AS = acute sinusitis.
[a] Satisfactory = eradication, eradication with colonization, or presumed eradication

6.4.3.4 Clinical cure rate by pathogen

Clinical cure rates at posttherapy/TOC for selected causative pathogens in the 5-day and 10-day telithromycin treatment groups are presented below for the PPb population. Details on the *S. pneumoniae* isolates resistant to either penicillin G or erythromycin A are given in the listing provided in *Section 6.4.3.5, S. pneumoniae resistant to penicillin G and/or erythromycin A.*

Table 6-41. Acute sinusitis: Clinical cure rate by pathogen – PPb population

Pathogen	Telithromycin						Comparators		
	5-day			10-day			10-day		
	N	n	(%)	N	n	(%)	N	n	(%)
S. pneumoniae	61	55	(90.2)	30	27	(90.0)	16	14	(87.5)
H. influenzae	48	42	(87.5)	16	15	(93.8)	15	13	(86.7)
M. catarrhalis	14	13	(92.9)	4	3	(75.0)	7	7	(100.0)
S. aureus	19	18	(94.7)	4	4	(100.0)	4	3	(75.0)
S. pyogenes	2	2	(100.0)	3	3	(100.0)	0		
Other	81	62	(76.5)	42	38	(90.5)	29	20	(69.0)
Total (all pathogens)	225	192	(85.3)	99	90	(90.9)	71	57	(80.3)

Pen-R = penicillin G-resistant; Ery-R = erythromycin A-resistant.

Clinical cure rates by pathogen in subjects treated for 5 days with telithromycin and for whom the pathogens were isolated by sinus puncture give similar rates (146/177 pathogens, 82.5%) when compared to all sample collection methods combined (192/225, 85.3%).

6.4.3.5 *S. pneumoniae* resistant to penicillin G and/or erythromycin A

Data for single pathogen infections are presented before pooled data from single and mixed pathogen infections.

Single pathogen infections

Clinical cure rates in subjects with resistant *S. pneumoniae* isolates from single pathogen infections are summarized in the table below.

Table 6-42. Acute sinusitis: Clinical efficacy in *S. pneumoniae* resistant isolates[a] from single pathogen infections in telithromycin-treated subjects at posttherapy/TOC – PPb population

Causative pathogen	All AS Studies								
	5 days			10 days			5 and 10 days		
	N	n	(%)	N	n	(%)	N	n	(%)
All *S. pneumoniae*	45	40	(88.9)	26	24	(92.3)	71	64	(90.1)
Pen-R	8	6	(75.0)	3	3	(100.0)	11	9	(81.8)
Ery-R	10	8	(80.0)	6	5	(83.3)	16	13	(81.2)
Pen-R or Ery-R	12	10	(83.3)	6	5	(83.3)	18	15	(83.3)

Pen-R = penicillin G-resistant (MIC ≥2.0 µg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 µg/mL).
[a]Subjects with *S. pneumoniae* isolates resistant to both penicillin G and erythromycin A are displayed in both subcategories.

The listing below provides detailed information on the 18 subjects with a single pathogen infection due to *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A. Narratives for the failure cases with an isolated *S. pneumoniae* resistant to erythromycin A (Subject 3002/0504/002) or with an isolated *S. pneumoniae* resistant to both penicillin G and erythromycin A (Subjects 3011/0604/007 and 3011/0659/018) are presented in *Appendix 8. Narratives for subjects with S. pneumoniae from single or mixed pathogen infections at entry who failed therapy* .

Table 6-43. Acute sinusitis: Subjects with *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A from single pathogen infections – PPb population at posttherapy/TOC (All AS Studies)

Subject (Study/Center/ Subject No.)	Age/ Treatment Duration[a]	Isolate Source	MIC Susceptibility μg/mL			Geno-type	Bacteriological Outcome	Clinical Outcome
			TEL	Pen G	Ery A			
3002/0504/002	34/10	Sinus S.	0.250 (S)	0.030 (S)	16.000 (R)	*mef*E	Pres persist	Failure
3002/0504/005	28/10	Sinus S.	0.060 (S)	0.120 (I)	32.000 (R)	*erm*B	Pres erad	Cure
3002/0603/046	24/10	Sinus S.	0.030 (S)	4.000 (R)	32.000 (R)	*erm*B	Pres erad	Cure
3002/0606/005	34/10	Sinus S.	0.060 (S)	4.000 (R)	32.000 (R)	*erm*B	Pres erad	Cure
3002/2102/006	28/10	Sinus S.	0.060 (S)	0.015 (S)	32.000 (R)	*erm*B	Pres erad	Cure
3005/0177/020	45/10	Sinus S.	0.060 (S)	2.000 (R)	8.000 (R)	*erm*B	Pres erad	Cure
3011/0604/007	36/5	Sinus S.	0.120 (S)	2.000 (R)	4.000 (R)	*mef*E	Pres persist	Failure
3011/0609/002	55/5	Sinus S.	0.250 (S)	2.000 (R)	8.000 (R)	*mef*E	Pres erad	Cure
3011/0628/016	54/5	Sinus S.	0.008 (S)	2.000 (R)	0.060 (S)	NA	Pres erad	Cure
3011/0654/001	37/5	Sinus S.	0.500 (S)	2.000 (R)	8.000 (R)	*mef*E	Pres erad	Cure
3011/0659/018	50/5	Sinus S.	0.060 (S)	2.000 (R)	2.000 (R)	*mef*E	Pres persist	Failure
3011/0661/001	67/5	Sinus S.	2.000 (I)	2.000 (R)	8.000 (R)	*erm*B	Pres erad	Cure
3011/0706/012	46/5	Sinus S.	0.008 (S)	2.000 (R)	0.060 (S)	NA	Pres erad	Cure
3011/0707/027	24/5	Sinus S.	0.030 (S)	0.250 (I)	8.000 (R)	*erm*B	Pres erad	Cure
3011/0707/031	20/5	Sinus S.	0.030 (S)	1.000 (I)	8.000 (R)	*erm*B	Pres erad	Cure
3011/0707/034	21/5	Sinus S.	0.060 (S)	0.500 (I)	8.000 (R)	*erm*B	Pres erad	Cure
3011/0751/001	28/5	Sinus S.	0.060 (S)	2.000 (R)	8.000 (R)	*mef*E	Pres erad	Cure
3011/0751/002	58/5	Sinus S.	0.500 (S)	0.030 (S)	8.000 (R)	*mef*E	Pres erad	Cure

AS = acute sinusitis. Isolate source: Sinus S. = sinus secretions. Susceptibility: S = susceptible, I = intermediate, R = resistant. Bacteriological outcome: Pres erad = presumed eradication, Pres persist = presumed persistence. Genotype for erythromycin A-resistant isolates: NA = not applicable.

[a]5 = 5 days of telithromycin treatment; 10 = 10 days of telithromycin treatment.

Overall, in addition to the 18 subjects with single pathogen infections, there were 5 subjects with a mixed pathogen infection that included a *S. pneumoniae* isolate resistant to either penicillin G, erythromycin A, or both.

Single and mixed pathogen infections

The tables below present pooled data from single and mixed pathogen infections.

Table 6-44. Acute sinusitis: Clinical efficacy in *S. pneumoniae* resistant isolates[a] from single and mixed pathogen infections in telithromycin-treated subjects at posttherapy/TOC – PPb population

Causative pathogen	All AS Studies								
	5 days			10 days			5 and 10 days		
	N	n	(%)	N	n	(%)	N	n	(%)
All *S. pneumoniae*	61	55	(90.2)	30	27	(90.0)	91	82	(90.1)
Pen-R	10	8	(80.0)	3	3	(100.0)	13	11	(84.6)
Ery-R	14	12	(85.7)	7	6	(85.7)	21	18	(85.7)
Pen-R or Ery-R	16	14	(87.5)	7	6	(85.7)	23	20	(87.0)

Pen-R = penicillin G-resistant (MIC ≥2.0 μg/mL); Ery-R = erythromycin A-resistant (MIC ≥1.0 μg/mL).
[a]Subjects with *S. pneumoniae* isolates resistant to both penicillin G and erythromycin A are displayed in both subcategories.

The listing below presents detailed information on the five subjects with mixed pathogen infections.

Table 6-45. Acute sinusitis: Subjects with *S. pneumoniae* isolates resistant to penicillin G and/or erythromycin A from mixed infections – PPb population at posttherapy/TOC (All AS Studies)

Subject (Study/Center/ Subject No.)	Age/ Treatment Duration[a]	Isolate Source	MIC Susceptibility μg/mL			Geno-type	Bacteriological Outcome	Clinical Outcome
			TEL	Pen G	Ery A			
3002/0502/006	19/5	Sinus S.	1.000 (S)	0.060 (S)	16.000 (R)	*mef*E	Pres erad	Cure
3002/0602/002	24/10	Sinus S.	0.015 (S)	0.120 (I)	32.000 (R)	*erm*B	Pres erad	Cure
3002/0603/026	34/5	Sinus S.	0.030 (S)	2.000 (R)	32.000 (R)	*erm*B	Pres erad	Cure
3011/0619/009	21/5	Sinus S.	0.500 (S)	2.000 (R)	8.000 (R)	*mef*E	Pres erad	Cure
3011/0707/009	32/5	Sinus S.	0.030 (S)	0.250 (I)	8.000 (R)	*erm*B	Pres erad	Cure

AS = acute sinusitis. Isolate source: Sinus S. = sinus secretions. Susceptibility: S = susceptible, I = intermediate, R = resistant. Bacteriological outcome: Pres erad = presumed eradication, Pres persist = presumed persistence. Genotype for erythromycin A-resistant isolates: NA = not applicable.
[a]5 = 5 days of telithromycin treatment; 10 = 10 days of telithromycin treatment.

6.4.3.6 Efficacy according to MIC

Bacteriological efficacy and clinical cure rates according to MIC did not show an absolute cut-off point of efficacy which can be determined from the rates.

6.4.3.7 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 6-46. Acute sinusitis: Clinical cure rate (PPc) at posttherapy/TOC by selected pretherapy/entry characteristics and prognostic factors in telithromycin-treated subjects

Subgroup	All AS Studies					
	5 days			10 days		
	N	n	(%)	N	n	(%)
Per protocol (overall)	458	383	(83.6)	273	223	(81.7)
Severity of infection (investigator assessment)						
Moderate	341	280	(82.1)	192	155	(80.7)
Severe	95	82	(86.3)	62	52	(83.9)
Sinus x-ray findings						
Total opacity	173	153	(88.4)	98	86	(87.8)
Mucosal thickening only[a]	126	94	(74.6)	69	50	(72.5)
Episodes of allergic rhinitis in previous 30 days	75	61	(81.3)	16	12	(75.0)
Sinus puncture	243	210	(86.4)	146	131	(89.7)

AS = acute sinusitis.
[a]Level of mucosal thickening in Studies 3002 and 3005 was ≥6 mm. The level in Study 3011 was ≥10 mm.

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.

6.4.3.8 Overall conclusions on the efficacy of telithromycin for acute sinusitis

Telithromycin 800 mg given orally once daily for 5 days or 10 days was equivalent in clinical efficacy at posttherapy/TOC and late posttherapy to amoxicillin/clavulanic acid 500/125 mg given orally tid for 10 days and cefuroxime axetil 250 mg given orally bid for 10 days in the treatment of adult subjects with acute sinusitis. In addition, treatment regimens of telithromycin 800 mg given orally once daily for 5 and 10 days were also equivalent in clinical efficacy.

The combined data for subjects treated with telithromycin for 5 days obtained in the three acute sinusitis studies show that the clinical cure rates by pathogen are favorable for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

High efficacy was obtained in resistant *S. pneumoniae* isolates for the 5-day treatment arm:

- For penicillin G-resistant *S. pneumoniae*, the clinical outcome was cure in 8/10 subjects treated for 5 days. For erythromycin A-resistant *S. pneumoniae* the clinical outcome was cure in 12/14 subjects treated for 5 days.
- When only single pathogen infections are considered, 6/8 of *S. pneumoniae* resistant to penicillin G and 8/10 of *S. pneumoniae* resistant to erythromycin A were clinically cured.

High efficacy was obtained in 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 subjects treated for either 5 or 10 days. For erythromycin A-resistant *S. pneumoniae*, the clinical outcome was cure in 18/21 subjects treated for either 5 or 10 days.

- When only single pathogen infections are considered, 9/11 of *S. pneumoniae* resistant to penicillin G and 13/16 of *S. pneumoniae* resistant to erythromycin A were clinically cured.

In conclusion, telithromycin 800 mg once daily for 5 days demonstrated efficacy in acute sinusitis against strains of *S. pneumoniae* resistant to penicillin G and/or erythromycin A. Telithromycin represents an alternative to the use of quinolones which are being used more frequently due to the emergence of resistant strains of *S. pneumoniae*. In addition, a 5 day treatment regimen has the advantage of reducing the likelihood of missing doses at the end of a prolonged treatment period, which could promote the selection of resistant pathogens.

6.4.4 Tonsillitis/pharyngitis

The clinical and bacteriological effectiveness of oral telithromycin 800 mg administered once daily for 5 days for the treatment of group A β-hemolytic streptococcal (GABHS) tonsillitis/pharyngitis infection in adults were evaluated in two international/multicenter, randomized, double-blind, active-controlled studies (see table below).

Table 6-47. Tonsillitis/Pharyngitis: Studies conducted

Study No.	Treatment regimen			No. in mITT
3004	TEL	5 d	800 mg qd	198
	PEN	10 d	500 mg tid	197
3008	TEL	5 d	800 mg qd	232
	CLA	10 d	250 mg bid	231
All Tons/Phar	TEL	5 d		430
	Comparators	10 d		428

PEN = penicillin VK;
CLA = clarithromycin

Study 3004 was an active-controlled, two-arm, parallel-group study comparing the efficacy and safety of oral telithromycin 800 mg administered once daily for 5 days (followed by placebo for 5 days) *vs* oral penicillin VK 500 mg tid for 10 days in subjects with acute GABHS tonsillitis/pharyngitis infection. Study 3008 was an active-controlled, two-arm, parallel-group study comparing the efficacy and safety of telithromycin 800 mg administered once daily for 5 days (followed by placebo for 5 days) *vs* oral clarithromycin 250 mg bid for 10 days in subjects with acute GABHS tonsillitis/pharyngitis infection.

Subject disposition is summarized in the table below.

Table 6-48. Tonsillitis/Pharyngitis: Subject disposition

	Telithromycin	Comparators	Total
Randomized	430	430	860
Treated	430	429	859
mITT population	430	428	858
bmITT	325	323	648
PP population	265	254	519

Demographic characteristics at pretherapy/entry, including sex, race, age, and weight, were similar between treatment groups in the mITT and PP populations. Pretherapy/entry characteristics were also generally similar among subjects who received telithromycin or comparator within each study and for the pooled analysis and were balanced between treatment groups (see table below).

Table 6-49. Tonsillitis/pharyngitis: Key demographic and pretherapy/entry characteristics for telithromycin-treated subjects – mITT population

Subgroup	Study 3004		Study 3008		All Tons/phar studies	
Total	198		232		430	
Sex						
Male	87	(43.9)	84	(36.2)	171	(39.8)
Female	111	(56.1)	148	(63.8)	259	(60.2)
Age (yrs)						
Mean	32.5		30.9		31.6	
13 to 18	17	(8.6)	24	(10.3)	41	(9.5)
>18 to <65	181	(91.4)	206	(88.8)	387	(90.0)
≥65	0	(0.0)	2	(0.9)	2	(0.5)
Race						
White	158	(79.8)	214	(92.2)	372	(86.5)
Black	22	(11.1)	13	(5.6)	35	(8.1)
Asian/Oriental	2	(1.0)	1	(0.4)	3	(0.7)
Other	16	(8.1)	4	(1.7)	20	(4.7)
Smokers	47	(23.7)	41	(17.7)	88	(20.5)
Signs and symptoms:						
Fever >39°C	62	(31.3)	36	(15.5)	98	(22.8)
Exudate	163	(82.3)	150	(64.7)	313	(72.8)
Cervical lymphadenopathy	185	(93.4)	210	(90.5)	395	(91.9)
>1 episode GABHS tons/phar in past year	31	(15.7)	17	(7.3)	48	(11.2)

In the mITT population, the mean duration of active treatment was 4.9 days (median 5.0, ranging from 1 to 5 days). The mean number of doses of active treatment was 4.8 doses (median 5.0, ranging from 1 to 5 doses).

6.4.4.1 Primary and secondary efficacy analyses

The primary analysis in GABHS tonsillitis/pharyngitis (Studies 3004 and 3008) was the per protocol (PP) analysis of bacteriological outcome at posttherapy/TOC (Days 16-23) performed in clinically and bacteriologically (positive culture for GABHS) evaluable subjects. For purposes of consistency, clinical outcome is presented first in this section even though it is a secondary efficacy endpoint in this indication.

6.4.4.2 Clinical outcome

Clinical outcome at posttherapy/TOC is presented by study and treatment in the table below for the mITT and PP populations, respectively.

Table 6-50. Tonsillitis/pharyngitis: Clinical cure rate[a] by study for telithromycin and comparator(s) at posttherapy/TOC

Study	Telithromycin			Comparator			95% CI
	N	n	(%)	N	n	(%)	
PP population							
Study 3004	115	109	(94.8)	119	112	(94.1)	[-6.1; 7.4]
Study 3008	150	139	(92.7)	135	123	(91.1)	[-5.5; 8.6]
Combined	265	248	(93.6)	254	235	(92.5)	[-3.7; 5.8]
mITT population[b]							
Study 3004	198	170	(85.9)	197	169	(85.8)	[-7.3; 7.5]
Study 3008	232	193	(83.2)	231	192	(83.1)	[-7.2; 7.3]
Combined	430	363	(84.4)	428	361	(84.3)	[-5.0; 5.2]

[a] Indeterminate responses are classified as failures. Results excluding the indeterminates from the denominator give an overall clinical cure rate of 90.3% for telithromycin in the mITT population. See *Appendix 13. Clinical cure rates without indeterminate responses – mITT and bmITT populations* .

[b] mITT population includes all subjects with signs and symptoms of tonsillitis/pharyngitis of presumed GABHS origin based on a positive rapid streptococcal A test or a positive GABHS culture at the pretherapy/entry visit and who received at least 1 dose of study drug.

The clinical outcome at posttherapy/TOC in Study 3004 demonstrates equivalence for the 5-day telithromycin treatment and the 10-day penicillin VK treatment. Similarly, the clinical outcome in Study 3008 demonstrates equivalence for the 5-day telithromycin treatment and the 10-day clarithromycin treatment.

In each study, the results of clinical efficacy obtained in the mITT population confirmed the results obtained in the PP population.

Clinical outcome evaluated at late posttherapy (Days 31-45) was a secondary efficacy variable in the mITT and PP populations, respectively. In both studies, the analysis of clinical outcome at the late posttherapy visit (LPTV) reinforces the results obtained at posttherapy/TOC by demonstrating equivalence between telithromycin and the active comparators. Therefore the short treatment duration was not associated with a higher relapse rate.

Table 6-51. Tonsillitis/pharyngitis: Clinical cure rate [a] by study for telithromycin and comparator(s) at LPTV

Study	Telithromycin			Comparator			95% CI
	N	n	(%)	N	n	(%)	
PP population							
Study 3004	108	100	(92.6)	111	100	(90.1)	[-5.8; 10.9]
Study 3008	134	120	(89.6)	118	103	(87.3)	[-6.5; 11.0]
Combined	242	220	(90.9)	229	203	(88.6)	[-3.6; 8.2]
mITT population[b]							
Study 3004	198	161	(81.3)	197	163	(82.7)	[-9.5; 6.6]
Study 3008	232	178	(76.7)	231	170	(73.6)	[-5.2; 11.4]
Combined	430	339	(78.8)	428	333	(77.8)	[-4.7; 6.8]

[a] Indeterminate responses are classified as failures.

[b] mITT population includes all subjects with signs and symptoms of pharyngitis/tonsillitis of presumed GABHS origin based on a positive rapid streptococcal A test or a positive GABHS culture at the pretherapy/entry visit and who received at least 1 dose of study drug.

6.4.4.3 Bacteriological outcome by subject

The primary efficacy analysis in Studies 3008 and 3004 was the PP analysis of bacteriological outcome at posttherapy/TOC (Days 16-23) in clinically and bacteriologically (positive culture for GABHS) evaluable subjects. In this indication, the definition of persistence or recurrence was used only for pathogens of the same serotype. The isolation of a GABHS of a new serotype of the same organism in the presence of signs and symptoms of infection was classified as reinfection. Bacteriological outcome (satisfactory or unsatisfactory) by subject at posttherapy/TOC and late posttherapy is presented below by study and treatment for the PP population.

Table 6-52. Tonsillitis/pharyngitis: Satisfactory bacteriological outcome by study for telithromycin and comparator(s) at posttherapy/TOC

Study	Telithromycin			Comparator			95% CI
	N	n	(%)	N	n	(%)	
PP population							
Study 3004	115	97	(84.3)	119	106	(89.1)	[-14.3; 4.8]
Study 3008	150	137	(91.3)	135	119	(88.1)	[-4.6; 11.0]
Combined	265	234	(88.3)	254	225	(88.6)	[-6.2; 5.6]
bmITT population							
Study 3004	138	110	(79.7)	150	119	(79.3)	[-9.6; 10.4]
Study 3008	187	152	(81.3)	173	134	(77.5)	[-5.0; 12.8]
Combined	325	262	(80.6)	323	253	(78.3)	[-4.2; 8.8]

The bacteriological outcome at posttherapy/TOC in Study 3004 indicates equivalence between telithromycin and comparator treatments (5-day telithromycin *vs* 10-day penicillin VK). The lower bound of the confidence interval for the difference in satisfactory bacteriological outcome rates is -14.3%, which is greater than the standard limit of –15% for an efficacy rate of between 80% and 90%, and the upper bound is greater than 0% (4.8%). In this study, the lower bound of the confidence interval is –9.6% in the bmITT population.

In Study 3008, equivalence was also demonstrated for bacteriological outcome at posttherapy/TOC between the 5-day telithromycin treatment and the 10-day clarithromycin treatment.

In the two studies combined, a total of 234 (88.3%) subjects in the telithromycin group had a satisfactory bacteriological outcome at posttherapy/TOC compared with 225 (88.6%) comparator subjects.

Bacteriological outcome evaluated at the late posttherapy visit (Days 31-45) shows similar rates for telithromycin and the active comparators in the two studies combined.

Table 6-53. Tonsillitis/pharyngitis: Satisfactory bacteriological outcome by study for telithromycin and comparator(s) at LPTV

Study	Telithromycin			Comparator			95% CI
	N	n	(%)	N	n	(%)	
PP population							
Study 3004	108	89	(82.4)	111	94	(84.7)	[-13.0; 8.5]
Study 3008	136	112	(82.4)	120	98	(81.7)	[-9.5; 10.9]
Combined	244	201	(82.4)	231	192	(83.1)	[-8.0; 6.5]
bmITT population							
Study 3004	138	103	(74.6)	150	109	(72.7)	[-8.9; 12.8]
Study 3008	187	133	(71.1)	173	116	(67.1)	[-6.0; 14.2]
Combined	325	236	(72.6)	323	225	(69.7)	[-4.3; 10.2]

6.4.4.4 Clinical outcome according to bacteriological outcome

In the telithromycin group for both studies combined, a total of 231/234 (98.7%) with a posttherapy/TOC bacteriological outcome of satisfactory were clinically cured. Seventeen of 31 (54.8%) subjects in the telithromycin group and 12/29 (41.4%) comparator subjects (6/13 penicillin, and 6/16 clarithromycin) were designated as clinical cure despite a bacteriological response of unsatisfactory. The disparity between clinical and bacteriological outcomes is not unexpected in this indication where asymptomatic carriers are often identified. However, the overall agreement between clinical and bacteriological outcomes was still good, with 92.5% of the subjects having a concordant response.

6.4.4.5 Bacteriological and clinical outcomes by pathogen

The bacteriological eradication rate at posttherapy/TOC for the primary causative pathogen for GABHS tonsillitis/pharyngitis (*S. pyogenes*) infection in the PP population was 88.7% in telithromycin-treated subjects, 88.9% in clarithromycin treated subjects, and 89.1% in penicillin VK-treated subjects. At LPTV, the overall bacteriological eradication rate was 85.2% (208/244) in telithromycin-treated subjects, 82.5% (99/120) in clarithromycin-treated subjects, and 86.5% (96/111) in penicillin VK-treated subjects.

The clinical and bacteriological outcomes by pathogen for treatment with telithromycin and active comparators are summarized below by study for the PP population.

Table 6-54. Tonsillitis/pharyngitis: Clinical cure and bacteriological eradication rates - PP population (Study 3004)

	Telithromycin			Penicillin VK		
	N	**n**	**(%)**	**N**	**n**	**(%)**
Clinical cure						
Posttherapy/TOC	115	109	(94.8)	119	112	(94.1)
Late posttherapy	108	100	(92.6)	111	100	(90.1)
Bacterial eradication						
Posttherapy/TOC	115	98 [a]	(85.2)	119	106	(89.1)
Late posttherapy	108	93	(86.1)	111	96	(86.5)

[a] Includes one subject with bacterial eradication, but who had a reinfection and is therefore counted as unsatisfactory in the bacteriological outcome by subject

Table 6-55. Tonsillitis/pharyngitis: Clinical cure and bacteriological eradication rates - PP population (Study 3008)

	Telithromycin			Clarithromycin		
	N	**n**	**(%)**	**N**	**n**	**(%)**
Clinical cure						
Posttherapy/TOC	150	139	(92.7)	135	123	(91.1)
Late posttherapy	134	120	(89.6)	118	103	(87.3)
Bacterial eradication						
Posttherapy/TOC	150	137	(91.3)	135	120	(88.9)
Late posttherapy	136	115	(84.6)	120	99	(82.5)

Bacteriological eradication rates at posttherapy/TOC and late posttherapy were lower than the clinical cure rates for both telithromycin and the active comparators. This may be explained by the persistence of *S. pyogenes* in the throat culture in some subjects despite clinical cure at up to 3 to 5 weeks after completion of treatment (carrier state).

The clinical and bacteriological outcomes at posttherapy/TOC and LPTV for subjects with erythromycin A-resistant stains of *S. pyogenes* are presented below.

Table 6-56. Tonsillitis/pharyngitis: Clinical cure and bacteriological eradication rates at posttherapy /TOC and late posttherapy in subjects with erythromycin A-resistant strains of *S. pyogenes* - PP population

Treatment	Posttherapy/TOC		Late posttherapy	
	Clinical cure (n/N)	Bacteriological eradication (n/N)	Clinical cure (n/N)	Bacteriological eradication (n/N)
Study 3004				
TEL	6/6	1/6	5/6	2/6
PEN	8/9	8/9	8/9	8/9
Study 3008				
TEL	4/5	2/5	4/5	4/5
CLA	2/4	0/4	2/4	0/4
Total TEL	10/11	3/11	9/11	6/11

TEL = telithromycin; PEN = penicillin VK; CLA = clarithromycin

Despite good clinical efficacy, eradication of group A-resistant strains was lower in telithromycin group *vs* the penicillin group in Study 3004. However, eradication of these strains was greater than with clarithromycin in Study 3008 although the numbers are too small to draw definite conclusions.

The genotype results of the 11 strains of *S. pyogenes* that were resistant to erythromycin A by MIC testing (MIC ≥1 μg/mL) in telithromycin-treated subjects in the PP population showed no correlation between the presence of different erythromycin A resistance genes, identified in 10 strains, and the MIC of telithromycin for those pathogens. There was also no correlation between bacteriological outcome and a particular type of resistance gene. Of the 10 strains identified with resistance genes in the PP population that were treated with telithromycin, all were susceptible to telithromycin (see listing below).

Table 6-57. Listing of telithromycin-treated subjects with erythromycin A-resistant *S. pyogenes* (MIC ≥1 μg/mL) – PP population

Study No./ Invest. No./ Subject No.	MIC (μg/mL)			Genotype	Clinical cure		Bact. eradication	
	TEL	PEN	ERY		at TOC	at LPTV	at TOC	at LPTV
3004/0302/026	0.500	0.008	16.000	*erm*B	C	C	P	P
3004/0304/007	1.000	0.008	16.000	*mef*A, *erm*B	C	F	P	P
3004/0304/039	0.500	0.008	16.000	*mef*A, *erm*B	C	C	P	E
3004/0401/006	0.030	0.008	2.000	*erm*TR	C	C	R	R
3004/1704/001	0.030	0.008	2.000	-	C	C	E	E
3004/1717/011	0.500	0.008	16.000	*mef*A	C	C	P	P
3008/0219/006	0.500	0.030	8.000	*mef*A	C	C	P	E
3008/0261/012	0.030	0.030	8.000	*erm*TR	C	C	E	E
3008/0262/001	0.030	0.030	2.000	*erm*TR	C	C	E	E
3008/0262/025	0.060	0.030	2.000	*erm*TR	F	F	PP	PP
3008/0267/010	0.500	0.030	8.000	*mef*A	C	C	P	E

TEL = telithromycin; PEN = penicillin G; ERY = erythromycin A; TOC = test of cure; LPTV = late posttherapy visit; C = cure; P = persistence; F = failure; E = eradication; PP = presumed persistence, R = recurrence.

6.4.4.6 Analysis of results in population subsets

Clinical and bacteriological outcomes in population subsets by sex, age, race, and weight were similar to those observed in the overall PP population in subjects who received telithromycin for tonsillitis/ pharyngitis infection. No meaningful differences were observed in bacteriological outcome between subjects 13 to 18 years of age and subjects >18 to <65 years of age in the PP populations.

Table 6-58. Tonsillitis/pharyngitis: Clinical cure and bacteriological eradication rates (PP) at posttherapy/TOC by demographic subgroup for telithromycin-treated subjects

Subgroup	Clinical outcome: Cure			Bacteriological outcome: Satisfactory		
	N	n	(%)	N	n	(%)
Per protocol (overall)	265	248	(93.6)	265	234	(88.3)
Sex						
Male	105	99	(94.3)	105	97	(92.4)
Female	160	149	(93.1)	160	137	(85.6)
Age (yrs)						
13 to 18	23	20	(87.0)	23	20	(87.0)
>18 to <65	241	227	(94.2)	241	213	(88.4)
≥65	1	1	(100.0)	1	1	(100.0)
Race						
White	225	211	(93.8)	225	200	(88.9)
Black	25	22	(88.0)	25	21	(84.0)
Other	15	15	(100.0)	15	13	(86.7)

6.4.4.7 Overall conclusions on the efficacy of telithromycin for tonsillitis/pharyngitis

Telithromycin 800 mg given orally once a day for 5 days in subjects with tonsillitis/pharyngitis was equivalent in clinical and bacteriological efficacy to 10 days of penicillin VK, the standard first line therapy for this indication, and to 10 days of clarithromycin treatment, the standard therapy for subjects allergic to beta-lactams.

Eradication of *S. pyogenes* with telithromycin 5 days was similar to 10 days of treatment with penicillin VK and 10 days of treatment with clarithromycin at LPTV.

Despite good clinical efficacy, eradication of erythromycin A-resistant *S.pyogenes* strains was lower at LPTV in the telithromycin group *vs* the penicillin group in Study 3004 (2/6 *vs* 8/9). However, eradication of these strains was numerically superior with telithromycin than with clarithromycin in Study 3008 (4/5 *vs* 0/4), although the numbers are too small to draw definite conclusions.

6.4.5 *S. pneumoniae* susceptibility profile to telithromycin and other antibiotics across indications

The purpose of this section is to provide an overall presentation of the susceptibility of *S. pneumoniae* resistant isolates across all indications.

The analysis displayed below includes *S. pneumoniae* strains isolated in all treatment groups. The bmITT population was chosen to yield the largest number of *S. pneumoniae* isolated in the clinical program.

Overall across indications and treatment groups a total of 394 *S. pneumoniae* (from single or mixed pathogen infections) were isolated in the bmITT population. The table below displays the percentage of *S. pneumoniae* and *S. pneumoniae*-resistant isolates that were resistant to telithromycin, clarithromycin, cotrimoxazole, or cefuroxime axetil (as determined by MIC and using the tentative breakpoints given in *Section 6.2.3.2, Bacteriological evaluation*).

Table 6-59. All indications: Percent of *S. pneumoniae* isolated at baseline regardless of treatment group that were resistant to selected antibiotics – bmITT population

	Total *S. pneumoniae*	Penicillin G-resistant *S. pneumoniae*	Penicillin G-intermediate *S. pneumoniae*	Erythromycin A-resistant *S. pneumoniae*
No. of isolates (%)	394[a] (100.0)	47 (11.9)	41 (10.4)	58 (14.7)
Percent resistant to selected antibiotics				
Telithromycin	0.0%	0.0%	0.0%	0.0%
Clarithromycin	14.7%	63.8%	41.5%	98.3%
Cotrimoxazole	18.0%	87.2%	39.0%	60.3%
Cefuroxime axetil	14.7%	100.0%	26.8%	62.1%

[a]Not all the isolates had an MIC determination.

Using provisional breakpoints of ≥4 µg/mL to define resistance of *S. pneumoniae* to telithromycin, no strains were found to be resistant. Multiresistance was common in strains resistant to penicillin G or erythromycin A, and in strains with intermediate resistance to penicillin G.

The distribution of MICs to telithromycin for strains isolated in all treatment groups across indication is displayed in the table below.

Table 6-60. All indications: Distribution of MICs for telithromycin in *S. pneumoniae* isolates[a] from Phase III studies (Western studies)

MIC (µg/mL)	*S. pneumoniae*	Penicillin G-resistant *S. pneumoniae*	Penicillin G-intermediate *S. pneumoniae*	Erythromycin A-resistant *S. pneumoniae*
0.004	5	—	—	—
0.008	88	7	6	1
0.015[b]	205	8	14	3
0.03	54	13	11	19
0.06	19	8	6	14
0.12	7	2	2	5
0.25	4	3	—	4
0.5	6	4	—	6
1.0	4	—	2	4
2.0	2	2	—	2

[a]*S. pneumoniae* strains isolated at entry and pooled across all treatment groups (telithromycin and active comparators).
[b]MICs performed at 0.015 and 0.016 µg/mL were pooled.

A total of 394 *S. pneumoniae* were isolated and tested by MIC in the clinical program. Among the *S. pneumoniae* overall, 75.6% (298/394) of the strains were inhibited by 0.015 μg/mL or less, showing the very high level of in vitro susceptibility of this pathogen. In vitro data from isolates from clinical studies confirm the high efficacy in *S.pneumoniae* strains, resulting from the dual mechanism of action on the ribosomes. The MIC_{50} was 0.015 μg/mL and the MIC_{90} was 0.06 μg/mL. Among the resistant strains, a slight decrease in susceptibility was observed, consistent with that described in microbiology studies (see *Section 3.3.1, In vitro antipneumococcal activity*).

6.5 Conclusions on clinical efficacy

In CAP, telithromycin administered orally 800 mg once a day for 7-10 days exhibited efficacy comparable to a broad range of active comparators administered multiple times daily for 10 days (amoxicillin high dosage, 1 g three times a day; clarithromycin 500 mg twice a day; trovafloxacin 200 mg once a day). Telithromycin has demonstrated efficacy in the most vulnerable patients in the community: the elderly and subjects with pneumococcal bacteremia. In addition, excellent results have been obtained in subjects with a diagnosis of *S. pneumoniae* and *Legionella* infections, which are the infections most frequently associated with morbidity. This is particularly important because increasing numbers of elderly patients and patients at high risk are being treated as outpatients within the community. Telithromycin was also highly effective in treating resistant *S. pneumoniae* isolates: For penicillin G-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 16/19 subjects. For erythromycin A-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection, the clinical outcome was cure in 21/25 subjects. When only single pathogen infections are considered, 11/12 subjects with *S. pneumoniae* resistant to penicillin G and 15/17 subjects with *S. pneumoniae* resistant to erythromycin A were clinically cured.

In AECB, efficacy with a once daily treatment regimen of 800 mg for 5 days was demonstrated when compared with widely prescribed drugs considered the standard of care (cefuroxime axetil, amoxicillin/clavulanic acid,) given 2 to 3 times daily for 10 days. Efficacy was maintained in patients more likely to require hospitalization, such as the elderly and patients with COPD, (including those with severe obstruction [FEV_1/FVC <60%]).

In acute sinusitis, efficacy with telithromycin 800 mg once daily for 5 days was demonstrated against cefuroxime axetil and amoxicillin/clavulanic acid given 2 to 3 times daily for 10 days. In this indication two studies also demonstrated that 5 and 10 days of treatment with telithromycin were comparable in the treatment of subjects with *S. pneumoniae* resistant to erythromycin A and/or penicillin G. In addition, a 5-day regimen has the advantage of reducing the likelihood of missing doses at the end of a prolonged treatment period, which could promote the selection of resistant pathogens.

In tonsillitis/pharyngitis due to *S. pyogenes* (subjects were 13 years of age or older), telithromycin 800 mg given orally once a day for 5 days was equivalent in clinical and bacteriological efficacy to 10 days of penicillin VK, the standard first line therapy for this indication, and to 10 days of clarithromycin treatment, the standard therapy for subjects allergic to beta-lactams. Telithromycin was shown to be effective in the treatment of tonsillitis/pharyngitis infection due to *S.pyogenes*.

Thus, the results of 13 multinational Phase III efficacy studies support the use of telithromycin at a dose of 800 mg once daily in the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinusitis, and group A β-hemolytic streptococcal tonsillitis/pharyngitis, as indicated below.

Community-acquired pneumonia

(Treatment duration: 7 to 10 days)

Streptococcus pneumoniae (including strains resistant to penicillin G and erythromycin A)

Haemophilus influenzae

Moraxella catarrhalis

Chlamydia pneumoniae

Mycoplasma pneumoniae

Legionella pneumophila

Acute exacerbation of chronic bronchitis

(Treatment duration: 5 days)

Streptococcus pneumoniae (including strains resistant to penicillin G and erythromycin A)

Haemophilus influenzae

Moraxella catarrhalis

Staphylococcus aureus

Chlamydia pneumoniae

Acute sinusitis

(Treatment duration: 5 days)

Streptococcus pneumoniae (including strains resistant to penicillin G and erythromycin A)

Haemophilus influenzae

Moraxella catarrhalis

Staphylococcus aureus

GABHS tonsillitis/pharyngitis

(Treatment duration: 5 days)

Streptococcus pyogenes

7. SAFETY

This section focuses primarily on safety data from the Phase III studies, with supportive information obtained in the clinical pharmacology studies presented where appropriate. A summary of the adverse event data from the single and multiple oral dose clinical pharmacology studies is shown in *Appendix 14. TEAEs in clinical pharmacology studies*.

7.1 Definition of safety population

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

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

Number of Subjects				
All studies		Controlled		Uncontrolled
TEL	COMP	TEL	COMP	TEL
3265	1672	2045	1672	1220

TEL = telithromycin; COMP = pooled active comparators

7.2 Phase III studies

7.2.1 Demographics of safety population

The adverse event safety database consists of data from 13 Phase III studies in which 3265 subjects were treated with telithromycin and 1672 subjects were treated with a comparator. Demographic characteristics were well matched between the telithromycin and comparator treatment groups. The sex and age characteristics of the safety population are shown in the table below.

Table 7-2. Demographic characteristics of Phase III safety population

Demographic variable	Number (%) of Subjects			
	All studies	Controlled		Uncontrolled
	TEL (N=3265)	TEL (N=2045)	COMP (N=1672)	TEL (N=1220)
Sex				
Men	1631 (50.0)	949 (46.4)	785 (46.9)	682 (55.9)
Women	1634 (50.0)	1096 (53.6)	887 (53.1)	538 (44.1)
Age				
13 to 18 years	95 (2.9)	68 (3.3)	69 (4.1)	27 (2.2)
>18 to <65 years	2798 (85.7)	1720 (84.1)	1343 (80.3)	1078 (88.4)
≥65 years	372 (11.4)	257 (12.6)	260 (15.6)	115 (9.4)

TEL = telithromycin; COMP = pooled active comparators

7.2.2 Extent of exposure

Of the 4937 subjects evaluable for safety in the Phase III studies, 3265 were treated with telithromycin (800 mg qd) and 1672 were treated with a comparator (clarithromycin 250 mg or 500 mg bid, trovafloxacin 200 mg qd, amoxicillin 1000 mg tid, cefuroxime axetil 250 mg or 500 mg bid, amoxicillin/clavulanic acid 500/125 mg tid, or penicillin VK 500 mg tid).

The following table shows by indication, the number of subjects in the safety population exposed to telithromycin.

Table 7-3. Subjects exposed to telithromycin in completed Phase III studies

Indication	Treatment Regimen (Days)	Number of Subjects
CAP	7-10	1415
AECB	5	340
Acute sinusitis	5	662
	10	421
Tonsillitis/pharyngitis	5	427
Total treated for 5 days		1429
Total treated for 7-10 days [a]		1836
Total number of subjects		3265

CAP = community-acquired pneumonia; AECB = acute exacerbation of chronic bronchitis
[a] Includes those subjects treated for 10 days

As the above table shows, there is extensive experience with telithromycin for both 5-day and 10-day regimens.

7.2.3 Treatment-emergent adverse events

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 frequent during the treatment period, as determined by the investigators. The treatment period encompassed the period from the first day of study medication to 7 days after the last day of study medication. In addition, any on-treatment adverse event considered possibly related to study medication by the investigators that led to permanent discontinuation of study medication, or resulted in death, was considered treatment-emergent.

Possibly related TEAEs were those that the investigators reported as "possibly related" to study medication and those on-treatment adverse events with missing causality.

The TEAEs from the Phase III controlled studies are discussed in this section. Data from the four uncontrolled studies are given in *Appendix 15. Deaths and discontinuations for Phase III uncontrolled studies*. The results from the uncontrolled studies were similar to those found in the controlled studies, except for the slightly higher frequency of abnormal liver function tests in uncontrolled CAP Study 3000, in which there was a higher incidence of hospitalized subjects. These results will be discussed in *Section 7.4, Assessment of the effects of telithromycin on hepatic function*.

7.2.3.1 TEAEs in controlled Phase III studies

The percentage of subjects who reported at least one TEAE was similar for the telithromycin-treated and comparator-treated subjects: 1056 of 2045 subjects (51.6%) and 806 of 1672 subjects (48.2%), respectively. As shown in the following table, the majority of TEAEs in Phase III controlled studies were of mild or moderate intensity.

Table 7-4. Intensity of possibly related and all TEAEs in controlled Phase III studies

Intensity	Number (%) of Subjects			
	Possibly related TEAEs		All TEAEs	
	Telithromycin N=2045	Comparator N=1672	Telithromycin N=2045	Comparator N=1672
Mild	510 (24.9)	329 (19.7)	763 (37.3)	573 (34.3)
Moderate	254 (12.4)	180 (10.8)	473 (23.1)	366 (21.9)
Severe	66 (3.2)	34 (2.0)	117 (5.7)	83 (5.0)

The adverse event profile for telithromycin-treated subjects parallels that observed in comparator-treated subjects for all body systems, with the exception of the digestive system. Most TEAEs were not considered by the investigator to be possibly related to study drug, except for TEAEs of the digestive system. As shown in the following table, the two most frequently reported possibly related TEAEs were diarrhea and nausea in both the telithromycin- and comparator-treated groups.

Table 7-5. Frequency of possibly related and all TEAEs by coded term in controlled Phase III studies[a]

Coded Term	Number (%) of Subjects			
	Possibly related TEAEs		All TEAEs	
	Telithromycin N=2045	Comparator N=1672	Telithromycin N=2045	Comparator N=1672
Subjects with at least one TEAE	712 (34.8)	465 (27.8)	1056 (51.6)	806 (48.2)
Diarrhea	272 (13.3)	158 (9.4)	295 (14.4)	167 (10.0)
Nausea	166 (8.1)	64 (3.8)	184 (9.0)	73 (4.4)
Headache	45 (2.2)	51 (3.1)	118 (5.8)	118 (7.1)
Dizziness	73 (3.6)	26 (1.6)	91 (4.4)	48 (2.9)
Vomiting	57 (2.8)	24 (1.4)	67 (3.3)	40 (2.4)
Dyspepsia	39 (1.9)	20 (1.2)	50 (2.4)	30 (1.8)
Abdominal pain	32 (1.6)	19 (1.1)	40 (2.0)	26 (1.6)
Rhinitis	1 (0.05)	1 (0.1)	38 (1.9)	33 (2.0)
Taste perversion	34 (1.7)	35 (2.1)	36 (1.8)	37 (2.2)
Upper respiratory infection	1 (0.05)	3 (0.2)	35 (1.7)	33 (2.0)

[a]Based on a frequency of at least 2.0% for all TEAEs.

7.2.4 TEAEs of special interest

7.2.4.1 Diarrhea

Data from single and multiple oral dose clinical pharmacology studies showed the frequency of diarrhea to be dose-related (*Appendix 14. TEAEs in clinical pharmacology studies*). The incidence of diarrhea in the 9 controlled Phase III studies is shown in the table below.

The majority of diarrhea events in the controlled Phase III studies were mild in both the telithromycin and comparator treatment groups. The higher incidence of mild diarrhea with telithromycin accounted for the majority of the difference in the overall incidence of diarrhea between telithromycin and the pooled active comparators. The incidence of severe diarrhea and of discontinuations due to diarrhea was low in both treatment groups.

Table 7-6. Incidence, intensity, and discontinuations due to diarrhea in controlled Phase III studies

	Number (%) of Subjects			
	Possibly related diarrhea TEAEs		All diarrhea TEAEs	
	Telithromycin (N=2045)	Comparator (N=1672)	Telithromycin (N=2045)	Comparator (N=1672)
Incidence	272 (13.3)	158 (9.4)	295 (14.4)	167 (10.0)
Intensity				
Mild	188 (9.2)	105 (6.3)	203 (9.9)	112 (6.7)
Moderate	66 (3.2)	48 (2.9)	73 (3.6)	50 (3.0)
Severe	18 (0.9)	5 (0.3)	19 (0.9)	5 (0.3)
Discontinuations	19 (0.9)	13 (0.8)	20 (1.0)	13 (0.8)

In general, the diarrhea was transient and reversible for all study drugs. When compared to individual active comparators (see table and figure below), the frequencies of diarrhea seen with telithromycin were in the range observed for widely used antibiotics.

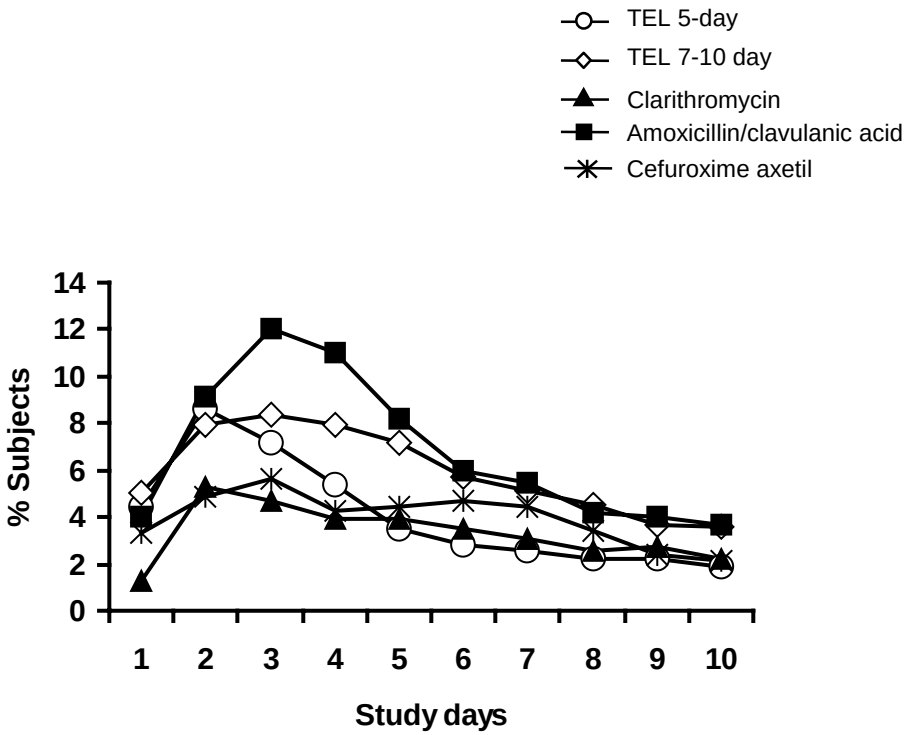
Table 7-7. Incidence of possibly related diarrhea by study and treatment within indication in controlled Phase III studies

Study No.	n/N (%) Subjects [a]							
	TEL 5-day	TEL 10-day	CLA 10-day	TVA 7-10-day	AMX 10-day	AMC 10-day	CXM 10-day	PEN VK 10-day
CAP								
3001		21/199 (10.6)			12/205 (5.9)			
3006		28/221 (12.7)	16/222 (7.2)					
3009		20/108 (18.5)[b]		7/109 (6.4)				
AECB								
3003	4/160 (2.5)					15/160 (9.4)		
3007	23/180 (12.8)						22/186 (11.8)	
Acute sinusitis								
3005	47/244 (19.3)	52/254 (20.5)				58/245 (23.7)		
3011	15/252 (6.0)						6/121 (5.0)	
Tonsillitis/pharyngitis								
3004	24/198 (12.1)							5/196 (2.6)
3008	38/229 (16.6)		17/228 (7.5)					

TEL = telithromycin, CLA = clarithromycin, TVA = trovafloxacin, AMX = amoxicillin, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil, and Pen VK = penicillin VK.
[a] n/N = number of subjects with TEAE/number of subjects in treatment group
[b] 7 to 10 day administration of telithromycin.

The following figure shows the prevalence of diarrhea for Days 1-10 for telithromycin *vs* clarithromycin, amoxicillin/clavulanic acid and cefuroxime axetil; the cases of diarrhea are included for each day they occurred from onset through last day of occurrence, with exception of cases of diarrhea in discontinued subjects, which were not counted after the day of withdrawal.

Figure 7-1. Prevalence of diarrhea in controlled Phase III studies: telithromycin *vs* clarithromycin, amoxicillin/clavulanic acid and cefuroxime axetil



Note: data in the figure above included for each day from onset through last day of occurrence.

The pattern of prevalence of diarrhea over time was within the range observed for other antibiotics commonly used to treat RTIs. Discontinuation rates due to diarrhea were low for both telithromycin and active comparators.

7.2.4.2 Nausea

In the clinical pharmacology studies, the incidence of nausea was dose related after a single oral dose of telithromycin (*Appendix 14. TEAEs in clinical pharmacology studies*). The incidence of nausea in the controlled Phase III studies is shown in the table below.

The incidence of nausea was higher in the telithromycin treatment group than in the active comparator group in the controlled Phase III studies. The majority of events were mild in both treatment groups. The incidence of severe nausea and of discontinuation due to nausea was low in both treatment groups.

Table 7-8. Incidence, intensity, and discontinuations due to nausea in controlled Phase III studies

	Number (%) of Subjects			
	Possibly related nausea TEAEs		All nausea TEAEs	
	Telithromycin (N=2045)	Comparator (N=1672)	Telithromycin (N=2045)	Comparator (N=1672)
Incidence	166 (8.1)	64 (3.8)	184 (9.0)	73 (4.4)
Intensity				
Mild	103 (5.0)	42 (2.5)	116 (5.7)	48 (2.9)
Moderate	50 (2.4)	18 (1.1)	54 (2.6)	21 (1.3)
Severe	13 (0.6)	4 (0.2)	14 (0.7)	4 (0.2)
Discontinuations	18 (0.9)	9 (0.5)	18 (0.9)	10 (0.6)

The following table presents the percentage of subjects reporting possibly related nausea by indication. With the exception of amoxicillin/clavulanic acid in AECB Study 3003, the incidence was generally higher in the telithromycin groups than in the active comparator treatment groups.

Table 7-9. Incidence of possibly related nausea by study and treatment within indication in controlled Phase III studies

Study No.	n/N (%) Subjects [a]							
	TEL 5-day	TEL 10-day	CLA 10-day	TVA 7-10-day	AMX 10-day	AMC 10-day	CXM 10-day	PEN VK 10-day
CAP								
3001		13/199 (6.5)			4/205 (2.0)			
3006		19/221 (8.6)	11/222 (5.0)					
3009		10/108 (9.3)[b]		5/109 (4.6)				
AECB								
3003	2/160 (1.3)					3/160 (1.9)		
3007	16/180 (8.9)						6/186 (3.2)	
Acute sinusitis								
3005	29/244 (11.9)	24/254 (9.4)				19/245 (7.8)		
3011	17/252 (6.7)						5/121 (4.1)	
Tonsillitis/pharyngitis								
3004	12/198 (6.1)							2/196 (1.0)
3008	24/229 (10.5)		9/228 (3.9)					

TEL = telithromycin, CLA = clarithromycin, TVA = trovafloxacin, AMX = amoxicillin, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil, and Pen VK = penicillin VK.
[a] n/N = number of subjects with TEAE/number of subjects in treatment group
[b] 7 to 10 day administration of telithromycin.

7.2.4.3 Vomiting

The incidence of vomiting in the controlled Phase III studies is shown in the table below.

The majority of vomiting episodes were mild in both the telithromycin and active comparator treatment groups. The incidence of severe vomiting and of discontinuations due to vomiting was low for the two treatment groups.

Table 7-10. Incidence, intensity, and discontinuations due to vomiting in controlled Phase III studies

	Number (%) of Subjects			
	Possibly related vomiting TEAEs		All vomiting TEAEs	
	Telithromycin (N=2045)	Comparator (N=1672)	Telithromycin (N=2045)	Comparator (N=1672)
Incidence	57 (2.8)	24 (1.4)	67 (3.3)	40 (2.4)
Intensity				
Mild	25 (1.2)	9 (0.5)	29 (1.4)	16 (1.0)
Moderate	24 (1.2)	11 (0.7)	30 (1.5)	20 (1.2)
Severe	8 (0.4)	4 (0.2)	8 (0.4)	4 (0.2)
Discontinuations	19 (0.9)	6 (0.4)	19 (0.9)	9 (0.5)

The following table shows the percentage of subjects reporting possibly related vomiting by indication and treatment. The rates were low and generally similar in the telithromycin and active comparator treatment groups.

Table 7-11. Incidence of possibly related vomiting by study and treatment within indication in controlled Phase III studies

Study No.	n/N (%) Subjects [a]							
	TEL 5-day	TEL 10-day	CLA 10-day	TVA 7-10-day	AMX 10-day	AMC 10-day	CXM 10-day	PEN VK 10-day
CAP								
3001		2/199 (1.0)			0/205 (0.0)			
3006		8/221 (3.6)	3/222 (1.4)					
3009		4/108 (3.7)[b]		2/109 (1.8)				
AECB								
3003	1/160 (0.6)					4/160 (2.5)		
3007	5/180 (2.8)						3/186 (1.6)	
Acute sinusitis								
3005	5/244 (2.0)	11/254 (4.3)				5/245 (2.0)		
3011	5/252 (2.0)						3/121 (2.5)	
Tonsillitis/pharyngitis								
3004	4/198 (2.0)							4/196 (2.0)
3008	12/229 (5.2)		0/228 (0.0)					

TEL = telithromycin, CLA = clarithromycin, TVA = trovafloxacin, AMX = amoxicillin, AMC = amoxicillin/clavulanic acid, CXM = cefuroxime axetil, and Pen VK = penicillin VK.
[a] n/N = number of subjects with TEAE/number of subjects in treatment group
[b] 7 to 10 day administration of telithromycin.

7.2.4.4 Dizziness

The frequency of dizziness TEAEs was dose-related in the clinical pharmacology studies (*Appendix 14. TEAEs in clinical pharmacology studies*). The incidence of dizziness in the controlled Phase III studies is shown in the table below.

The majority of dizziness events were mild in both the telithromycin and active comparator treatment groups. The incidence of severe dizziness and of discontinuations due to dizziness was low in both treatment groups.

Table 7-12. Incidence, intensity, and discontinuations due to dizziness in controlled Phase III studies

	Number (%) of Subjects			
	Possibly related dizziness TEAEs		All dizziness TEAEs	
	Telithromycin (N=2045)	Comparator (N=1672)	Telithromycin (N=2045)	Comparator (N=1672)
Incidence	73 (3.6)	26 (1.6)	91 (4.4)	48 (2.9)
Intensity				
Mild	49 (2.4)	22 (1.3)	62 (3.0)	38 (2.3)
Moderate	18 (0.9)	4 (0.2)	22 (1.1)	8 (0.5)
Severe	6 (0.3)	0 (0.0)	7 (0.3)	2 (0.1)
Discontinuations	5 (0.2)	1 (0.1)	5 (0.2)	1 (0.1)

All subjects with TEAEs of dizziness recovered without sequelae and none of the events were serious. When comparing telithromycin with individual active comparators, dizziness occurred more frequently with telithromycin (range 0.6% to 8.3%) than with clarithromycin, amoxicillin, amoxicillin/clavulanic acid, or cefuroxime axetil (range 0% to 3.7%), but less frequently than with trovafloxacin (3.7% *vs* 12.8% in Study 3009).

In elderly subjects (≥65 years), the prevalence of dizziness considered possibly related to telithromycin was 2.7% and lower than in the overall subject population. There was no report of convulsion as an adverse event related to telithromycin treatment. No specific concomitant medication was found associated with these findings.

In conclusion, dizziness was reported at a slightly higher rate in telithromycin-treated subjects than in those treated with clarithromycin, but much less than with trovafloxacin. These events were generally mild, leading to discontinuation in only 0.2% of subjects.

7.2.4.5 Blurred vision

In clinical pharmacology studies, blurred vision occurred primarily at supra-therapeutic doses of telithromycin (a single report was received with blurred vision at 800 mg). These events appeared on average within 2 hours after drug intake, were reversible, and lasted 2 to 23 hours. Ophthalmic examinations were performed during two clinical pharmacology studies with telithromycin; the examinations included assessment of the fundi, visual acuity (left and right), and the visual field (left and right). There were no clinically noteworthy effects on visual fields, fundi or lenses in any subject, although visual acuity was affected in one subject (reverted to normal the day after dosing).

The incidence of blurred vision in the controlled Phase III studies is shown in the table below.

Among the 10 cases of blurred vision considered possibly related to telithromycin, 6 occurred in young women (<40 years of age), mostly in Study 3008 (5 of the 10 cases). No cases occurred in elderly or adolescent subjects. The symptoms varied in duration from 1 to 10 days, were generally reversible with continuing therapy, and were primarily mild (two cases were reported as moderate in intensity; see table below). Four of the reported cases lasted longer than one day, but all had resolved by the end of therapy. A single patient with mild symptoms discontinued therapy as the result of blurred vision and recovered without counteractive medication administration. No specific pattern of medical history or concomitant medication was found in these subjects.

Table 7-13. Incidence, intensity, and discontinuations of blurred vision in controlled Phase III studies

	Number (%) of Subjects			
	Possibly related blurred vision TEAEs		All blurred vision TEAEs	
	Telithromycin (N=2045)	Comparator (N=1672)	Telithromycin (N=2045)	Comparator (N=1672)
Incidence	10 (0.5)	0 (0.0)	14 (0.7)	1 (0.1)
Intensity				
Mild	8 (0.4)	0 (0.0)	11 (0.5)	1 (0.1)
Moderate	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Discontinuations	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)

Blurred vision has been reported as an infrequent event for numerous compounds including anti-infectives, such as tetracycline, penicillins, sulfamethoxazole [33].

7.2.5 Deaths and other serious adverse events

7.2.5.1 Deaths

A total of 13 subjects died in the Phase III clinical program. Of these 13 subjects, one subject (0301/020) treated with telithromycin in Study 3009 was enrolled at a site from which all data have been censored at the request of the FDA, and one subject screened for enrollment, but not treated with study medication, experienced a myocardial infarction that resulted in death on the same day as the screening; these two subjects are not discussed further in this section.

Ten of the 11 deaths in treated subjects occurred in the CAP studies; CAP subjects had more significant underlying clinical morbidity as compared to the non-CAP subjects. The deaths in the CAP studies occurred in subjects who had conditions or illnesses that have been associated with increased mortality from pneumonia, including severe disease requiring hospitalization or co-morbid conditions (e.g., chronic obstructive pulmonary disease, cardiovascular disease, diabetes mellitus, age >60 years). None of the deaths were considered related to study medication by the investigator.

Death rates in controlled studies were similar in the telithromycin (2 [0.10%] of 2045 subjects) and active comparator (4 [0.24%] of 1672 subjects) treatment groups. As noted above, all but one of the deaths in the controlled studies occurred in CAP studies (2 [0.38%] of 528 for telithromycin and 3 [0.56%] of 536 for active comparators).

A summary of the 11 subjects who died in the Phase III studies is presented in the following table.

Table 7-14. Summary of subjects who died in Phase III studies

Study No./ Subject No.	Indication[a]	Age/ Sex/ Race[b]	Treatment[c]	Last day on study med/ Day of death	Cause of death (Investigator terms)	Related to study drug
Controlled Studies						
3001 1002/027	CAP	71/F/W	TEL	3/4	Multiorgan failure	No
3001 1301/004	CAP	80/M/W	TEL	10/10	Cardiac insufficiency	No
3001 0111/004	CAP	52/M/W	AMX	8/34	Asthmatic crisis	No
3006 0060/002	CAP	70/F/W	CLA	10/155	Lung carcinoma	No
3006 0386/018	CAP	43/F/W	CLA	10/30	Worsening pneumonia	No
3004 1306/008	Tonsillitis/ Pharyngitis	55/F/W	PEN	3/47	Acute lymphoid leukemia	No
Uncontrolled Studies						
3000 0703/1466	CAP	57/M/W	TEL	4/24	Acute leptospirosis/ARDS	No
3000 0803/1520	CAP	65/M/W	TEL	9/32	Gram-negative septicemia	No
3009OL 0369/108	CAP	37/F/B	TEL	7/12	Cardiomyopathy/ Immunosuppression/Liver failure/Cardiac arrhythmia/ Multiorgan failure/ Respiratory failure/ sepsis	No
3010 473/009	CAP	77/M/W	TEL	5/5	Acute aspiration	No
3010 537/009	CAP	44/M/B	TEL	2/2	Acute myocardial infarction	No

[a] CAP = community-acquired pneumonia
[b] Sex: M = male, F = female; Race: W = white: B = black
[c] TEL = telithromycin, AMX = amoxicillin, CLA = clarithromycin, PEN = penicillin VK

Brief narratives for each of the deaths in the table above are presented in *Appendix 16. Narratives for deaths in the Phase III studies*.

7.2.5.2 Nonfatal serious adverse events in controlled Phase III studies

The incidence of all nonfatal serious TEAEs in controlled Phase III studies was similar between the telithromycin and comparator treatment groups: 40 (2.0%) of 2045 and 41 (2.5%) of 1672 subjects, respectively. All nonfatal serious TEAEs reported in the Phase III controlled studies are shown in the following table.

Table 7-15. All nonfatal serious adverse events by coded term in controlled Phase III studies

Coded Term	Number (%) of Subjects	
	Telithromycin (N=2045)	Comparator (N=1672)
Subjects with at least one serious TEAE	**40 (2.0)**	**41 (2.5)**
Pneumonia	3 (0.1)	10 (0.6)
Pleural effusion	2 (0.1)	1 (0.1)
Abscess	5 (0.2)	2 (0.1)
Bronchitis	2 (0.1)	5 (0.3)
Neoplasm	1 (0.05)	1 (0.1)
Accidental injury	1 (0.05)	0 (0.0)
Allergic reaction	2 (0.1)	1 (0.1)
Pulmonary embolus	1 (0.05)	0 (0.0)
Gastroenteritis	1 (0.05)	0 (0.0)
Left heart failure	1 (0.05)	0 (0.0)
Liver damage[a]	2 (0.1)	0 (0.0)
Multi organ failure	1 (0.05)	0 (0.0)
Respiratory disorder	1 (0.05)	1 (0.1)
Abnormality of accommodation	1 (0.05)	0 (0.0)
Asthma	1 (0.05)	0 (0.0)
Atelectasis	1 (0.05)	0 (0.0)
Bronchospasm	1 (0.05)	1 (0.1)
Carcinoma of lung	0 (0.0)	1 (0.1)
Cardiomyopathy	0 (0.0)	1 (0.1)
Pseudomembranous colitis	1 (0.05)	1 (0.1)
Diabetes mellitus	1 (0.05)	0 (0.0)
Diarrhea	1 (0.05)	0 (0.0)
Erythema multiforme	1 (0.05)	0 (0.0)
Heart failure	1 (0.05)	1 (0.1)
Herpes simplex	1 (0.05)	0 (0.0)
Hyperglycemia	0 (0.0)	2 (0.1)
Hypoglycemia	1 (0.05)	0 (0.0)
Hypotension	1 (0.05)	0 (0.0)
Myocardial infarct	0 (0.0)	1 (0.1)
Kidney calculus	1 (0.05)	0 (0.0)
Malaise	1 (0.05)	0 (0.0)
Neurosis	1 (0.05)	0 (0.0)
NPN increased	1 (0.05)	0 (0.0)
Kidney pain	1 (0.05)	0 (0.0)

[a] Investigator term, represents asymptomatic increases in transaminases.

Table 7-15. All nonfatal serious adverse events by coded term in controlled Phase III studies (continued)

Coded Term	Number (%) of Subjects	
	Telithromycin (N=2045)	Comparator (N=1672)
Subjects with at least one serious TEAE	**40 (2.0)**	**41 (2.5)**
Eosinophilic pneumonia	1 (0.05)	0 (0.0)
Sarcoidosis	1 (0.05)	0 (0.0)
Duodenal ulcer perforation	1 (0.05)	0 (0.0)
Vomiting	1 (0.05)	1 (0.1)
Abortion	0 (0.0)	1 (0.1)
Acute leukemia	0 (0.0)	1 (0.1)
Angina pectoris	0 (0.0)	1 (0.1)
Anxiety	0 (0.0)	1 (0.1)
Bone fracture (not spontaneous)	0 (0.0)	2 (0.1)
Chest pain	0 (0.0)	1 (0.1)
Colitis	0 (0.0)	1 (0.1)
Confusion	0 (0.0)	1 (0.1)
Drug level increased	0 (0.0)	1 (0.1)
Dyspnea	0 (0.0)	2 (0.1)
Gastrointestinal disorder	0 (0.0)	1 (0.1)
Gastrointestinal hemorrhage	0 (0.0)	1 (0.1)
Hypertension	0 (0.0)	1 (0.1)
Jaundice	0 (0.0)	1 (0.1)
Lack of drug effect	0 (0.0)	1 (0.1)
Pericardial effusion	0 (0.0)	1 (0.1)

As shown in the following table, possibly related nonfatal serious TEAEs in the controlled Phase III studies were few in number and were similar between the telithromycin and the active comparator treatment groups.

Table 7-16. Possibly related nonfatal serious adverse events by coded term in controlled Phase III studies

Coded Term	Number (%) of Subjects	
	Telithromycin (N=2045)	Comparator (N=1672)
Subjects with at least one possibly related serious TEAE	**8 (0.4)**	**4 (0.2)**
Liver damage[a]	2 (0.1)	0 (0.0)
Allergic reaction	2 (0.1)	1 (0.1)
Gastroenteritis	1 (0.05)	0 (0.0)
Pseudomembranous colitis	1 (0.05)	1 (0.1)
Erythema multiforme	1 (0.05)	0 (0.0)
Vomiting	1 (0.05)	0 (0.0)
Dyspnea	0 (0.0)	1 (0.1)
Gastrointestinal disorder	0 (0.0)	1 (0.1)

[a] Coded term, represents asymptomatic increases in transaminases.

Both events of liver damage in the telithromycin group were asymptomatic transient increases of transaminases. Telithromycin was discontinued due to the event and the subject recovered. Subject 0060/039 in Study 3006 had an AST >8xULN and an ALT >13xULN. Her baseline AST was slightly higher than the upper limit of normal (ULN). Subject 0259/005 in Study 3008 had an AST >7xULN and an ALT >2xULN. The event was associated with binge alcohol ingestion the evening before the laboratory tests were drawn. Neither subject had a concomitant serum bilirubin above 22 mmol/L (ULN = 21 mmol/L) (see discussion on hepatic TEAEs in *Section 7.4, Assessment of the effects of telithromycin on hepatic function*). All other possibly related, nonfatal serious TEAEs were moderate or severe in intensity in both telithromycin- and comparator-treated subjects.

The following table summarizes the events and outcome of the 12 subjects in telithromycin and comparator treatment groups with possibly related serious TEAEs in controlled Phase III studies.

Table 7-17. Possibly related nonfatal serious adverse events in controlled Phase III studies by indication

Study no. Subject no.	Age/sex/race	Treatment	Adverse event (Investigator's term)	Outcome
CAP studies				
3006 0060/039	76/F/W	Telithromycin	Liver injury[a]	Recovered, no sequelae
3006 0387/001	24/F/W	Telithromycin	Vomiting	Recovered, no sequelae
3001 0608/003	20/M/B	Telithromycin	Bullous erythema multiforme	Recovered, no sequelae
3001 0106/005	34/F/O	Amoxicillin	Allergy reaction	Recovered, no sequelae
AECB studies				
3003 0603/011	66/M/W	Amoxicillin/ clavulanic acid	Gastrointestinal disorder	Recovered, no sequelae
Acute sinusitis studies				
3005 0188/032	33/F/W	Telithromycin 10-day	Suspicion of pseudomembranous colitis[b]	Recovered, no sequelae
3005 0194/012	30/F/A	Telithromycin 10-day	Gastroenteritis	Recovered, no sequelae
3005 0174/003	34/F/W	Telithromycin 10-day	Allergic reaction	Recovered, no sequelae
3005 0194/008	30/F/W	Amoxicillin/ clavulanic acid	Pseudomembranous colitis[c]	Recovered, no sequelae
3011 0652/004	72/F/W	Cefuroxime axetil	Dyspnea	Ongoing, follow-up not deemed necessary
Tonsillitis/pharyngitis studies				
3008 0259/005	19/M/W	Telithromycin 5-day	Liver injury[a]	Recovered, no sequelae
3008 0264/013	34/M/W	Telithromycin 5-day	Allergic reaction to drug	Recovered, no sequelae

[a] Asymptomatic increase of transaminases without clinically noteworthy increase in bilirubin.
[b] *C. difficile* toxin A was negative (sample obtained after 1 or 2 doses of ciprofloxacin).
[c] Stool sample tested for *C. difficile* toxin was positive.
Key: CAP = community-acquired pneumonia; AECB = acute exacerbation of chronic bronchitis. Sex: M = male; F = female.
Race: W = white; B = black; A = asian/oriental; O = other races

A brief narrative for each of the possibly related serious adverse events in both telithromycin and comparator treatment groups in the controlled Phase III studies is provided in *Appendix 17. Narratives for possibly related serious adverse events in the completed phase III studies*.

7.2.5.3 Discontinuations due to TEAEs in controlled Phase III studies

Discontinuations due to a possibly related TEAE occurred in 76 of 2045 (3.7%) telithromycin-treated subjects and 51 of 1672 (3.1%) comparator-treated subjects. Discontinuations due to all TEAEs

occurred in 98 of 2045 (4.8%) telithromycin-treated subjects and 73 of 1672 (4.4%) comparator-treated subjects.

Most discontinuations in both the telithromycin and comparator groups in the controlled studies were due to TEAEs in the digestive body system, primarily diarrhea, vomiting, and nausea (see *Section 7.2.4, TEAEs of special interest*).

7.2.6 TEAEs in populations of special interest

7.2.6.1 Drug-demographic interactions

Age

The elderly were studied at escalating doses up to 2000 mg in clinical pharmacology Study 1030. Single escalating oral doses of telithromycin at 1200, 1600, and 2000 mg in elderly subjects (age range 60-72 years), with interspersed placebo, were administered in a 4-period, double-blind, placebo-controlled study with 8 subjects. Subjects then received multiple doses of the maximum tolerated dose for 5 days. Generally, the number of subjects with TEAEs increased with dose. The most frequent adverse events possibly related to telithromycin were gastrointestinal effects (nausea and diarrhea). There were no serious adverse events. No subjects were discontinued due to TEAEs.

In Study 1054, 800 mg telithromycin was administered once daily for 5 to 10 days to 18 adolescent patients (age range 12 to 17 years) with bacterial RTIs (sinusitis, N=10; pharyngitis, N=1; combined sinusitis/pharyngitis, N=7). Telithromycin was well tolerated throughout the study. No serious adverse events were reported and no patient withdrew because of an adverse event. Nine TEAEs (7 nausea events and 2 headache events) were reported in five patients. Six of the nausea events reported in three patients were considered by the investigator to be related to study medication. All TEAEs were of mild intensity and all patients recovered from the events without sequelae.

In the controlled Phase III studies, there were no apparent differences in the incidence of TEAEs, reported in subjects who received telithromycin *vs* comparator antibiotics among the different age groups (13 to 18, >18 to <65, and ≥65 years) as shown in the following table.

Table 7-18. Frequency of all TEAEs (>2%) by age and body system in controlled Phase III studies

Body system/ Coded term	13-18 years		>18-<65 years		≥65 years	
	TEL (N=68)	Comparator (N=69)	TEL (N=1720)	Comparator (N=1343)	TEL (N=257)	Comparator (N=260)
% subjects with TEAEs	35.3	44.9	53.4	49.4	44.4	42.7
Digestive system						
Diarrhea	7.4	7.2	15.0	9.8	12.5	11.9
Nausea	7.4	2.9	9.4	4.7	6.6	3.1
Vomiting	2.9	1.4	3.6	2.6	1.2	1.5
LFT abnormal	2.9	1.4	1.3	1.6	2.7	1.2
Dyspepsia	1.5	0.0	2.5	2.2	2.3	0.4
Gastroenteritis	4.4	1.4	0.6	0.3	0.4	0.4
Nervous system						
Headache	4.4	10.1	6.2	7.6	3.5	3.5
Dizziness	2.9	1.4	4.7	3.1	3.5	2.3
Dry mouth	1.5	2.9	1.8	1.6	0.0	1.2
Respiratory system						
Rhinitis	2.9	2.9	2.0	2.3	0.4	0.0
Upper respiratory infection	2.9	2.9	1.9	2.2	0.4	0.4
Pharyngitis	1.5	5.8	1.3	1.8	0.8	0.0
Cough increased	1.5	2.9	0.9	1.5	0.0	0.4
Bronchitis	0.0	0.0	0.5	0.6	1.2	4.2
Body as a whole						
Abdominal pain	1.5	1.4	2.0	1.6	1.9	1.2
Urogenital system						
Vaginal moniliasis	0.0	0.0	1.7	2.3	0.0	0.4
Special senses						
Taste perversion	1.5	0.0	1.8	2.3	1.6	2.3

TEL = telithromycin

As shown in the table below, there was no clinically relevant difference in the frequency of severe TEAEs or discontinuations due to TEAEs in elderly subjects compared with subjects aged >18 to <65 years. For subjects aged 13 to 18 years, the frequency of severe TEAEs and discontinuations due to TEAEs was lower than in the other age subgroups in both telithromycin and comparator treatment groups.

Table 7-19. Frequency of all severe TEAEs and discontinuation due to all TEAEs by age in controlled Phase III studies

	Number (%) of Subjects					
	13-18 years		>18-<65 years		≥65 years	
	TEL (N=68)	Comparator (N=69)	TEL (N=1720)	Comparator (N=1343)	TEL (N=257)	Comparator (N=260)
Subjects with severe TEAEs	2 (2.9)	2 (2.9)	100 (5.8)	70 (5.2)	15 (5.8)	11 (4.2)
Discontinuation due to TEAEs	2 (2.9)	1 (1.4)	82 (4.8)	56 (4.2)	14 (5.4)	16 (6.2)

TEL = telithromycin

Other demographic subgroups

The frequency of TEAEs was also assessed according to sex, body weight, and race, and no findings of clinical concern were observed in any of these subgroups.

7.2.6.2 Drug-disease interactions

The frequency of TEAEs associated with telithromycin therapy in Phase III studies was generally similar in subjects with and without certain underlying disease states, such as diabetes mellitus, cardiovascular diseases, ischemic heart disease, chronic respiratory disease, abnormal electrocardiogram (ECG) at pretherapy/entry, and risk conditions such as increased electrocardiographic QTc interval at pretherapy/entry, risk factors for torsades de pointes, renal insufficiency, and liver disease.

Table 7-20. Frequency of all TEAEs by presence of underlying disease/risk conditions in controlled Phase III studies

Disease state/ risk condition	Subjects with disease/risk condition n/N (%) Subjects[a]		Subjects without disease/risk condition n/N (%) Subjects[a]	
	Telithromycin	Comparator	Telithromycin	Comparator
Diabetes mellitus	46/93 (49.5)	35/73 (47.9)	1010/1952 (51.7)	771/1599 (48.2)
Cardiovascular disease	211/408 (51.7)	176/341 (51.6)	845/1637 (51.6)	630/1331 (47.3)
Ischemic heart disease	41/87 (47.1)	41/89 (46.1)	1015/1958 (51.8)	765/1583 (48.3)
Chronic respiratory disease	361/822 (43.9)	302/654 (46.2)	695/1223 (56.8)	504/1018 (49.5)
Abnormal ECG at pretherapy/entry	261/476 (54.8)	205/437 (46.9)	795/1569 (50.7)	601/1235 (48.7)
Increased QTc at pretherapy/entry	49/102 (48.0)	46/104 (44.2)	1007/1943 (51.8)	760/1568 (48.5)
Risk factors for torsades de pointes [b]	418/796 (52.5)	328/652 (50.3)	638/1249 (51.1)	478/1020 (46.9)
CL_{CR} <50 mL/min	30/73 (41.1)	30/65 (46.2)	1026/1972 (52.0)	776/1607 (48.3)
CL_{CR} <80 mL/min	183/420 (43.6)	150/363 (41.3)	873/1625 (53.7)	656/1309 (50.1)
Liver disease	16/29 (55.2)	18/27 (66.7)	1040/2016 (51.6)	788/1645 (47.9)

[a] n/N = number of subjects with TEAEs/total number of subjects in category
[b] risk factors for torsades de pointes were increased QTc at baseline, cardiovascular disease, concomitant drugs that increase QTc, potassium levels below normal, and heart rate <60 bpm.

CL_{CR} = creatinine clearance

7.2.6.3 TEAEs in subjects taking concomitant medications of interest

In Phase III studies, the safety of telithromycin when coadministered with concomitant drugs of interest was examined in order to assess the clinical relevance of potential telithromycin drug-drug interactions. The safety of telithromycin was compared with the safety of marketed antibacterial agents (comparator drugs) in patients taking the concomitant drugs of interest.

As shown in the following table, among subjects in the Phase III controlled studies taking concomitant theophylline, antithrombotics, CYP3A4 inhibitors, drugs metabolized by CYP3A4, drugs metabolized by CYP2D6, drugs with potential to increase the electrocardiographic QTc interval, corticosteroids, or CNS drugs (antidepressant and antipsychotic medications), the respective incidences of TEAEs were generally similar for telithromycin-treated subjects who took the concomitant drugs and for telithromycin-treated subjects who did not take the concomitant drugs (note that a few of the subgroups represented small numbers of subjects).

Table 7-21. Frequency of all TEAEs by concomitant drug/class of drug in controlled Phase III studies

Concomitant drug/class	n/N (%) Subjects [a]			
	Subjects who received concomitant drug/class of drug		Subjects who did not receive concomitant drug/class of drug	
	Telithromycin	Comparator	Telithromycin	Comparator
Theophylline	14/29 (48.3)	20/34 (58.8)	1042/2016 (51.7)	786/1638 (48.0)
Antithrombotics (anticoagulants)	80/137 (58.4)	70/136 (51.5)	976/1908 (51.2)	736/1536 (47.9)
Warfarin	8/13 (61.5)	3/8 (37.5)	1048/2032 (51.6)	803/1664 (48.3)
Cardiac glycosides	1/6 (16.7)	4/8 (50.0)	1055/2039 (51.7)	802/1664 (48.2)
Drugs that inhibit CYP3A4	123/207 (59.4)	96/164 (58.5)	933/1838 (50.8)	710/1508 (47.1)
Drugs metabolized by CYP3A4	436/766 (56.9)	356/643 (55.4)	620/1279 (48.5)	450/1029 (43.7)
Drugs metabolized by CYP2D6	155/255 (60.8)	139/227 (61.2)	901/1790 (50.3)	667/1445 (46.2)
Drugs with potential to increase QTc interval	74/145 (51.0)	41/94 (43.6)	982/1900 (51.7)	765/1578 (48.5)
Corticosteroids	120/275 (43.6)	111/221 (50.2)	936/1770 (52.9)	695/1451 (47.9)
CNS drugs	89/172 (51.7)	86/154 (55.8)	967/1873 (51.6)	720/1518 (47.4)
Antiarrhythmics	5/8 (62.5)	2/7 (28.6)	1051/2037 (51.6)	804/1665 (48.3)

Note: Columns are not additive for TEAEs or population.
[a]n/N = number of subjects with TEAEs/total number of subjects in category.

7.3 Clinical laboratory evaluations

Clinically noteworthy abnormal laboratory values (CNALVs) are laboratory values occurring during the study that are; a) abnormally high or low (i.e., outside the limits of the normal range or the extended normal range); b) abnormal laboratory values considered medically important by the Sponsor according to the predefined criteria shown in the following table.

Table 7-22. Clinically noteworthy criteria for laboratory analytes: Phase III studies

Variable	Unit	Clinically noteworthy criteria
Hemoglobin	mmol/L	Decrease of 1.2412 from baseline
	g/dL	Decrease of 2 from baseline
Leukocyte	g/L	<3.0
	/mm3	<3000
Neutrophils	g/L	<1.5
	/mm3	<1500
Eosinophils	g/L	>1.0
	/mm3	>1000
Platelets	g/L	<100
	/mm3	<100,000
INR	-	>1.3
SGPT/ALT	U/L	>3 ULN
SGOT/AST	U/L	>3 ULN
Alkaline phosphatase	U/L	>1.5 ULN
Bilirubin	mmol/L	>2 ULN
Serum creatinine	mmol/L	>2 ULN
Creatinine clearance	mL/sec	<0.8333
	mL/min	<50
Serum potassium	mmol/L	<3 or >5.5

ULN = upper limit of normal

7.3.1 CNALVs in Phase III clinical studies

The following table presents the percentage of subjects with CNALV for hematology and clinical chemistry laboratory values in controlled Phase III studies (CAP and non-CAP studies). The number of subjects with CNALVs was low and similar between the telithromycin and active comparator treatment groups for all analytes. No differences between telithromycin and comparator values were noted.

Table 7-23. Percentage of subjects with clinically noteworthy abnormal laboratory values (CNALVs) in controlled Phase III studies

Laboratory parameter	n/N (%) Subjects [a]				
	CAP studies		Non-CAP studies		
	Telithromycin (7-10 day)	Comparator (7-10 day)	Telithromycin (5 day)	Telithromycin (10 day)	Comparator (10 day)
Hematology					
Hemoglobin ↓	0/527 (0.0)	1/532 (0.2)	0/1253 (0.0)	0/254 (0.0)	0/1131 (0.0)
Platelets ↓	1/526 (0.2)	1/532 (0.2)	0/1250 (0.2)	0/254 (0.0)	1/1129 (<0.1)
PT INR ↑	21/470 (4.5)	21/469 (4.5)	22/917 (2.4)	12/252 (4.8)	27/922 (2.9)
Leukocytes ↓	8/527 (1.5)	11/532 (2.1)	10/1253 (0.8)	5/254 (2.0)	2/1131 (0.2)
Neutrophils (Abs.) ↓	18/527 (3.4)	21/532 (3.9)	26/1253 (2.1)	7/254 (2.8)	21/1130 (1.9)
Eosinophils (Abs.) ↑	10/527 (1.9)	8/532 (1.5)	9/1253 (0.7)	1/254 (0.4)	15/1130 (1.3)
Chemistry					
SGOT/AST ↑	12/527 (2.3)	10/532 (1.9)	8/1256 (0.6)	1/254 (0.4)	10/1130 (0.9)
SGPT/ALT ↑	16/527 (3.0)	17/532 (3.2)	13/1256 (1.0)	4/254 (1.6)	14/1130 (1.2)
Alkaline phosphatase ↑	8/527 (1.5)	14/532 (2.6)	3/1255 (0.2)	0/254 (0.0)	2/1130 (0.2)
Total bilirubin ↑	0/527 (0.0)	2/530 (0.4)	2/1248 (0.2)	0/254 (0.0)	1/1125 (<0.1)
Creatinine clearance ↓	22/527 (4.2)	24/532 (4.5)	46/1256 (3.7)	1/254 (0.4)	36/1130 (3.2)
Creatinine ↑	1/527 (0.2)	1/532 (0.2)	0/1256 (0.0)	0/254 (0.0)	1/1130 (<0.1)
Potassium ↑	19/527 (3.6)	20/532 (3.8)	12/1255 (1.0)	2/254 (0.8)	10/1130 (0.9)

[a] n/N = number of subjects with CNALV for specific analyte/number of subjects with measurement of analyte
Note: subjects did not require baseline analyte assessment to meet the criteria for a CNALV.
Key: ↑ or ↓ = outside the limits of the normal range or the extended normal range

The effect of telithromycin on liver function tests was also carefully examined for CNALVs (see *Section 7.4, Assessment of the effects of telithromycin on hepatic function* for a more comprehensive discussion of telithromycin and liver function.). No specific risk was detected for liver function.

7.4 Assessment of the effects of telithromycin on hepatic function

7.4.1 Preclinical studies

In these studies, effects typical of macrolide antibiotics were observed with telithromycin. In rat, dog, and monkey toxicity studies, elevations of liver enzymes associated with histological correlates of liver cytolysis were noted at high doses in some but not all studies. These effects were slight, dose related and fully reversible during the recovery periods.

The No Observed Adverse Effect Level (NOAEL) of 50 mg/kg/day in the rat and dog was constant across studies, whatever their duration of treatment, and there were no new signs or aggravation of toxicity with longer treatment. The AUC ratios of animal/human exposure at the NOAEL for telithromycin were greater than for clarithromycin but less than for azithromycin.

Studies conducted to assess the tissue distribution of telithromycin in rats showed no accumulation of telithromycin in the liver.

Telithromycin, clarithromycin, and roxithromycin behaved similarly in terms of uptake into and efflux from in vitro cultured hepatocytes of mouse, rat, dog, monkey, and human. Azithromycin was more concentrated in mouse, rat, and dog hepatocytes and its efflux was slower than that of other compounds.

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. Telithromycin did not induce cytochrome P450 complex formation using a hepatic microsomal suspension from dexamethasone-treated rats.

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

7.4.2 Phase III clinical studies

7.4.2.1 Laboratory findings

The frequency of CNALVs (see *Section 7.3, Clinical laboratory evaluations* for a definition of CNALV) for hepatic enzymes was similar between telithromycin and active comparators, but was higher in subjects with CAP or subjects with elevations at baseline. The following table presents the frequencies of CNALVs for ALT, AST, alkaline phosphatase, and total bilirubin from all controlled Phase III CAP and non-CAP studies, and for subjects with normal or abnormal values at baseline.

Table 7-24. Selected laboratory analytes in controlled Phase III studies

Analyte Criterion	n/N (%) Subjects [a]			
	CAP studies		Non-CAP studies	
	Telithromycin	Comparators	Telithromycin	Comparators
AST (>3 ULN)				
Normal Baseline	4/411 (1.0)	3/394 (0.8)	3/1333 (0.2)	2/1000 (0.2)
Abnormal Baseline	8/85 (9.4)	7/89 (7.9)	6/103 (5.8)	8/66 (12.1)
ALT (>3 ULN)				
Normal Baseline	5/395 (1.3)	3/388 (0.8)	3/1251 (0.2)	2/936 (0.2)
Abnormal Baseline	10/101 (9.9)	13/96 (13.5)	14/182 (7.7)	12/130 (9.2)
Alkaline phosphatase (>1.5 ULN)				
Normal Baseline	5/431 (1.2)	9/426 (2.1)	0/1364 (0.0)	2/1010 (0.2)
Abnormal Baseline	3/67 (4.5)	5/68 (7.4)	3/95 (3.2)	0/65 (0.0)
Total Bilirubin (>2 ULN)				
Normal Baseline	0/453 (0.0)	1/432 (0.2)	0/1348 (0.0)	0/997 (0.0)
Abnormal Baseline	0/31 (0.0)	1/42 (2.4)	2/37 (5.4)	1/41 (2.4)

[a] n/N = number of subjects with CNALV for specific analyte/number of subjects with measurement of analyte.
Note: subjects had to have baseline analyte assessment.
Includes Studies 3001, 3006, 3009 (CAP) and 3003, 3004, 3005, 3007, 3008 and 3011 (non-CAP).

There was no significant difference in the frequency of CNALVs, in particular ALT, between subjects who were treated for either 5 or 10 days in the acute sinusitis Studies 3002 and 3005 (subjects with a normal or abnormal baseline who had CNALVs for ALT were 0.4% and 5.1%, respectively, with 5 day treatment and 0% and 10.0%, respectively, for 10 day treatment).

In the uncontrolled CAP Study 3000, there was a higher incidence of CNALVs for ALT which was associated with a higher percentage of subjects with abnormal ALT at baseline (see table below). This higher incidence was not observed in the other uncontrolled CAP studies (3009OL and 3010) and may be due to differences in the study populations, e.g. the rate of patient hospitalization was higher in Study 3000 (74%) than Study 3009OL (10%).

Table 7-25. CNALVs for selected laboratory analytes in subjects treated with telithromycin in the uncontrolled CAP Studies 3000, 3009OL and 3010

Analyte	n/N (%) Subjects [a]		
	Study 3000	Study 3009OL	Study 3010
AST			
Normal Baseline	1/173 (0.6)	1/152 (0.7)	2/318 (0.6)
Abnormal Baseline	5/41 (12.2)	7/51 (13.7)	13/81 (16.0)
ALT			
Normal Baseline	4/171 (2.3)	2/168 (1.2)	2/332 (0.6)
Abnormal Baseline	13/43 (30.2)	4/36 (11.1)	12/67 (17.9)

[a] n/N = number of subjects with CNALV for specific analyte/number of subjects with measurement of analyte.

Shift tables presenting the frequency of subjects with normal and high analyte values at pretherapy/entry followed by the presentation of the frequency of subjects with varying degrees of elevation of that analyte during treatment (>1xULN, >2xULN, >3xULN, >5xULN, and >8xULN) are available in *Appendix 18. Shift tables for ALT (SGPT).* Significant increases in transaminases (>5 ULN) were well balanced between telithromycin and pooled active comparators. These increases were only rarely observed in the controlled Phase III studies: ALT >5xULN in 6 (0.3%) of 1929 telithromycin-treated subjects *vs* 8 (0.5%) of 1550 subjects treated with pooled active comparators; and AST >5xULN in 8 (0.4%) of 1932 telithromycin-treated subjects *vs* 5 (0.3%) of 1549 subjects treated with pooled active comparators.

The same conclusion can be drawn from these shift tables as from the analysis of CNALVs. The frequency of elevation is similar between telithromycin and comparator and is increased when ALT is elevated at baseline. Similar results were seen for the subpopulations of sex (men and women) and age (≥65 years and <65 years) in both the CAP and non-CAP studies, where there appeared to be no meaningful effect of gender or age.

7.4.2.2 Hepatic adverse events

Almost all reports of hepatic adverse events refer to asymptomatic liver enzyme abnormalities, which were generally mild and reversible. The frequency of these hepatic adverse events was well balanced between telithromycin and active comparators, as already reported for laboratory abnormalities.

Deaths and other serious or potentially serious hepatic events

No subjects died due to a hepatic adverse event.

In all studies, serious hepatic TEAEs occurred in 3 of 3265 (0.1%) subjects treated with telithromycin and 1 of 1672 (0.1%) subjects treated with comparator (jaundice in subject 0425/011 in Study 3006 who was treated with clarithromycin) (see table below).

Table 7-26. Serious hepatic TEAEs for all subjects in the Phase III studies

Coded Term	Indication and Study No.	Subject No.	Treatment
Hepatitis	CAP 3000	502/1069	Telithromycin 7-10 d
Jaundice[a]	CAP 3006	0425/011	Clarithromycin 10 d
Liver damage[b]	CAP 3006	0060/039	Telithromycin 10 d
	TONS/PHAR 3008	0259/005	Telithromycin 5 d

[a] assessed as not related to study drug by investigator
[b] asymptomatic transaminase increase (see below)

The three serious hepatic TEAEs in the telithromycin subjects consisted of one asymptomatic case that had been improving dramatically (as shown by transaminase levels) prior to discontinuation of telithromycin (Subject 0060/039), an apparent hypersensitivity in a subject with abnormal baseline transaminases who experienced a second episode 9 months later without treatment with telithromycin or other macrolides (Subject 502/1069), and a third with significant ethanol intake during the study period as a plausible alternative explanation (Subject 0259/005). In the comparator group, jaundice was observed in one subject receiving clarithromycin (Subject 0425/011).

Brief narratives for the 3 subjects treated with telithromycin with serious hepatic events are presented in *Appendix 19. Narratives for subjects treated with telithromycin who experienced serious hepatic events.*

7.4.3 Conclusion

Liver function abnormalities, which were generally mild and reversible, occurred at the same low frequency and intensity for telithromycin as with other antibiotics used as active comparators in the clinical development program. Hepatic adverse events, which in general represented asymptomatic liver enzyme abnormalities, were well balanced between telithromycin and active comparators. Populations at risk, such as the elderly and patients with renal or hepatic insufficiency, did not display an increased risk for hepatic injury with telithromycin treatment.

7.5 Assessment of the effects of telithromycin administration on cardiac repolarization

Erythromycin and several other macrolides have been shown to produce delayed cardiac repolarization that results in an increase of the electrocardiographic QT interval. The structural similarity of telithromycin to the macrolide family necessitated a comprehensive assessment of its effects on cardiac repolarization. This analysis was carried out in 25 preclinical studies, 8 clinical pharmacology studies, and 10 Phase III studies.

From February 1998 to February 1999 (during a period in which roughly 1700 patients were enrolled), those at high-risk due to medical history (including known long QT syndrome, a baseline QTc >450 ms, bradycardia, severe hypokalemia and sick sinus syndrome) were excluded from entry into the studies. After review by the Data Safety Monitoring Board, protocols were amended to

accept the inclusion of these high-risk patients (except for long QT syndrome). Approximately 1500 additional subjects were treated during this broadened enrollment period, allowing for the assessment of 146 patients with prolonged QT interval at baseline and 13 patients on antiarrhythmics.

This extensive program of preclinical and clinical studies has generated a significant body of data addressing the effect of telithromycin on cardiac repolarization. The purpose of this document is to provide a synthesis of this clinical information to provide insight into the following questions:

1) What is the magnitude of the effect of telithromycin on cardiac repolarization?

2) Is there a relationship between telithromycin concentration and cardiac repolarization?

3) What is the magnitude of the effect on cardiac repolarization in subpopulations (e.g. females, elderly)?

4) What can be determined regarding individual risk apart from the general population data (outliers and their characteristics, multiple impairments)?

Telithromycin exhibits a weak inhibitory effect on the cardiac I_{kr} channel. In an extensive cohort of patients with respiratory infections treated with telithromycin, the mean change in the QT interval, corrected for heart rate by the Bazett formula, was approximately 1 ms. Moreover, a shallow relationship was observed between telithromycin plasma concentration and change in corrected QT interval over a wide range of plasma concentrations. Further, no excess in cardiovascular adverse events was seen with telithromycin when compared to other macrolide and non-macrolide active antibiotics.

7.5.1 Preclinical studies

The effects of telithromycin have been examined on the principal components of the repolarization current in the myocardium; I_{kr} (HERG channel), I_{ks} in the ventricles, and Ikur for the auricles.

Telithromycin, erythromycin and clarithromycin inhibited HERG channels expressed in Chinese hamster ovary (CHO) cells with IC_{50} values in the range of 40-55 µM. For telithromycin this corresponds to a ratio of IC_{50} to free concentrations reached clinically of about 50. Data obtained with different compounds on CHO cells in the same laboratory are summarized in the table below.

Table 7-27. Plasma levels and HERG affinity of selected antibiotics

Drug	Oral dose (mg)	Peak free [plasma] (μM)	HERG IC_{50} (μM)	Ratio IC_{50}:[plasma]
Sparfloxacin	400	1.8	17.9	9
Moxifloxacin	400	5.9	129	22
Clarithromycin	500	1.9	54.5	29
Telithromycin	800	0.84	42.5	50
Erythromycin	1000	0.9	50.7	56
Levofloxacin	500	12	915	83

Note: investigations on HERG were all conducted at the same laboratory using the same methodology (CHO cells)

Telithromycin had a weak effect in inhibiting I_{ks} channels. Telithromycin, erythromycin, and azithromycin were also weak inhibitors of the Ikur current in human atrial myocytes giving 16-21% inhibition at 100 μM, while clarithromycin showed slightly greater inhibitory effect, 40% at 100 μM.

Telithromycin increased action potential duration in isolated rabbit Purkinje fibers at concentrations of 10 μM (8 μg/mL) and above, with a similar threshold for clarithromycin. Little or no evidence of early after-depolarizations was seen, even under conditions simulating severe bradycardia. Comparison of cardiovascular effects in the conscious dog after an intravenous bolus of 15 mg/kg showed telithromycin, erythromycin and clarithromycin to have similar effects in increasing heart rate and QTf (QT interval corrected by Fridericia formula, see *Section 7.5.3.1, Electrocardiographic QT interval findings in patients receiving telithromycin*).

7.5.2 Telithromycin effect on heart rate

Preclinical data revealed an increase in heart rate when telithromycin was administered by intravenous bolus at high doses in dogs (15 mg/kg). Eighty-six healthy volunteers given the therapeutic dose of 800 mg experienced an average increase in heart rate of 11 bpm. In contrast, when telithromycin was administered to patients with respiratory infections, a decrease in heart rate was observed (see table below). The difference in heart rate response between patients and healthy volunteers is not currently understood, although clinical improvement in the former may be responsible.

Table 7-28. Change in heart rate in telithromycin-treated subjects in Phase III studies (controlled and uncontrolled)

	Telithromycin (5 day)		Telithromycin (7-10 day)	
	On-therapy (N=1137)	Posttherapy [a] (N=962)	On-therapy (N=1152)	Posttherapy [a] (N=903)
ΔHeart rate (bpm)	–1.9 ± 12.1	–4.4 ± 13.3	–6.3 ± 15.3	–10.3 ± 17.3

[a] Last observation posttherapy

Data are mean ± SD.

7.5.3 Clinical studies

7.5.3.1 Electrocardiographic QT interval findings in patients receiving telithromycin

A total of 1872 subjects had on-therapy electrocardiographic data in 10 Phase III studies and the ECG analyses from these studies are presented below. For Studies 3000 through 3009 (except Study 3004 in which only selected subjects had an ECG recording on-therapy), twelve-lead ECGs were recorded in all subjects at pretherapy, during therapy with the active drug/comparator, and posttherapy. Time windows were defined as follows.

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

To provide uniform evaluation and interpretation of ECG data across study sites and across clinical protocols, the ECGs were overread by a central reader. The central reader, blinded to treatment, read the ECGs in a random sequence for any given subject without details of demographics or 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, QT interval was derived by calculating the mean value of the longest and shortest QT intervals. Results are presented using descriptive statistics.

For the subjects enrolled in 8 of the 9 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 (*see Section 7.5.4, Telithromycin exposure vs QTc interval*).

Relevant ECG data from Studies 3009OL, 3010 and 3011 are also presented but were not pooled with results from the other Phase III studies. These studies were not included in the original NDA submission and there were methodological differences in the way ECG data were obtained. In Study 3009OL, which was an open-label, uncontrolled extension study, ECGs were not overread by the same central reader as in Studies 3000 through 3009, and a posttherapy ECG was obtained inconsistently. ECGs in Studies 3010 and 3011 were not overread by the same central reader and were performed only on subjects deemed at potential increased risk due to prolonged QTc interval at baseline, concomitant medications that impact cardiac conduction, or other concomitant relevant risk factors by medical history (chronic obstructive pulmonary disease, respiratory insufficiency, congestive heart failure, hepatic or renal disease).

Analyses performed in the Phase III program to evaluate the effect of telithromycin on cardiac repolarization were as follows:

1. It is well known that the QT interval is influenced by changes in heart rate. Many different correction formulae have been developed to account for this heart rate effect. Similar results were obtained for these ECG analyses regardless of the correction formulae used. For this reason, only the results of the QTc (Bazett) formula are presented.
   - Bazett correction: QTc (ms) = QT (ms)/ $\sqrt{RR(\text{sec})}$.

[1] Investigators were requested to obtain the on-therapy ECGs within 2-3 hours post dose.

In order to provide the most robust investigation of repolarization effects, analyses of the mean QTc interval data were also performed using two other formulae:

- Fridericia (QTf) (QTf (ms) = QT (ms)/ $\sqrt[3]{RR(\text{sec})}$)
- A new formula (QTn) (QTn = QT/(RR/1000)^0.4017), which was developed using the relationship between baseline QT values and RR interval in this patient population.

2. In addition to analyzing mean QTc interval data and variance, individual QTc increases of ≥30 and <60 ms, as well as individual increases ≥60 ms were also analyzed. These changes in variability seen for telithromycin were compared to the changes observed for active comparators (clarithromycin, cefuroxime, amoxicillin, amoxicillin-clavulanate, penicillin, and trovafloxacin) since QT intervals showed a high degree of inter- and intra-individual variability (up to ± 70 ms) [64].
3. Analysis of QT dispersion was also performed and defined as the difference between the longest and shortest QT interval measured in the same ECG.

7.5.3.2 QT interval data

Patients treated with telithromycin

A summary of the electrocardiographic data obtained for subjects treated with telithromycin in 10 Phase III studies (Studies 3000 through 3009) is provided in the table below.

Table 7-29. QT interval data for telithromycin-treated subjects in Phase III studies [a]

Variable	Pretherapy (N=2129)	On-therapy (N=1872)[b]	Posttherapy (N=1578)[c]
QTc (ms)	406.9 ± 22.9	407.7 ± 22.4	404.2 ± 22.4
ΔQTc (ms)	–	1.0 ± 21.1[d]	-2.6 ± 22.8[e]
QTc increase (n/N (%) subjects)			
≥30 and <60 ms	–	134/1872 (7.2)	98/1578 (6.2)
≥60 ms	–	8/1872 (0.4)	6/1578 (0.4)
QTc outlier (n/N (%) subjects)			
≥450 ms (men)	31/1026 (3.0)	21/917 (2.3)	11/768 (1.4)
≥470 ms (women)	9/1103 (0.8)	6/973 (0.6)	4/810 (0.5)
≥500 ms (men or women)	4/2129 (0.2)	2/1890 (0.1)	1/1578 (0.1)
QT dispersion (ms)	21.8 ± 9.9	21.0 ± 9.8	21.8 ± 10.0

Data are mean ± SD

[a] Includes studies 3000, 3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008, and 3009.

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

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

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

[e] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

The mean on-therapy change in QTc was 1 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 posttherapy. The proportion of subjects considered to have a QTc outlier value was higher at pretherapy than either on-therapy or posttherapy. No change in QT dispersion was observed.

With the addition of pretherapy and on-therapy ECGs from Study 3009OL (posttherapy ECGs were obtained inconsistently), there were no relevant changes in the mean QTc interval and ΔQTc. Although there appeared to be an increase in the frequency of subjects with changes ≥30 ms and <60 ms and those ≥60 ms, the incidence of outliers within this population, including Study 3009OL, was comparable in the pretherapy and on-therapy periods.

Table 7-30. QT interval data for telithromycin-treated subjects in Phase III studies [a] (including Study 3009OL)

Variable	Pretherapy (N=2342)	On-therapy (N=2078) [b]
QTc (ms)	407.1 ± 22.7	408.5 ± 22.8
ΔQTc (ms)	–	1.5 ± 21.9[c]
QTc increase (n/N (%) subjects)		
≥30 and <60 ms	–	177/2078 (8.5)
≥60 ms	–	18/2078 (0.9)
QTc outlier (n/N (%) subjects)		
≥450 ms (men)	37/1162 (3.2)	37/1051 (3.5)
≥470 ms (women)	9/1180 (0.8)	11/1048 (1.0)
≥500 ms (men or women)	4/2342 (0.2)	3/2099 (0.1)
QT dispersion (ms)	22.6 ± 11.3	22.3 ± 12.2

Data are mean ± SD
[a] Includes studies 3000, 3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008, 3009, and 3009OL.
[b] Represents number of subjects with both a pretherapy and on-therapy ECG
[c] ΔQTc represents the QTc interval on-therapy minus QTc interval pretherapy

Of the 10 subjects from Study 3009OL with an increase in QTc ≥60 ms, 7 had another on-therapy ECG with a QTc change <60 ms (data from ECGs with the largest change are identified in the table above). Despite a higher proportion of subjects with underlying cardiopulmonary disease enrolled in Study 3009OL (and underlying abnormal ECGs complicating the assessment of the QT interval), no adverse clinical cardiovascular sequelae attributable to QTc lengthening were noted.

In the noncomparative, open-label CAP Study 3010, a 12-lead ECG was to be performed for each subject at the pretherapy/entry visit. The 12-lead ECG was to be repeated at subsequent visits only if the subject had a QTc ≥500 ms at the pretherapy/entry visit or if the subject was taking concomitant medication(s) that impacted cardiac conduction (e.g., antiarrhythmics).

There was no clinically relevant change in mean QTc at on-therapy (-3.7 ± 31.6 ms, n = 33) compared with baseline. There were 6 telithromycin -treated subjects who had increases in the QTc interval ≥30 to <60 ms and 1 telithromycin-treated subject (500/001) who had an increase in QTc interval ≥60 ms from 375.9 ms to 440 ms. Subject 500/001 did not report any adverse events during the study and did not take concomitant medication with the potential for pharmacokinetic or pharmacodynamic interaction during the study.

In sinusitis Study 3011 (double-blind comparison with cefuroxime axetil), all subjects were to undergo 12-lead ECGs at the pretherapy/entry visit and on-therapy if they met one or more of the following criteria: the subject received specified concomitant medications, and/or the subject had a concomitant relevant risk factor for chronic obstructive pulmonary disease, respiratory insufficiency,

congestive heart failure, hepatic or renal disease. Repeat ECGs were to be performed if a serious adverse event occurred. Only 1 telithromycin-treated subject and no cefuroxime-treated subjects had paired ECG data (pretherapy/entry and 1 or more postbaseline assessment). Subject 709/001 in the telithromycin group underwent ECG recordings at visits 1, 3, and 4 because she received concomitant aminophylline (QTc interval was 393.9 ms at pretherapy and 408.9 ms at posttherapy Day 11; no on-therapy ECG was available). The subject did not experience any adverse events in the study.

QT interval data within 6 hours of dosing with telithromycin

An additional analysis was undertaken examining on-therapy responses within 6 hours of dosing (expected C_{max} 1-4 hours after dosing) in telithromycin-treated subjects. The results (shown below) were comparable to the entire on-therapy cohort shown above for Studies 3000 through 3009.

Table 7-31. QT interval data for telithromycin-treated subjects in Phase III studies who had on-therapy ECG recording within 6 hours of dosing

Variable	ECG within 6 hr (N=1207)
QTc (ms)	408 ± 21.8
ΔQTc (ms)	1.3 ± 20.9
QTc increase (n/N (%) subjects)	
≥30 and <60 ms	86 (7.2%)
≥60 ms	6 (0.5%)
QTc outlier (n/N (%) subjects)	
≥450 ms (men)	7/580 (1.2%)
≥470 ms (women)	4/627 (0.6%)
≥500 ms (men or women)	1/1207 (0.1%)
QT dispersion (ms)	21.0 ± 9.8

Comparison of telithromycin to clarithromycin

Data derived from CAP Study 3006 and tonsillitis/pharyngitis Study 3008 provide an opportunity to compare QT interval data to clarithromycin. The QTc findings are summarized in the table below.

Table 7-32. QT interval data for telithromycin *vs* clarithromycin (controlled Studies 3006 and 3008)

Variable	Pretherapy		On-therapy		Posttherapy	
	TEL (N=446)	CLA (N=440)	TEL (N=393)[a]	CLA (N=414)[a]	TEL (N=340)[b]	CLA (N=329)[b]
QTc (ms)	404.9 ± 18.5	407.8 ± 18.2	408.8 ± 17.8	410.0 ± 17.5	406.3 ± 18.7	408.8 ± 18.1
ΔQTc (ms)	–	–	3.6 ± 17.8[c]	2.3 ± 18.1[c]	1.3 ± 21.1[d]	0.6 ± 20.8[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	30/393 (7.6)	29/414 (7.0)	31/340 (9.1)	23/329 (7.0)
≥60 ms	–	–	0/393 (0.0)	0/414 (0.0)	2/340 (0.6)	1/329 (0.3)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	1/192 (0.5)	4/195 (2.1)	1/175 (0.6)	1/190 (0.5)	0/146 (0.0)	2/147 (1.4)
≥470 ms (women)	0/254 (0.0)	1/245 (0.4)	0/219 (0.0)	0/231 (0.0)	0/194 (0.0)	0/182 (0.0)
≥500 ms (men or women)	0/446 (0.0)	0/440 (0.0)	0/394 (0.0)	0/421 (0.0)	0/340 (0.0)	0/329 (0.0)
QT dispersion (ms)	23.6 ± 10.4	23.0 ± 8.8	22.5 ± 9.3	23.7 ± 9.5	23.6 ± 9.1	23.4 ± 9.8

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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

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

Of note, there were no subjects with an increase in the QTc interval of 60 ms or more in either the clarithromycin or telithromycin on-therapy treatment groups.

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 and 3008 had a QTc value ≥500 ms.

Comparison of telithromycin to non-macrolide antibiotics

QTc interval data for telithromycin compared with other active comparators not known to impact cardiac repolarization (penicillin, amoxicillin, amoxicillin/clavulanic acid, cefuroxime axetil, and trovafloxacin) are summarized in the table below.

Table 7-33. QT interval data for telithromycin *vs* non-macrolide active comparators in controlled Phase III studies

Variable	Pretherapy		On-therapy		Posttherapy	
	TEL (N=1119)	COMP (N=873)	TEL (N=975)[a]	COMP (N=820)[a]	TEL (N=792)[b]	COMP (N=576)[b]
QTc (ms)	408.9 ± 23.2	409.4 ± 23.8	410.1 ± 21.8	406.4 ± 21.9	405.4 ± 22.2	404.9 ± 23.6
ΔQTc (ms)	–	–	1.3 ± 20.9[c]	–2.6 ± 22.1[c]	–3.3 ± 22.7[d]	–4.6 ± 22.6[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	73/975 (7.5)	52/820 (6.3)	40/792 (5.1)	30/576 (5.2)
≥60 ms	–	–	3/975 (0.3)	2/820 (0.2)	1/792 (0.1)	3/576 (0.5)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	19/542 (3.5)	21/435 (4.8)	17/480 (3.5)	10/417 (2.4)	7/390 (1.8)	7/290 (2.4)
≥470 ms (women)	6/577 (1.0)	2/438 (0.5)	4/508 (0.8)	1/427 (0.2)	4/402 (1.0)	0/286 (0.0)
≥500 ms (men or women)	4/1119 (0.4)	2/873 (0.2)	2/988 (0.2)	1/844 (0.1)	1/792 (0.1)	1/576 (0.2)
QT dispersion (ms)	22.5 ± 9.8	22.1 ± 9.7	21.7 ± 9.3	21.4 ± 9.4	22.8 ± 9.6	22.5 ± 9.8

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

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

There was a small change in QTc of ~1 ms observed in telithromycin-treated patients, which is consistent with that seen in the other Phase III studies. Although a small difference was noted in comparison to the non-macrolide active 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 two groups.

7.5.3.3 Subjects with QTc values ≥500 ms

Details of the telithromycin- and comparator-treated subjects with QTc values ≥500 ms in the Phase III studies are provided in the table below.

Table 7-34. 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	Posttherapy
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	465	32.1	508.3
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

AMX = amoxicillin, AMC = amoxicillin/clavulanic acid
[a] No follow up QTc available as patient in recurrent atrial fibrillation

As outlined in the table above, 4 of the 5 telithromycin-treated subjects with QTc ≥500 ms had this prolongation at the baseline (pretherapy) visit. A single patient from both the telithromycin and comparator (amoxicillin) treated groups had an on-therapy increase to greater then 500 ms. Brief details for these subjects are given below.

Subject 1403/002 in AECB Study 3003: a 68-year-old female with medical history of congestive heart failure, coronary artery disease, emphysema, left bundle branch block, hypertension and pulmonary embolism. The subject had a prolonged QTc (488.1 ms) at baseline, which increased to 531.2 ms on-therapy with telithromycin. At subsequent posttherapy assessments (days 12, 19 and 36), the QTc value had decreased to below baseline values. The associated QTf and heart rate values were as follows: 453 ms and 94 (baseline), 494.7 and 92 (on therapy), and 442.4 ms/83 bpm, 458.7 ms/84 bpm, and 458.3 ms/82 bpm (posttherapy), respectively. No matched telithromycin plasma concentration was available for the on-therapy ECG. The subject had a TEAE of left heart failure of

moderate intensity on day 11 (6 days after completion of active treatment) that was considered unrelated to the study medication by the investigator.

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, which increased to 504 ms on-therapy with amoxicillin. At subsequent posttherapy assessment, the QTc value had decreased to 440 ms. The associated QTf values were as follows: 415 ms (baseline), 489 (on-therapy), and 440 ms (posttherapy), respectively. 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.

In addition to the above, one telithromycin-treated subject in Study 3009OL and one in Study 3010 had a QTc interval ≥500 ms. These subjects are described below.

Subject 0355/149 in CAP Study 3009OL: a 69-year-old male with a medical history of hypertension, chronic obstructive pulmonary disease, asthma, Buerger's disease, benign prostatic hyperplasia, and fibrositis. At baseline the subject had a QTc of 432.9 ms, which increased to 465 ms on therapy (Day 5). At the subsequent on-therapy assessment on Day 9, the QTc value had increased to 508.3 ms (increase of 75.4 ms from baseline). A complete right bundle branch block was noted on the ECG at baseline and at the two on-therapy visits. The subject had TEAEs of myositis and asthma during the study; no cardiovascular adverse events or arrhythmias were noted.

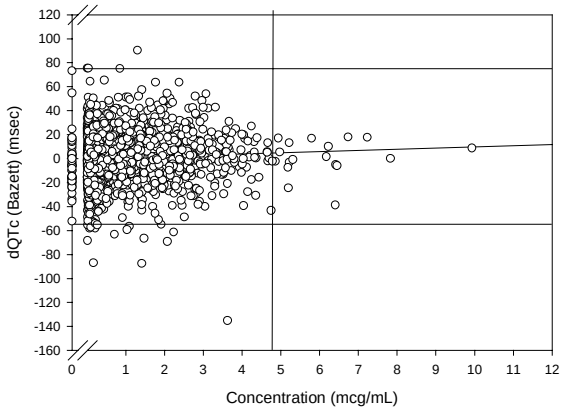
Subject 525/001 in CAP Study 3010: a 75-year-old white male with a history of atrial fibrillation, congestive heart failure, and hypertension, as well as a history of cigarette smoking for 14 years. On Day 5, the subject met criteria for a clinically noteworthy QTc interval (QTc = 512.3 ms). No baseline ECG data were available. At posttherapy (Day 10), the subject had a QTc value of 478.8 ms. On Day10, worsening pneumonia was reported as an adverse event, which was considered not related to telithromycin. No other adverse events reported. Concomitant medications included amiodarone.

7.5.4 Telithromycin exposure *vs* QTc interval

This analysis was done to delineate the relationship of telithromycin exposure to corrected QT interval in the 1715 subjects in 8 Phase III studies (3000, 3001, 3002, 3003, 3005, 3006, 3007 and 3008) who had matched data (within 1 hour) for both ECG and plasma concentration data (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 ± 1.18 µg/mL. Mean baseline QTc was 406 ± 22 ms and remained virtually unchanged after treatment at 407 ± 22 ms; mean heart rate decreased from 78 ± 16 bpm (baseline) to 75 ± 13 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 7-2. Relationship between telithromycin plasma concentration and ΔQTc (all patients in on-therapy cohort)

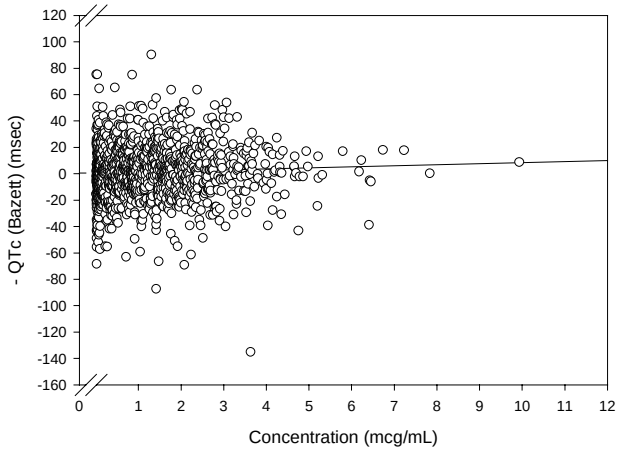


N=1611 datapoints from 1557 subjects
r^2=0.003
P<0.05
Slope=0.98 ms/µg/mL
Mean conc = 1.08 ± 1.18 µg/mL

A linear best-fit between concentration and ΔQTc was described by the relationship shown in the above figure. Similar findings were observed for the QTf and QTn correction formulae (data not shown). A very shallow slope was observed over a wide range of plasma concentrations (0.05 to 9.9 µg/mL), which was approximately 3-fold higher than the mean C_{max} measured in patients (2.9 µg/mL, Study 3000).

In addition to the above, a separate analysis was done taking only those observations where plasma concentration and ECG data were obtained within 6 hours of dosing, and this is presented below. No difference was observed with this subset.

Figure 7-3. Relationship between telithromycin plasma concentration and ΔQTc (patients in on-therapy cohort with ECG within 6 hours of dosing and plasma concentration above 0.05 µg/mL)



N=1227 datapoints from 1175 subjects
r^2=0.002
P=0.10
Slope=0.80 ms/µg/mL
Mean conc = 1.29 ± 1.23 µg/mL

A linear best-fit between concentration and ΔQTc was described by the relationship shown in the above figure.

7.5.4.1 Subgroups: exposure *vs* QTc interval

Analyses were also 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 subgroups limited the conclusions that could be drawn, the slope of the relationship ΔQTc *vs* concentration was similar to that seen for the population as a whole.

Table 7-35. Regression analysis of on-therapy telithromycin plasma concentration and ΔQTc in at-risk subgroup populations

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

N = number of matched data points, TEL = telithromycin

For both the general population studied and a variety of subgroups, a shallow relationship between plasma concentration and change in QTc was observed.

7.5.4.2 Relationship between plasma concentrations of telithromycin and QTc in clinical pharmacology studies

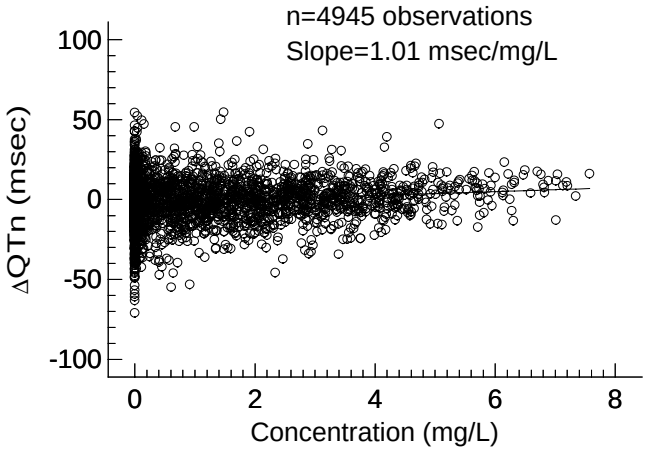
To explore the relationship between plasma telithromycin concentration and ΔQTc in subjects without RTIs, a population pharmacodynamic analysis using a mixed effect modeling approach was performed. Data from eight Phase I clinical studies (1030, 1031, 1032, 1037, 1041, 1045, 1046 and 1049) were pooled for analysis.

The database included 185 subjects and 4945 ECG records measured on telithromycin treatment alone and during the placebo sessions. Doses studied in these 8 protocols ranged from 800 mg to 3200 mg (up to four times the intended therapeutic dose) given by oral administration. In each study, multiple ECGs were measured simultaneously with the pharmacokinetic samples. Multiple ECGs were also obtained during the placebo sessions in each study.

The QT interval was initially corrected for heart rate to remove the dependence of QT on heart rate, using QTc (Bazett) or QTf (Fridericia). However, when ΔQTc or ΔQTf were plotted against the RR interval, a correlation was still present with heart rate, showing inadequate correction for heart rate response by these formulae. In this volunteer program, a separate formula for heart rate correction, (QTn = QT/(RR/1000)^0.284) was derived using the relationship between baseline QT *vs* RR interval which was then applied to correct the QT interval in the studies.

The relationship between telithromycin plasma concentration and change in QT corrected by the new formula (the most appropriate correction for heart rate) is presented below.

Figure 7-4. Relationship between ΔQTn and concentration for 8 Phase I studies with doses from 800 to 3200 mg



A linear best-fit between concentration and ΔQTn was described by the relationship shown in the above figure. The slope of the relationship between QTn and telithromycin concentration is again shallow, at 1.01 ms/µg/mL, and illustrates the small effect on corrected QT.

7.5.5 TEAEs of potential relevance to electrocardiographic findings

In addition to electrocardiographic changes, adverse events of the cardiovascular system and events that could be potential symptoms of arrhythmia were reviewed and are presented below.

7.5.5.1 TEAEs of the cardiovascular system

TEAEs of the cardiovascular system were observed in 2.6% (61/2365) of all telithromycin-treated subjects. In controlled studies, 2.6% (47/1793) of telithromycin-treated subjects experienced a TEAE of the cardiovascular system, comparable to 3.0% (46/1551) of the comparator-treated subjects. The events in controlled trials are summarized below.

Table 7-36. All and possibly related TEAEs of the cardiovascular body system in controlled Phase III studies [a]

Coded term	Number (%) of Subjects			
	Possibly related TEAEs		All TEAEs	
	Telithromycin (N=1793)	Comparator (N=1551)	Telithromycin (N=1793)	Comparator (N=1551)
All subjects with cardiovascular TEAEs	**10 (0.6)**	**11 (0.7)**	**47 (2.6)**	**46 (3.0)**
Hypertension	0 (0.0)	0 (0.0)	5 (0.3)	6 (0.4)
Migraine	0 (0.0)	1 (0.1)	5 (0.3)	1 (0.1)
Vasodilatation	3 (0.2)	1 (0.1)	5 (0.3)	4 (0.3)
Atrial arrhythmia	1 (0.1)	1 (0.1)	3 (0.2)	2 (0.1)
Hypotension	1 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Chest pain	1 (0.1)	1 (0.1)	4 (0.2)	4 (0.3)
QT interval prolonged	1 (0.1) [b]	1 (0.1)	1 (0.1) [b]	1 (0.1)
Tachycardia	0 (0.0)	0 (0.0)	4 (0.2)	3 (0.2)
Palpitation	1 (0.1)	1 (0.1)	3 (0.2)	7 (0.5)
Bradycardia	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Bundle branch block	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Cardiovascular disorder	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
ECG abnormal	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Pulmonary embolus	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Heart failure	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Left heart failure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Postural hypotension	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Syncope	0 (0.0)	0 (0.0)	2 (0.1) [c]	1 (0.1)
Angina pectoris	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Bigeminy	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Hemorrhage	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cerebral ischemia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
PR interval prolonged	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
AV block first degree	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Arrhythmia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Extrasystoles	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

Note: Columns are not additive because a subject may have had more than one adverse event.

[a] Studies 3001, 3003, 3004, 3005, 3006, 3007, 3008 and 3009

[b] Not confirmed on expert overread.

[c] Both events were non-serious and were not related to study drug. One event occurred posttreatment.

Table 7-36. All and possibly related TEAEs of the cardiovascular body system in controlled Phase III studies [a] (continued)

Coded term	Number (%) of Subjects			
	Possibly related TEAEs		All TEAEs	
	Telithromycin (N=1793)	Comparator (N=1551)	Telithromycin (N=1793)	Comparator (N=1551)
All subjects with cardiovascular TEAEs	**10 (0.6)**	**11 (0.7)**	**47 (2.6)**	**46 (3.0)**
Myocardial infarct	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pericardial effusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
QT interval shortened	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Supraventricular tachycardia	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

Note: Columns are not additive because a subject may have had more than one adverse event.
[a] Studies 3001, 3003, 3004, 3005, 3006, 3007, 3008 and 3009

Most of the cardiovascular events that were reported were considered related to underlying cardiovascular diseases and not to treatment with telithromycin or other antibiotics. Cardiovascular events considered possibly related to the administration of study drug in controlled studies were reported for 0.6% (10/1793) and 0.7% (11/1551) subjects treated with telithromycin and active comparators, respectively.

There was no difference in the percentage of subjects who experienced serious TEAEs of the cardiovascular system with telithromycin (0.2%) compared to those subjects treated with active comparators (0.5%) in controlled studies. In addition, none of the serious cardiovascular events from the controlled studies were considered possibly related to study medication and none were suggestive of a ventricular tachyarrhythmia.

7.5.5.2 TEAEs potentially representing clinical manifestations of cardiac arrhythmia (TEAEs of special interest)

No episodes of torsades de pointes or other malignant ventricular arrhythmias were reported in the Phase III program. An analysis of adverse events which may represent clinical manifestations of cardiac arrhythmias (regardless of relationship to drug) is described below.

Table 7-37. TEAEs of special interest (potential clinical manifestation of cardiac arrhythmias) in controlled Phase III studies [a]

Coded term	Number (%) of Subjects			
	Possibly related TEAEs		All TEAEs	
	TEL (N=1793)	Comp (N=1551)	TEL (N=1793)	Comp (N=1551)
Dizziness	66 (3.7)	26 (1.7)	84 (4.7)	46 (3.0)
Sweating increased	2 (0.1)	3 (0.2)	6 (0.3)	6 (0.4)
Vertigo	4 (0.2)	2 (0.1)	4 (0.2)	6 (0.4)
Palpitation	1 (0.1)	1 (0.1)	3 (0.2)	7 (0.5)
Hypotension	1 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Syncope	0 (0.0)	0 (0.0)	2 (0.1) [b]	1 (0.1)
Bigeminy	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Arrhythmia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

TEL = telithromycin, Comp = pooled active comparators (clarithromycin, amoxicillin, amoxicillin-clavulanate, penicillin, trovafloxacin, cefuroxime)

[a] Studies 3001, 3003, 3004, 3005, 3006, 3007, 3008 and 3009

[b] Both events were non-serious and were not related to study drug. One event occurred posttreatment.

With the exception of dizziness, the frequency of adverse events was similar between telithromycin and other antibiotics used as active comparators. The mean QT and corrected QT intervals of this group of patients with TEAEs of interest were similar at pretherapy, on-therapy and posttherapy to that observed for the rest of the telithromycin-treated population. The incidence of QTc outliers was comparable to the overall population.

Table 7-38. Frequency of QTc increase and QTc outliers in telithromycin-treated subjects with TEAEs of special interest

ECG variable	n/N (%) subjects		
	Pretherapy	On-therapy	Posttherapy
QTc increase			
≥30 and <60 ms	–	5/94 (5.3)	7/86 (8.1)
≥60 ms	–	1/94 (1.1)	0/86 (0.0)
QTc outlier			
≥450 ms (men)	0/46 (0.0)	0/40 (0.0)	1/35 (2.9)
≥470 ms (women)	0/60 (0.0)	0/54 (0.0)	0/51 (0.0)
≥500 ms (men or women)	0/106 (0.0)	0/94 (0.0)	0/86 (0.0)

With respect to dizziness, analysis of this subgroup revealed neither an increase in mean QTc interval nor an increased frequency in patients with a QTc increase ≥30 ms, suggesting no association of the reported dizziness to QT interval prolongation.

7.5.6 Analysis of special populations

An evaluation of the effects of telithromycin on QT interval was conducted for the following subgroups felt to be at increased risk for QTc prolongation or for higher telithromycin drug levels: elderly subjects (≥65 years), subjects with hepatic impairment, subjects with renal impairment, females, subjects with cardiovascular disease, subjects with prolonged baseline QTc, subjects receiving concomitant CYP3A4 inhibitors, and subjects receiving concomitant drugs metabolized by CYP3A4. The electrocardiographic QT data for these groups is presented below.

7.5.6.1 Elderly subjects

The QTc analysis of subjects aged 65 years or older receiving telithromycin in the Phase III program is presented in the table below.

Table 7-39. QTc data in telithromycin-treated subjects by age: Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	<65 years (N=1871)	≥65 years (N=258)	<65 years (N=1653)[a]	≥65 years (N=219)[a]	<65 years (N=1401)[b]	≥65 years (N=177)[b]
QTc (ms)	405.7 ± 22.2	415.4 ± 25.8	406.6 ± 21.5	416.0 ± 27.0	403.4 ± 21.9	410.5 ± 25.2
ΔQTc (ms)	–	–	1.1 ± 21.1[c]	0.0 ± 21.7[c]	–2.3 ± 22.6[d]	–5.1 ± 24.3[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	124/1653 (7.5)	10/219 (4.6)	89/1401 (6.4)	9/177 (5.1)
≥60 ms	–	–	8/1653 (0.5)	0/219 (0.0)	6/1401 (0.4)	0/177 (0.0)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	18/882 (2.0)	13/144 (9.0)	12/795 (1.5)	9/122 (7.4)	7/667 (1.0)	4/101 (4.0)
≥470 ms (women)	5/989 (0.5)	4/114 (3.5)	3/875 (0.3)	3/98 (3.1)	2/734 (0.3)	2/76 (2.6)
≥500 ms (men or women)	2/1871 (0.1)	2/258 (0.8)	1/1670 (0.1)	1/220 (0.5)	1/1401 (0.1)	0/177 (0.0)
QT dispersion (ms)	21.8 ± 9.7	22.0 ± 11.1	21.3 ± 9.8	18.9 ± 9.1	21.9 ± 10.0	21.3 ± 10.6

Data are mean ± SD

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy,

In elderly subjects, the baseline QTc was higher than that seen in the group aged <65 years. However, there was no increase in the mean change in QTc in the elderly cohort nor the frequency of elderly patients with an increase in QTc ≥30 ms and <60 ms or ≥60 ms. The increase in frequency of outlier values for QTc in the elderly as compared to the younger subgroup would appear to be a reflection of the increased frequency at baseline. QT dispersion was unchanged.

7.5.6.2 Subjects with hepatic impairment

A total of 34 subjects with liver disease (including viral and non-viral hepatitis, non-specific hepatic laboratory abnormalities, and metabolic liver diseases) received telithromycin treatment in the Phase

III controlled and uncontrolled studies. Baseline QTc values were similar in telithromycin-treated subjects with and without liver disease. At on-therapy, mean QTc values tended to decrease in the subjects with liver disease (see table below).

Table 7-40. QTc and QT dispersion data in telithromycin-treated subjects by presence of liver disease: Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	With liver disease (N=34)	Without liver disease (N=2095)	With liver disease (N=29)[a]	Without liver disease (N=1843)[a]	With liver disease (N=19)[a]	Without liver disease (N=1559)[a]
QTc (ms)	405.7 ± 22.9	406.9 ± 22.9	403.1 ± 32.2	407.8 ± 22.3	391.8 ± 34.1	404.3 ± 22.2
ΔQTc (ms)	–	–	–2.4 ± 36.9[c]	1.1 ± 20.8[c]	–11.8 ± 34.1[d]	–2.5 ± 22.5[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	3/29 (10.3)	131/1843 (7.1)	3/19 (15.8)	95/1559 (6.1)
≥60 ms	–	–	1/29 (3.4)	7/1843 (0.4)	1/19 (5.3)	5/1559 (0.3)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	0/24 (0.0)	31/1002 (3.1)	0/20 (0.0)	21/897 (2.3)	0/15 (0.0)	11/753 (1.5)
≥470 ms (women)	0/10 (0.0)	9/1093 (0.8)	0/9 (0.0)	6/964 (0.6)	0/4 (0.0)	4/806 (0.5)
≥500 ms (men or women)	0/34 (0.0)	4/2095 (0.2)	0/29 (0.0)	2/1861 (0.1)	0/19 (0.0)	1/1559 (0.1)
QT dispersion (ms)	21.6 ± 11.2	21.8 ± 9.8	21.9 ± 9.5	21.0 ± 9.8	16.3 ± 9.0	21.9 ± 10.0

Data are mean ± SD

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

A higher proportion of subjects with liver disease (3 of the 29 subjects) experienced QTc increase ≥30 ms to <60 ms and ≥60 ms at on-therapy; none of the patients had a QTc interval greater than 450 ms (males) or 470 ms (females). QT dispersion was unchanged in each subgroup at on-therapy.

Additionally, a pharmacokinetic repeat-dose study in patients with hepatic impairment (which includes ECG recording) is ongoing.

7.5.6.3 Subjects with renal impairment

Significant renal impairment was defined in the clinical program as creatinine clearance <50 mL/min. As renal excretion represents approximately 30% of the total elimination for telithromycin, an analysis of this subgroup with respect to potential QTc prolongation was done. A total of 49 subjects with creatinine clearance <50 mL/min received telithromycin in the Phase III controlled and uncontrolled studies.

Mean baseline QTc values were higher in telithromycin-treated subjects with renal impairment than those without (see table below). Mean QTc changes were similar between the two groups at on-therapy.

Table 7-41. QTc and QT dispersion data in telithromycin-treated subjects by presence of renal impairment (creatinine clearance <50 mL/min): Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	CrCl <50 mL/min (N=49)	CrCl ≥ 50 mL/min (N=2080)	CrCl <50 mL/min (N=40)[a]	CrCl ≥ 50 mL/min (N=1832)[a]	CrCl <50 mL/min (N=28)[b]	CrCl ≥ 50 mL/min (N=1550)[b]
QTc (ms)	419.6 ± 27.8	406.6 ± 22.6	422.4 ± 24.2	407.4 ± 22.3	409.5 ± 28.0	404.1 ± 22.3
ΔQTc (ms)	–	–	0.8 ± 20.6 [c]	1.0 ± 21.2[c]	–12.3 ± 21.8 [d]	–2.4 ± 22.8 [d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	2/40 (5.0)	132/1832 (7.2)	1/28 (3.6)	97/1550 (6.3)
≥60 ms	–	–	0/40 (0.0)	8/1832 (0.4)	0/28 (0.0)	6/1550 (0.4)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	4/24 (16.7)	27/1002 (2.7)	4/20 (20.0)	17/897 (1.9)	0/14 (0.0)	11/754 (1.5)
≥470 ms (women)	1/25 (4.0)	8/1078 (0.7)	1/21 (4.8)	5/952 (0.5)	1/14 (7.1)	3/796 (0.4)
≥500 ms (men or women)	1/49 (2.0)	3/2080 (0.1)	0/41 (0.0)	2/1849 (0.1)	0/28 (0.0)	1/1550 (0.1)
QT dispersion (ms)	22.2 ± 9.9	21.8 ± 9.9	18.8 ± 8.7	21.1 ± 9.8	19.2 ± 11.2	21.9 ± 10.0

Data are mean ± SD CrCl = creatinine clearance

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

The frequency of on-therapy QTc increase ≥30 ms and <60 ms or ≥60 ms was not increased for telithromycin-treated subjects with and without renal impairment. The frequency of subjects with outlier QTc intervals was higher in the subgroup with renal impairment across both pretreatment and on-treatment periods, suggesting non-drug causes for the discrepancy. None of the patients with moderate-to-severe renal impairment had an on-therapy QTc greater than 500 ms. QT dispersion remained unchanged.

7.5.6.4 Female subjects

A total of 1103 women received telithromycin in the Phase III program. The QTc analysis for this subgroup is compared with that of male telithromycin-treated subjects in the table below.

Table 7-42. QTc and QT dispersion data in telithromycin-treated subjects by sex: Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	Male (N=1026)	Female (N=1103)	Male (N=906)[a]	Female (N=966)[a]	Male (N=768)[b]	Female (N=810)[b]
QTc (ms)	404.1 ± 24.5	409.4 ± 20.9	404.1 ± 24.1	411.1 ± 20.2	400.8 ± 23.8	407.3 ± 20.5
ΔQTc (ms)	–	–	0.4 ± 22.9[c]	1.6 ± 19.3[c]	–3.0 ± 23.8[d]	–2.2 ± 21.8[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	67/906 (7.4)	67/966 (6.9)	54/768 (7.0)	44/810 (5.4)
≥60 ms	–	–	4/906 (0.4)	4/966 (0.4)	3/768 (0.4)	3/810 (0.4)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	31/1026 (3.0)	–	21/917 (2.3)	–	11/768 (1.4)	–
≥470 ms (women)	–	9/1103 (0.8)	–	6/973 (0.6)	–	4/810 (0.5)
≥500 ms (men or women)	3/1026 (0.3)	1/1103 (0.1)	0/917 (0.0)	2/973 (0.2)	0/768 (0.0)	1/810 (0.1)
QT dispersion (ms)	22.0 ± 10.4	21.7 ± 9.3	21.2 ± 10.1	20.9 ± 9.5	21.8 ± 10.4	21.9 ± 9.7

Data are mean ± SD

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

Mean QTc was slightly higher in female than male subjects at pretherapy, on-therapy and posttherapy; on-therapy changes in mean QTc were comparable in women and men. The frequency of on-therapy QTc increase ≥30 ms and <60 ms or ≥60 ms was similar between men and women treated with telithromycin. The frequencies of female and male subjects with outlier values were low at all visits. Again, QT dispersion was unchanged.

7.5.6.5 Subjects with cardiovascular disease

Mean QTc values were higher at pretherapy, on-therapy and posttherapy in telithromycin-treated subjects with cardiovascular disease compared to those without (see table below). The mean change from baseline in QTc was similar between the two groups.

Table 7-43. QTc and QT dispersion data in telithromycin-treated subjects by presence of cardiovascular disease: Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	With CVD (N=410)	Without CVD (N=1719)	With CVD (N=358)[a]	Without CVD (N=1514)[a]	With CVD (N=299)[b]	Without CVD (N=1279)[b]
QTc (ms)	414.1 ± 25.0	405.2 ± 22.0	414.7 ± 26.1	406.1 ± 21.2	411.8 ± 23.4	402.4 ± 21.8
ΔQTc (ms)	–	–	0.9 ± 21.1[c]	1.0 ± 21.2[c]	–1.8 ± 23.4[d]	–2.7 ± 22.7[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	25/358 (7.0)	109/1514 (7.2)	18/299 (6.0)	80/1279 (6.3)
≥60 ms	–	–	1/358 (0.3)	7/1514 (0.5)	2/299 (0.7)	4/1279 (0.3)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	16/215 (7.4)	15/811 (1.8)	15/184 (8.2)	6/733 (0.8)	4/154 (2.6)	7/614 (1.1)
≥470 ms (women)	5/195 (2.6)	4/908 (0.4)	4/176 (2.3)	2/797 (0.3)	3/145 (2.1)	1/665 (0.2)
≥500 ms (men or women)	3/410 (0.7)	1/1719 (0.1)	2/360 (0.6)	0/1530 (0.0)	1/299 (0.3)	0/1279 (0.0)
QT dispersion (ms)	22.2 ± 10.2	21.7 ± 9.8	20.5 ± 9.1	21.2 ± 9.9	22.2 ± 9.8	21.7 ± 10.1

Data are mean ± SD, CVD = cardiovascular disease

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

The proportion of subjects with QTc increase ≥30 ms to <60 ms and ≥60 ms was similar between those with and without cardiovascular disease. In addition, there was essentially no change in the frequency of QTc outliers at on-therapy compared with baseline. QT dispersion was unchanged.

In addition to the above Phase III data, a specific clinical pharmacology study was conducted in high-risk patients with cardiovascular disease, as described below.

Subjects with cardiovascular disease in clinical pharmacology study (Study1049)

To assess the effect of telithromycin on QTc in subjects with underlying cardiovascular disease, a comparative safety study of single dose telithromycin (800 mg and 1600 mg) and clarithromycin (500 mg bid) was performed (Study 1049). The study population included 24 subjects with ischemic heart disease revascularized (8 subjects) or not (5 subjects), arrhythmias (7 subjects), valvular heart disease (5 subjects), hypertension with left ventricular hypertrophy (3 subjects) and congestive heart failure (3 subjects). The classes of concomitant cardiovascular medications were: coronary vasodilators (18 subjects), serum lipid reducing agents (14 subjects), antithrombotics (15 subjects), agents acting on the renin-angiotensin system (10 subjects), beta-blocking agents (10 subjects), diuretics (7 subjects), calcium channel blockers (7 subjects), digoxin (2 subjects), and other antihypertensives (1 subject taking doxazosin). In addition to frequent ECGs, Holter monitoring was also included in this trial.

In this study, an analysis was performed to compare QT at constant RR between baseline and on-drug period in order to avoid bias due to changes in heart rate and the need for correction formulae. The results of this analysis are shown in the table below.

Table 7-44. Mean QT and ΔQT intervals at selected beats on Holter monitoring at individual t_{max} post-dose ± 1h30 or corresponding time (morning) at predose

Treatment	N	S	RR interval (ms)	QT interval predose (ms)	QT interval post dose (ms)	ΔQT (ms) [range]	C_{max} (µg/mL) (CV%)
Placebo	240	23	981 ± 162	418 ±30	420 ± 31	1 ± 7 [-24 + 23]	-
Telithromycin 800 mg	235	20	894 ± 125	404 ± 22	405 ± 24	1 ± 7 [-35 +20]	1.81 (48)
Telithromycin 1600 mg	301	24	891 ± 149	403 ± 31	408 ± 33	5 ±7 [-16 +20]	3.12 (32)
Clarithromycin 500 mg	252	23	933 ± 160	411 ± 28	412 ± 29	1 ± 8 [-19 + 23]	2.50 (48)

N = total number of RR intervals; S = number of subjects analyzed by period

tmax= the time at which maximum concentration was observed

Data are mean ± SD

As with the patient population in Phase III studies where a wide range of concentrations were observed, the mean change in QT was 1 ms at the 800 mg telithromycin dose, and this was not different from that seen for placebo. With a dose increase to 1600 mg, (mean Cmax = 3.12 µg/mL) an increase in ΔQT occurred, as expected.

One event of syncope (possibly related serious TEAE) was reported in a woman receiving telithromycin 1600 mg. The event occurred in the context of gastrointestinal symptoms (nausea and epigastric pain) in this subject with a history of aortic stenosis and fosinopril as a concomitant treatment. The Holter monitor recording at the time of the event demonstrated a decrease in heart rate (suggesting a vasovagal reaction) without evidence of QT prolongation or ventricular arrhythmia.

Following a request of the FDA, we have analyzed the mean of the maximum ΔQT observed across all time periods. These values are displayed in the table below.

Table 7-45. Mean maximum changes from baseline in QTc and QTf in Study 1049

Parameter	Mean ± standard deviation			
	Placebo	TEL 800 mg	TEL 1600 mg	CLA 500 mg bid
Mean max ΔQTc (ms)	11 ± 12	14 ± 10	18 ± 9	14 ± 10
Mean max ΔQTf (ms)	13 ± 8	13 ± 8	15 ± 7	16 ± 5

TEL = telithromycin; CLA = clarithromycin

Similar mean maximum changes in QTc interval were seen 3 to 4 hours post dose with telithromycin 800 mg and clarithromycin 500 mg bid; the mean maximum QTc change was greater in the 1600 mg group. The frequency of subjects with QTc increase of ≥30 and <60 ms was the same for placebo, telithromycin 800 mg and telithromycin 1600 mg (2 subjects in each treatment group) and comparable to clarithromycin (1 subject). No changes from baseline of ≥60 ms were reported in any treatment group. No QTc values above 500 ms were observed. Of note, the effect on QTf was similar for telithromycin 1600 mg and clarithromycin.

7.5.6.6 Subjects with prolonged QTc interval at baseline

Increased QTc at baseline was defined as a QTc value of ≥430 ms for men and ≥450 ms for women. Subjects with a prolonged QTc may be at greater risk of experiencing cardiovascular events when treated with drugs that have the potential to increase QTc.

QTc data for the subgroup with prolonged QTc at baseline are shown below.

Table 7-46. QTc and QT dispersion data in telithromycin-treated subjects by presence of prolonged QTc at baseline: Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	With increased QTc (N=146)	Without increased QTc (N=1983)	With increased QTc (N=127)[a]	Without increased QTc (N=1745)[a]	With increased QTc (N=115)[b]	Without increased QTc (N=1463)[b]
QTc (ms)	450.0 ± 18.2	403.7 ± 19.7	432.2 ± 27.0	405.9 ± 21.0	424.7 ± 25.1	402.5 ± 21.4
ΔQTc (ms)	–	–	–18.0± 24.2[c]	2.4 ± 20.2[c]	–24.5 ± 25.1[d]	–0.8 ± 21.6[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	2/127 (1.6)	132/1745 (7.6)	2/115 (1.7)	96/1463 (6.6)
≥60 ms	–	–	0/127 (0.0)	8/1745 (0.5)	0/115 (0.0)	6/1463 (0.4)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	31/114 (27.2)	0/912 (0.0)	16/99 (16.2)	5/818 (0.6)	9/91 (9.9)	2/677 (0.3)
≥470 ms (women)	9/32 (28.1)	0/1071 (0.0)	6/29 (20.7)	0/944 (0.0)	2/24 (8.3)	2/786 (0.3)
≥500 ms (men or women)	4/146 (2.7)	0/1983 (0.0)	2/128 (1.6)	0/1762 (0.0)	1/115 (0.9)	0/1463 (0.0)
QT dispersion (ms)	19.0 ± 9.9	22.1 ± 9.8	19.8 ± 10.8	21.1 ± 9.7	21.0 ± 10.6	21.9 ± 10.0

Data are mean ± SD

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

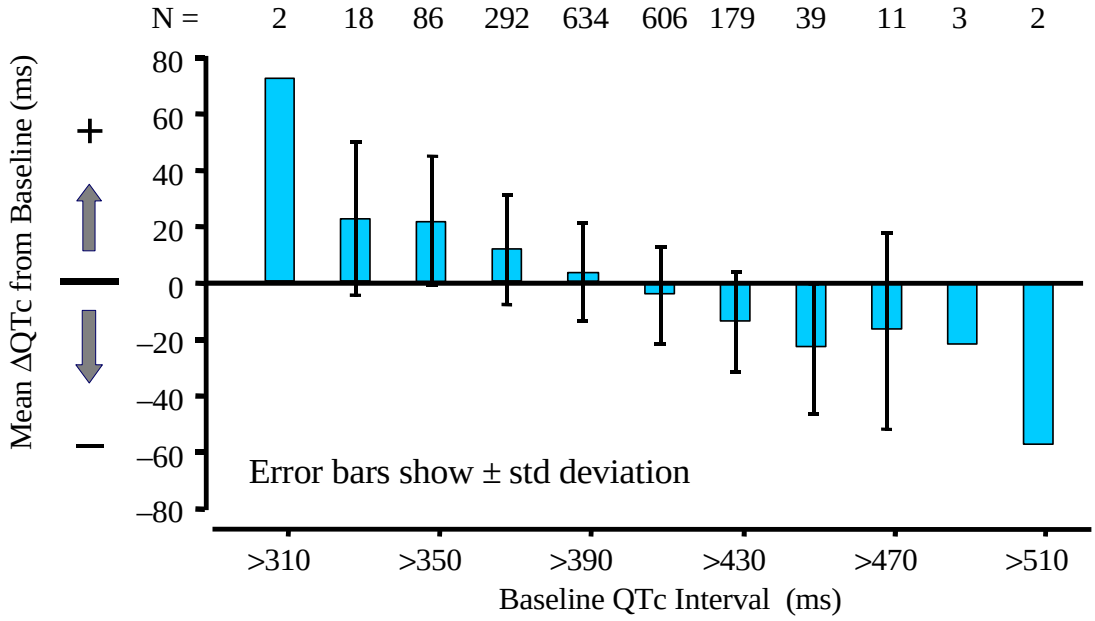
[b] Represents number of subjects from the on-therapy group who also had a posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

In subjects with prolonged QTc at baseline, there was in fact a decrease in QTc on-therapy (see figure below). While the likely explanation is regression to the mean, the prolonged QT intervals at baseline did not lengthen further.

Figure 7-5. Association between baseline QTc and QTc change from baseline in all Phase III studies



The frequency of QTc increase ≥30 ms to <60 ms and ≥60 ms was lower in the subgroup with prolonged QTc at baseline than those without.

7.5.6.7 Subjects taking concomitant cytochrome P450 3A4 (CYP3A4) inhibitors

Telithromycin is principally metabolized in the liver via CYP3A4. Drug interaction studies have been carried out to determine the potential for levels of telithromycin to increase in the setting of concomitant administration of medications that are known inhibitors of CYP3A4. These studies suggest that there is a small increase (1.2- to 1.5-fold) in Cmax in the presence of known inhibitors.

The mean change in QTc for the subgroup of subjects in the Phase III studies receiving concomitant inhibitors of CYP3A4 is within the range of the overall magnitude of effect seen for the entire study population. The frequency of subjects with QTc increase ≥30 ms to <60 ms was also similar for this subgroup, with essentially no differences seen in the frequency of subjects with ≥60 ms increases (see table below). QT dispersion was unchanged.

Table 7-47. QTc and QT dispersion data in telithromycin-treated subjects by intake of concomitant CYP3A4 inhibitors: Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	With inhibitor (N=176)	Without inhibitor (N=1953)	With inhibitor (N=154)[a]	Without inhibitor (N=1718)[a]	With inhibitor (N=130)[b]	Without inhibitor (N=1448)[b]
QTc (ms)	405.9 ± 21.5	407.0 ± 23.0	408.7 ± 21.6	407.6 ± 22.5	405.1 ± 20.5	404.1 ± 22.6
ΔQTc (ms)	–	–	3.2 ± 19.7[c]	0.8 ± 21.3[c]	–0.3 ± 20.5[d]	–2.8 ± 23.0[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	9/154 (5.8)	125/1718 (7.3)	8/130 (6.2)	90/1448 (6.2)
≥60 ms	–	–	1/154 (0.6)	7/1718 (0.4)	0/130 (0.0)	6/1448 (0.4)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	3/50 (6.0)	28/976 (2.9)	4/42 (9.5)	17/875 (1.9)	1/35 (2.9)	10/733 (1.4)
≥470 ms (women)	0/126 (0.0)	9/977 (0.9)	1/116 (0.9)	5/857 (0.6)	0/95 (0.0)	4/715 (0.6)
≥500 ms (men or women)	0/176 (0.0)	4/1953 (0.2)	0/158 (0.0)	2/1732 (0.1)	0/130 (0.0)	1/1448 (0.1)
QT dispersion (ms)	23.1 ± 10.5	21.7 ± 9.8	21.2 ± 9.5	21.0 ± 9.8	22.3 ± 8.7	21.8 ± 10.1

Data are mean ± SD

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

The Phase III data presents patients on a variety of CYP3A4 inhibitors with varying potency. In addition to this data, a clinical pharmacology study looking at one of the most potent CYP3A4 inhibitors, ketoconazole, was performed and is presented below.

CYP3A4 inhibitors: ketoconazole

The potential for increased plasma levels of telithromycin and QTc prolongation when telithromycin was co-administered with the potent CYP3A4 inhibitor ketoconazole was evaluated.

When telithromycin was given with ketoconazole, a potent CYP3A4 inhibitor (and the most potent inhibitor among the azole compounds), a 1.5-fold increase in telithromycin Cmax was observed; AUC was increased 2-fold. For QTc, the maximum mean increases were 12 ms for telithromycin alone, 19 ms for ketoconazole alone, and 16 ms for concomitant treatment of ketoconazole and telithromycin, versus 9 ms for placebo. However, there was a significant increase in heart rate (8-11 bpm) in the young subjects receiving telithromycin or telithromycin with ketoconazole. Thus, when the Fridericia correction was applied, the maximum mean increases in QTf were 2 ms for placebo, 2 ms for telithromycin, 10 ms for ketoconazole, and 8 ms for ketoconazole with telithromycin.

7.5.6.8 Subjects taking concomitant drugs metabolized by CYP3A4

As telithromycin is metabolized by CYP3A4, plasma concentrations of telithromycin can theoretically be increased when coadministered with drugs metabolized by the same pathway, but with a higher affinity for the enzyme. Similarly, telithromycin may increase plasma concentrations of drugs metabolized by CYP3A4 that have a lower affinity for the enzyme.

Mean and mean change in QTc was similar in telithromycin subjects with and without concomitant drugs metabolized by CYP3A4 (see table below).

Table 7-48. QTc and QT dispersion data in telithromycin-treated subjects by intake of concomitant drugs metabolized by CYP3A4: Phase III studies (controlled and uncontrolled)

ECG variable	Pretherapy		On-therapy		Posttherapy	
	With drugs (N=710)	Without drugs (N=1419)	With drugs (N=630)[a]	Without drugs (N=1242)[a]	With drugs (N=536)[b]	Without drugs (N=1042)[b]
QTc (ms)	407.8 ± 23.3	406.4 ± 22.6	409.2 ± 23.5	407.0 ± 21.8	404.3 ± 23.7	404.1 ± 21.7
ΔQTc (ms)	–	–	1.5 ± 21.6[c]	0.8 ± 20.9[c]	–3.0 ± 23.7[d]	–2.4 ± 22.2[d]
QTc increase (n/N (%) subjects)						
≥30 and <60 ms	–	–	53/630 (8.4)	81/1242 (6.5)	33/536 (6.2)	65/1042 (6.2)
≥60 ms	–	–	1/630 (0.2)	7/1242 (0.6)	2/536 (0.4)	4/1042 (0.4)
QTc outlier (n/N (%) subjects)						
≥450 ms (men)	15/314 (4.8)	16/712 (2.2)	11/283 (3.9)	10/634 (1.6)	3/242 (1.2)	8/526 (1.5)
≥470 ms (women)	4/396 (1.0)	5/707 (0.7)	3/354 (0.8)	3/619 (0.5)	2/294 (0.7)	2/516 (0.4)
≥500 ms (men or women)	2/710 (0.3)	2/1419 (0.1)	1/637 (0.2)	1/1253 (0.1)	0/536 (0.0)	1/1042 (0.1)
QT dispersion (ms)	22.0 ± 9.1	21.8 ± 10.2	20.9 ± 9.5	21.1 ± 9.9	22.9 ± 9.6	21.3 ± 10.2

Data are mean ± SD

[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 posttherapy ECG

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

[d] ΔQTc represents QTc interval posttherapy minus QTc interval pretherapy

QTc increase ≥30 ms to <60 ms and ≥60 ms was observed at a similar frequency in the subgroup receiving concomitant drugs metabolized by CYP3A4 subjects compared to those without concomitant drugs metabolized by CYP3A4. In addition, the proportion of subjects considered as QTc outliers was generally similar between the two groups at pretherapy, on-therapy and posttherapy. QT dispersion was unchanged.

In addition to the above analysis in patients from the Phase III studies, a clinical pharmacology study was performed with cisapride (Study 1041). In this study, telithromycin increased the plasma levels of cisapride by 2-fold and AUC by 3-fold. This led to an increase in ΔQTc from 6.3 ms for cisapride alone to 29.3 ms for the combination[2]. The same findings have also been published for clarithromycin [76]. As with clarithromycin, concomitant use of telithromycin with cisapride or pimozide is contraindicated.

Other drug interactions: Sotalol

This study was performed to assess the possible effect of a single oral dose of telithromycin on sotalol-induced prolongation of ventricular repolarization. In a two-way crossover, randomized, double-blind (for telithromycin) design, 25 females aged 19 to 36 years received sotalol with placebo

[2] Values obtained after subtracting out the placebo effect. Respective values for the multiple dose arms were 9.1 ms for cisapride and 38.0 ms for the combination.

in one period and with telithromycin in the other period. Twelve-lead ECGs were performed at the time of PK sampling, and 24-hour Holter monitoring was performed on the first day of each period.

The results revealed a moderate decrease (20%) of sotalol bioavailablility in the presence of telithromycin: AUC and C_{max} decreased 20% and 34%, respectively. This interaction is due to a decrease of sotalol absorption in the presence of telithromycin. Due to this decrease, the mean QTc (as well as the mean maximum QTc) was lower in the presence of telithromycin. The relationship between sotalol plasma concentration and QTc was not overtly modified by telithromycin.

7.5.7 Studies comparing changes in QT at predefined heart rates with telithromycin

QT intervals vary with heart rate. Correction formulae used to standardize to a heart rate of 60 bpm have limitations, particularly with bradycardias or tachycardias [34]. Accordingly, two studies were performed in a manner that controls, rather than corrects for, heart rate.

In this model, the QT intervals were measured at a time approximating the expected C_{max} (i.e. 2 hours post drug), at rest and then at different heart rates induced by exercise. For each subject, a curve of QT interval *vs* RR intervals was set up and QT intervals at 1000, 900, 800, 700, 600, 500 and 400 ms were extrapolated from the formulae used to describe the QT *vs* RR relationship ($QT = a-b \times \exp^{(-c \times RR)}$). The QT measured at 1000 ms (60 bpm) was thus used as an unbiased measurement of the QT interval.

This approach allowed:

- Comparison between treatments and subjects at identical heart rates.
- Comparison with several compounds that have been tested in the same unit (Pr Funck-Brentano, Paris, France), i.e. under the same conditions. In addition, data in patients are already available for several compounds tested in this model, confirming the findings obtained and attesting to the sensitivity of the model.

7.5.7.1 Telithromycin at therapeutic dose and comparison with clarithromycin

A three-way crossover study was conducted with clarithromycin (500 mg single dose and 500 mg bid repeated dose), telithromycin at therapeutic dose (800 mg single and repeated dose) and placebo in young healthy subjects (N=16). The comparison of QT at fixed heart rate showed that neither telithromycin nor clarithromycin had a significant effect on QT interval at therapeutic dose compared to placebo.

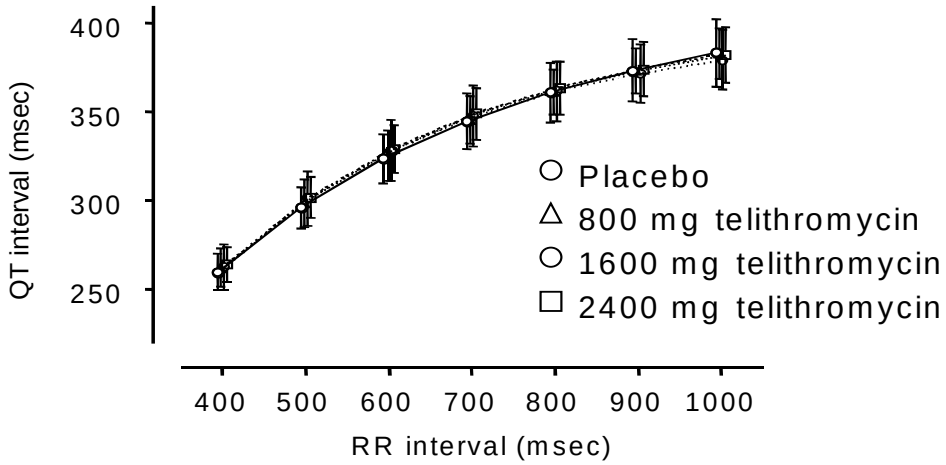
In this study, the concentrations of telithromycin at the time of exercise following single dose (mean 0.637 µg/mL; range 0.617 to 1.375) and repeated dose (mean 0.84 µg/mL; range 0.806 to 1.725) were lower than the Cmax obtained in healthy volunteers after single dose (mean 1.90 µg/mL; range 0.964 to 3.256) and repeated dose (mean 2.27 µg/mL; range 1.395 to 3.770). This was due to variation in tmax among healthy volunteers, whereas the timing of exercise was fixed. Therefore, additional studies at a higher dose were conducted.

7.5.7.2 Effect at supratherapeutic doses up to 2400 mg

This same methodology of fixed heart rate conditions was also applied in a further study that was designed to evaluate the effect of supratherapeutic doses using a four-way crossover design in young healthy subjects with single doses of telithromycin at 800, 1600 and 2400 mg and placebo.

Telithromycin did not increase the QT interval at any heart rate at rest and during exercise when administered as single doses of 800 mg, 1600 mg or 2400 mg; the effect was similar to placebo for all doses studied as shown by the figure below:

Figure 7-6. The effect of supratherapeutic doses of telithromycin on QT interval at different heart rates induced by exercise tolerance test



Plasma concentrations obtained at two hours in this study were also lower than expected, but still covered the range of mean therapeutic C_{max} concentration obtained in healthy volunteers (see table below).

Table 7-49. Telithromycin plasma concentrations in healthy volunteers from Phase I studies who received therapeutic and supra-therapeutic doses of telithromycin

Plasma concentration (µg/mL)	1600 mg single dose (N=16)	2400 mg single dose (N=16)	800 mg repeated dose (Once daily for 7 days) (N=18)
Mean concentration	1.56	1.95	2.27
Minimum concentration	0.617	0.806	1.395
Maximum concentration	2.590	3.395	3.770

Some subjects in this study had concentration >2 µg/mL at the time of exercise. The plasma concentrations were between 2.03 and 3.395 µg/mL for 6 subjects at the dose of 2400 mg, and between 2.256 and 2.590 µg/mL for 4 subjects at the dose of 1600 mg. The QT intervals for these subjects at a RR interval of 1000 ms (QT1000) (i.e. 60 bpm) were similar to placebo. Thus at

concentrations >2 µg/mL, the effect was not different from placebo and was within the range of values obtained at lower concentrations.

7.5.7.3 Comparison to other antibiotics

The methodology described above was published by the same unit for various other compounds, such as class III antiarrhythmics and antibiotics such as quinolones. A comparison of the effect on QT interval at a heart rate of 60 bpm between different antibiotics using the same methodology in this same clinical unit (i.e. historical active comparators) are displayed in the figures below [25,26,27]. Dofetilide, a potassium channel blocker, is included as a positive control. Figure A shows the telithromycin *vs* clarithromycin data from Study 1032. Figure B shows a comparison with two quinolone antibiotics and dofetilide.

Figure 7-7. Comparison of QT effects between different drugs at a given heart rate (60 bpm)

Figure A

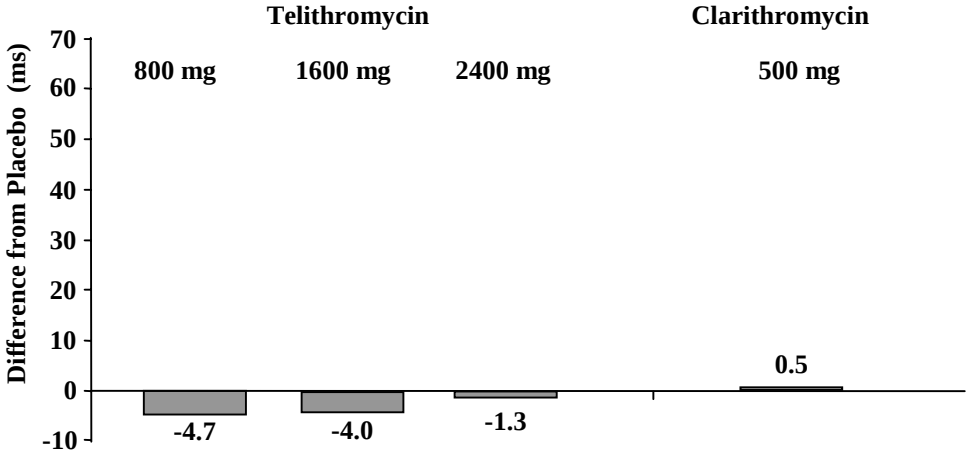
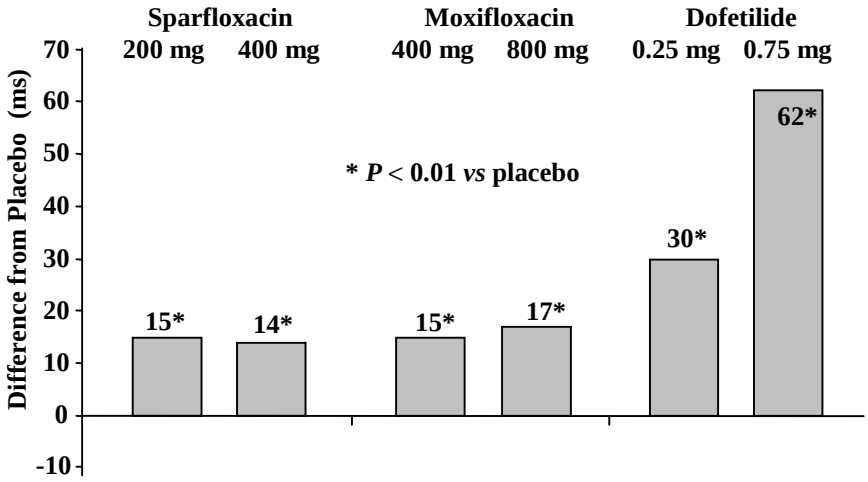


Figure B



Data from Prof C. Funck-Brentano (France) [34]

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7.5.8 Conclusions

The full analysis of the extensive QT interval data obtained in the telithromycin clinical development program revealed the following:

- In patients with RTIs treated with telithromycin, the mean change in QTc observed was small (~1 ms).
- A shallow relationship of concentration to corrected QT interval was established across a wide range of observed plasma concentrations in both patient and healthy volunteer populations.
- There was no difference in the frequency of QTc outliers between telithromycin and macrolide and non-macrolide antibiotics.
- An extensive analysis of at-risk subpopulations did not reveal a propensity for enhanced effect on cardiac repolarization in such patients.
- No increase in the incidence of cardiovascular adverse events was noted when compared to macrolide and non-macrolide active comparators.

In conclusion, this integrated analysis does not reveal a significant effect of telithromycin on cardiac repolarization for either the population as a whole or for individual predefined risk groups.

8. BENEFIT/RISK ANALYSIS

Respiratory tract infections (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 typical bacterial pathogens such as *S. pneumoniae, H. influenzae, M. catarrhalis,* and *S. pyogenes* as well as atypical and intracellular pathogens such as, *M. pneumoniae, C. pneumoniae,* and *L. pneumophila*. The choice of antimicrobial regimens for these indications is complex because of the varied classes of pathogens and the emergence of resistance to many of the older agents. Beta lactams, a cornerstone of outpatient RTI therapy, are inactive against beta-lactamase producing strains of *H. influenzae* and *M. catarrhalis*; they have no activity against atypicals and are increasingly threatened by the emergence of penicillin resistance among *S. pneumoniae*. Quinolones have variable activity against *S. pneumoniae* and their widespread use for common infections poses very real concerns about the long-term utility of these drugs due to emergent resistance. The recently recognized increase in the prevalence of macrolide resistance now threatens the utility of this class [36,83]. In 1999, 20.3% of *S. pneumoniae* strains tested were resistant to erythromycin in the US according to the Active Bacterial Core Surveillance (ABCs) Report, Emerging Infections Program Network [14] (www.cdc.gov/ncidod/dbmd/abcs). While there has been some debate about the clinical importance of this rise in in vitro resistance [4,6,61], there are an increasing number of reports of adverse clinical outcomes in patients with erythromycin A-resistant *S. pneumoniae* who were treated with macrolides [13,35,45,48,52,79]. Because most of these macrolide-resistant *S. pneumoniae* are resistant to beta-lactams, trimethoprim-sulfa, and tetracyclines, there remain few options for oral therapy in patients infected with these strains.

Telithromycin is the first in a new class of antimicrobial agents, the ketolides. It binds to domain II of the 23s rRNA of the 50S ribosomal subunit and interferes with assembly of the 30s ribosomal subunit. Telithromycin also exhibits additional ribosomal activity associated with macrolides: binding to domain V of the 23s rRNA and disruption of assembly of the 50s ribosomal subunit. This novel mechanism of action results in outstanding activity against sensitive strains of *S. pneumoniae*, far more potent than that of macrolides, as well as potent activity against macrolide-resistant strains. *S. pneumoniae* is the pathogen most associated with risk of morbidity and mortality in community-acquired RTIs. Reliable activity against this pathogen is the most important feature of an antibiotic for treatment of these infections. In addition to its outstanding activity against *S. pneumoniae*, telithromycin is active against the full spectrum of respiratory pathogens, both common and atypical, including *L. pneumophila*, which is associated with mortality in pneumonia. Its activity against penicillin- and erythromycin-resistant pathogens is crucial in this age of increasing resistance. As would be expected from its mechanism of action, there is no cross resistance to beta lactams or quinolones.

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. This assures efficacy in infected tissues as well as in undetected bacteremia in outpatients. The brief, simple regimen will promote patient compliance, an important factor in reducing further pressure for development of resistance due to missed doses at the end of prolonged therapy [39].

The clinical efficacy of telithromycin was studied in 3,125 patients with the following community-acquired RTIs: community acquired pneumonia (CAP, 1,373 patients), acute bacterial sinusitis (980 patients), acute exacerbation of chronic bronchitis (AECB, 342 patients), and tonsillitis/pharyngitis due to *S. pyogenes* (430 patients). Excellent efficacy was demonstrated in all patient populations and against all key pathogens in each of the clinical trials in the four proposed indications. Telithromycin

was effective in treating CAP subjects with pneumococcal bacteremia, with *Legionella pneumophila*, in the elderly in both CAP and AECB, in AECB subjects with severe bronchial obstruction, and in subjects at greater risk for morbid sequelae. Telithromycin demonstrated efficacy in AECB, acute sinusitis, and tonsillitis/pharyngitis with a treatment regimen of 5 days.

Telithromycin is effective in vitro against macrolide-, beta-lactam-, and quinolone-resistant *S. pneumoniae.* Clinical efficacy in infections due to *S. pneumoniae* resistant to penicillin G or erythromycin was demonstrated with overall cure rates of 91.7% (11/12 subjects) in CAP subjects with single pathogen infections of penicillin G-resistant strains and 88.2% (15/17 subjects) for erythromycin A-resistant strains. Similarly, efficacy against penicillin G- and erythromycin A-resistant *S. pneumoniae* was also demonstrated in patients with acute sinusitis.

The safety of telithromycin was assessed in 3,265 patients with RTIs. This population included a broad spectrum of patients with underlying diseases, who received a wide variety of concomitant medications, as well as elderly patients with additional risk factors for morbidity and mortality. Telithromycin exhibited an excellent safety profile, comparable to that of other marketed outpatient antibiotics and, in particular, to that of the macrolides. The incidence of gastrointestinal adverse events, while slightly higher than that of the new macrolides, falls within the range of marketed antibiotics. There is no evidence of excess risk of hepatic adverse events. Treatment with telithromycin, which has a weak inhibitory effect on the cardiac Ikr channel, was associated with a small (approximately 1 ms) change in the electrocardiographic QT interval (corrected for heart rate). No excess in adverse cardiovascular events was observed with telithromycin administration.

Telithromycin is metabolized in part by cytochrome P450 (CYP3A4). Concomitant administration with a potent inhibitor of CYP3A4 (ketoconazole) was associated with a modest elevation in plasma concentrations in a clinical pharmacology study. No excess of adverse events was observed in telithromycin treated patients who received concomitant therapy with CYP3A4 inhibitors.

Thus, telithromycin is highly effective in the treatment of outpatient RTIs. It has excellent activity against *S. pneumoniae*, including macrolide- and penicillin G-resistant strains, and all the other major common, intracellular and atypical pathogens. Telithromycin provides an alternative to quinolones for physicians who are increasingly concerned about beta-lactam- and macrolide-resistant *S. pneumoniae* and atypical and intracellular pathogens in community respiratory infections. Telithromycin can be given in a convenient regimen and is safe in patients intolerant to beta lactams or quinolones. Few oral antibiotics fulfill all of these requirements. Telithromycin will therefore be an important addition to the outpatient antimicrobial therapeutic armamentarium.

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Inhibition of Translation and 50S Ribosomal Subunit Formation in *Staphylococcus aureus* Cells by 11 Different Ketolide Antibiotics

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Abstract. Eleven structurally similar ketolide antibiotics were tested at a concentration of 1 μg/ml for their relative inhibitory effects on growth and ribosome activities in *Staphylococcus aureus* cells. Ten of the compounds examined had an inhibitory effect on protein synthesis at this concentration and eight of the 11 compounds were also effective inhibitors of the formation of the 50S ribosomal subunit. All of the drugs tested inhibited protein synthesis to a greater extent than they affected 50S subunit formation The decline in growth rate and cell number was proportional to the effect on ribosome formation and function The growth of an *ermC* erythromycin-resistant strain of *S aureus* was also significantly inhibited by nine ketolide compounds, suggesting that they were not inducers of methylase gene expression These inhibitory activities can be related to structural differences between these ketolide antibiotics

The current resurgence of numerous antibiotic-resistant bacterial strains has stimulated the search for new targets and for more effective antimicrobial agents Macrolide antibiotics like erythromycin, which are specific inhibitors of the function of the large 50S ribosomal subunit [23], have been used for the treatment of infectious diseases for a number of years [32] Many Gram-positive infections respond well to the inhibitory effects of these antibiotics New semisynthetic derivatives of erythromycin like azithromycin, clarithromycin, and roxithromycin are now used for the treatment of additional infectious diseases [15, 17] These compounds are generally more effective and persistent as antimicrobial agents compared with erythromycin [34]. A second generation of synthetic macrolides, the ketolide antibiotic compounds, have recently been described [1, 2] These are molecules with the cladinose sugar at the 3 position of the macrolactone ring substituted by a ketone function They are also 6-methoxy-substituted like clarithromycin In addition many are 11,12-carbamate derivatives with additional aliphatic or aromatic substitutions on the carbamate ring [26, 27]

The ketolides, like the macrolides, are very effective inhibitors of the translation functions of the 50S ribosomal subunit [2] We have recently shown that the macrolide antibiotics erythromycin, clarithromycin, and azithromycin will also inhibit a second cellular function, the formation of the 50S ribosomal subunit [8, 9, 10, 11] Nine different macrolide antibiotics have recently been shown to have varying degrees of inhibition of this novel target with activities related to structural differences between the compounds [12] The availability of a number of ketolide compounds prompted us to investigate their relative inhibitory activities on translation and on the formation of the 50S subunit Each compound was tested at the same concentration for inhibitory effects on growth rate, cell viability, protein synthesis, and 50S subunit formation A range of inhibitory activities was found, with the most effective compounds having large aromatic ring substitutions on the carbamate ring Differences in the inhibition of protein synthesis and 50S subunit biosynthesis were found between the different drugs tested. Predictions relating the structure and the relative inhibitory activity can be made from this investigation

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Materials and Methods

Measurements of cell growth, subunit assembly, and translation rates. Studies were conducted on *S aureus* strain RN 1786, provided by J Sutcliffe of Pfizer Nine of the ketolides used were gifts from Abbott Labs; two others (HMR3004 and HMR3647) were gifts from Hoechst Marion Roussel Stock solutions were made at 1 mg/ml in methanol

Cells were grown at 37°C in tryptic soy broth (TSB) in the presence and absence of each macrolide at 1 μg/ml as described previously [11, 12] Growth rates were measured by following the increase in cell density in a Klett-Summerson colorimeter To examine ribosomal subunit assembly, cells were labeled with ^{3}H-uridine (1 μCi/ml; 2 μg/ml) and allowed to grow for two doublings in the presence of each drug Isotope incorporation was halted by adding uridine to a final concentration of 50 μg/ml followed by a 30-min chase period The rate of protein synthesis was determined in each culture during the chase period by adding ^{35}S-methionine and cysteine (TRAN^{35}S-LABEL, ICN Pharmaceuticals) to 1 μCi/ml Three samples of 0 2 ml were collected at 5-min intervals, precipitated with 10% TCA and ^{35}S-methionine and cysteine in proteins were measured by liquid scintillation counting At the end of the chase period, viable cell counts were measured by serial dilution of cells in A salts [22], followed by plating 10 μl on square TSB agar plates, after the method of Jett et al [16] Colonies were counted after 48 h at 37°C

Cell lysis and sucrose gradient sedimentation of ribosomal subunits were performed as described previously [10, 11, 12] except that an SW40 rotor was used to increase subunit separation and the centrifugation was at 200,000 *g* for 4 h The absorbance at 254 nm for each gradient was detected with an ISCO Model UA-5 absorbance monitor and captured for computer storage by Dynamax software (Rainin) Gradient fractions were mixed with 3 ml of ScintiSafe Gel and the incorporation of ^{3}H-uridine into RNA was measured by liquid scintillation counting

MIC determination. The minimal inhibitory concentration of each ketolide used was determined by a dilution method [24] Tubes containing 1 ml of TSB received antibiotics over a concentration range of 0 1–10 μg/ml and 50 μl of an overnight culture of *S. aureus* cells. The tubes were incubated at 37°C for 24 h and the absorbance at 600 nm was recorded

Induction assay. The induction assay was modified from the procedure of Bonnefoy at al [7] Four milliliters of 0 8% TSB soft agar was inoculated with 50 μl of an overnight culture of strain RN 4220 (pE194 *ermC*) and poured onto a square TSB plate Filter paper disks received 10 μl (10 μg) of each compound to be tested Zones of inhibition were measured after 12 h at 37°C

Results

The structures of the 11 ketolides used are shown in Fig 1 Compared with the macrolide clarithromycin, each has the 3-cladinose sugar substituted with a ketone group and each is a 6-methoxy compound Ten of these compounds are 11,12-carbamates with a different N-substituted group. A55 is an 11,12-carbonate ketolide [5] Each compound has been assigned a simplified name for purposes of comparison; the Abbott or HMR number is indicated in parentheses

The MIC was measured for each ketolide in order to establish an effective concentration The 11 compounds tested fell into three catagories A22, A51, and A53 had an MIC of 5 μg/ml The MIC for A11, A23, and A52 was 1 μg/ml The five remaining compounds (A24, A54, A55, HMR3004, and HMR3647) had a MIC of 0 1 μg/ml Based on these results, *S aureus* cells were grown in the presence of each compound at a concentration of 1 μg/ml to compare their relative inhibitory effects on the growth rate and cell viability Protein synthesis rates and the formation of the ribosomal subunits were also examined in inhibited cells.

A constant rate of incorporation of labeled amino acids into proteins was found for each drug tested Figures 2A and B show the relative rates for control and ketolide-treated cells. At 1 μg/ml, the two HMR compounds were the most effective inhibitors of translation. A22 was not inhibitory at this same concentration

A specific inhibitory effect on 50S ribosomal subunit assembly has been described for *S. aureus* cells growing in the presence of macrolide antibiotics [8]. Eight of the 11 ketolide compounds tested showed this same inhibitory activity (Table 1). Fig. 3 shows representative sucrose gradient profiles for six of the antibiotics examined. A reduction in the amount of 50S ribosomes formed in the presence of the ketolides is apparent. Five of the compounds tested at this concentration (A24, A54, A55, HMR3647, and HMR3004) also reduced the net formation of 30S ribosomal subunits (Table 1)

The inhibitory effects of these compounds on the four parameters measured are listed in Table 1 in rank order of effectiveness and are compared to control cells not treated with a ketolide. The 11 compounds examined can be grouped into three catagories; those having a minor inhibitory effect, those having a moderate effect, and those severely affecting the cells. The compounds A22, A51, and A53 had only a slight effect on the cells The doubling times and viable cell numbers were only slightly different from untreated cells The rates of protein synthesis were reduced by a maximum of 25% relative to the control culture (Fig. 2A) and ribosomal subunit formation was not affected by any of these three drugs (Figs 3A and B)

Moderate inhibitory effects were exhibited by three other compounds, A11, A23, and A52 The growth rates were reduced by two- to fourfold and viable cell numbers were reduced by 25–50% of untreated cells (Table 1) This inhibitory effect was seen in a 50 to 80% reduction in the protein synthesis rate (Fig. 2A) The formation of the 50S ribosomal subunit was similiarily affected by these ketolides, being reduced by up to 66% of the control amount (Fig 3C).

The most effective inhibitors of each cellular activity measured were the five compounds A24, A54, A55, HMR3647, and HMR3004 (Table 1) Each of these reduced the growth rate by 8–10-fold and the viable cell number was less than 50% of the control value (Table 1) Protein synthesis was very severely affected, with rates of only 5–10% of the control (Fig 2B) Major effects on 50S subunit formation were also found (Figs 3D–F) Less than 50% of the normal formation of the large subunit

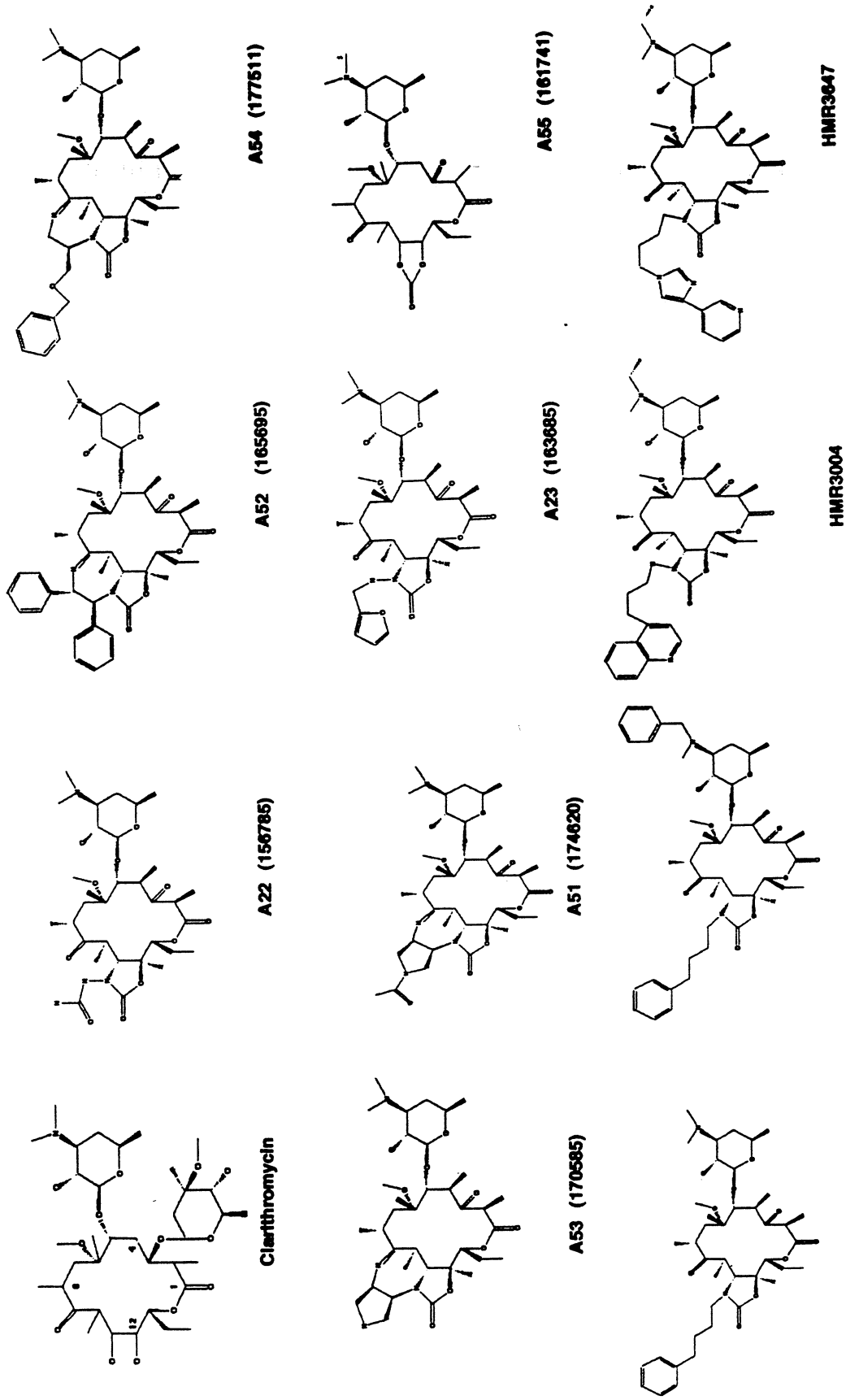

Fig. 1. Structures of the 11 ketolide antibiotics used in this study and the macrolide compound clarithromycin. Positions in the macrolactone ring of clarithromycin are numbered. The Abbott or HMR drug number is indicated in parentheses.

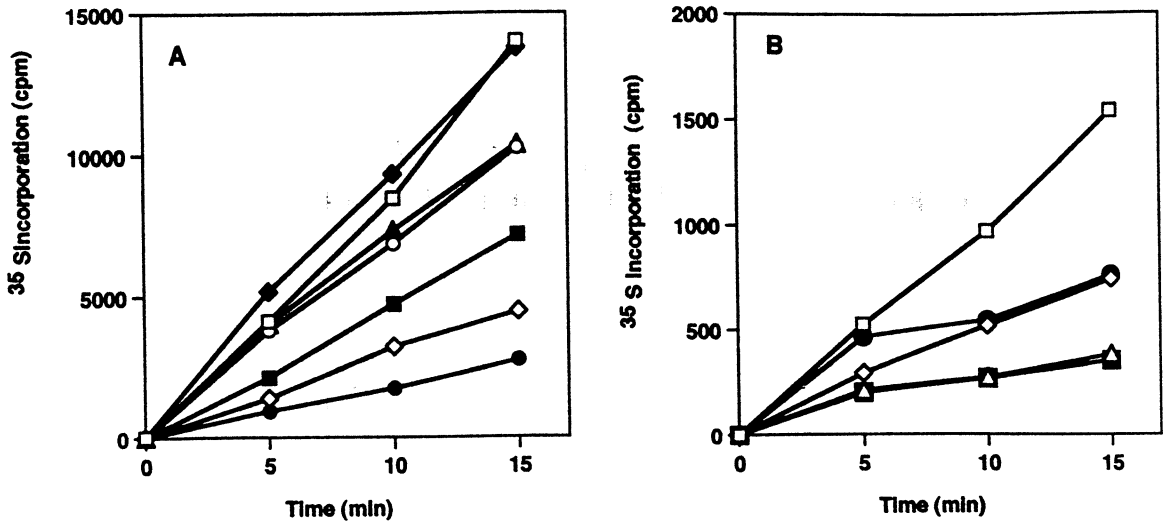

Fig 2 Relative protein synthesis rates in the presence or absence of ketolide antibiotics ^{35}S-amino acid incorporation in growing *S aureus* cells with antibiotics present at 1 μg/ml (A) (□) no antibiotic, (◆) A22, (○) A53, (▲) A51, (■) A11, (◇) A23, and (●) A52 (B) ^{35}S-amino acid incorporation in the presence of (□) A24, (◇) A54, (●) A55, (△) HMR3674, and (■) HMR3004 Average of three experiments with an average SEM of ± 11 6%

Table 1 Ketolide antibiotic inhibition of growth rate, cell viability, protein synthesis, and 50S ribosomal subunit assembly in *S aureus* cells

Antibiotic	Doubling time (min)	Cell no (×10^8/ml)	Protein synthesis (^{35}S cpm/15 min)	% Total cpm 30S	% Total cpm 50S
No drug	48	2 6	14,003 (100)	17	35 (100)
A22	46	2 0	13,785 (98)	19	38 (100)
A53	57	2 5	10,270 (73)	20	40 (100)
A51	54	2 7	10,380 (74)	20	36 (100)
A11	104	1 7	7,170 (51)	20	28 (80)
A23	198	1 7	4,462 (32)	17	23 (66)
A52	160	1 2	2,732 (20)	19	25 (71)
A24	324	1 0	1,547 (11)	11	16 (46)
A54	340	1 1	746 (5)	7	11 (31)
A55	256	0 75	765 (5)	8	11 (31)
HMR3647	440	0 1	386 (3)	8	8 (23)
HMR3004	440	0 1	355 (3)	5	4 (11)

Results for doubling times, cell numbers, and protein synthesis rates are the averages of three experiments with the SEM of ±11% The percent of the total radioactivity in the 50S and 30S subunit region of each sucrose gradient are indicated Ribosomal subunit synthesis results are the average of at least two experiments The percentage of the control protein synthesis rate and the 50S subunit area is given in parentheses

was found in cells growing with these compounds present.

A good correlation was found between the relative inhibitory effect of each compound on protein synthesis or 50S subunit formation and the inhibition of cell viability Figure 4A shows this relationship for the effect on protein synthesis (r = 0 89) and Fig 4B shows the effect on 50S subunit formation (r = 0 94) No inhibition of 30S subunit formation was found until the ketolides used caused the doubling time to increase sixfold and the viable cell number to be reduced by 60% or more (Table 1)

It has been reported that some ketolide antibiotics are not inducers of 23S rRNA methylase synthesis in *S aureus* cells [7]. This observation was tested with the compounds examined in this study. Fig. 5 shows that each ketolide tested exhibited some degree of inhibition of the growth of an *ermC*-inducible strain of *S aureus*, unlike clarithromycin, which induced complete resistance The zone of inhibition of growth found by this assay was proportional to the effect of each compound on cell viability.

Discussion

The ketolide compounds examined in this work represent a new generation of semisynthetic macrolide antibiotics [1, 2] The HMR compounds in particular, have been shown to be effective against an number of clinical isolates of different Gram-positive organisms, both aerobes and anerobes [3, 4, 13, 14, 18, 20, 25, 30, 33] Significantly, these do not induce the synthesis of *ermC* gene expression in MLS strains and are effective inhibitors of the growth of these resistant organisms [7, 28]

The killing effects of the ketolides studied can be related to both their effects on protein synthesis and to the inhibition of 50S ribosomal subunit formation in these cells We have demonstrated that both of these processes are equivalent targets for the macrolide compounds erythromycin, clarithromycin, and azithromycin [9, 11] Inhibition of 30S ribosomal subunit formation was not affected by three ketolides which did reduce the assembly of the large subunit (A11, A23, and A52, Fig 4B, Table

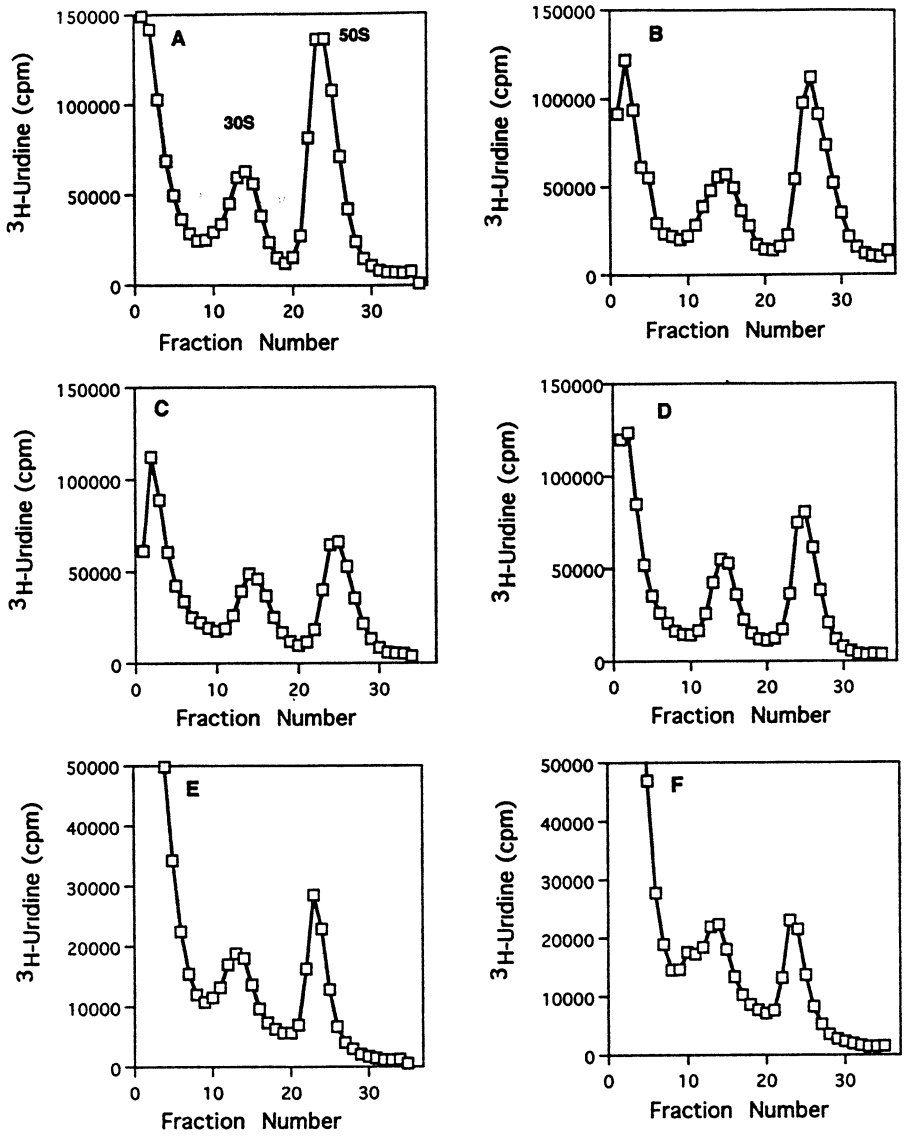

Fig 3 Sucrose gradient profiles of lysates of *S aureus* cells labeled with ^{3}H-uridine Sedimentation from left to right Ribosomal subunits from cells grown in the presence of: A, A22; B, A51; C, A11; D, A52, E, A55; and F, HMR3004

1) The five best inhibitors reduced the rate of overall protein synthesis to such an extent (< 10% of the control) that synthesis of 30S subunit proteins was also impaired

The results of this present study reveal that the relative inhibitory activity of these compounds can be related to features of the drug structure The three compounds with no significant inhibitory activity (A22, A51, and A53) are N-substituted 11,12-carbamate molecules A51 and A53 are tetracyclic N-pyrrolidine-carbamate derivatives, A22 is an N-uryl derivative These structural modifications reduce the relative inhibitory effectiveness of these compounds compared with erythromycin or clarithromycin at the same concentrations [12, 27]

Compounds A11 and A23 are N-substituted benzyl and furanyl structures, A52 is a tricyclic dibenzyl substituted carbamate [26]. The aromatic side chains of these molecules enhance their inhibitory effectiveness, making them comparable to erythromycin and roxithromycin in relative inhibitory activity [12] Significantly, each of these three compounds had a much greater inhibitory effect on translation compared with the inhibition of 50S assembly

Maximum inhibitory effectiveness was exhibited by the benzyl-substituted tricyclic compound A54 and by the three N-substituted 11,12-carbamates A24, HMR3647, and HMR3004 [1, 26, 27]. The large aromatic side chains of these four drugs imparted significant inhibitory activity to these compounds and made them equal to or greater than the inhibition observed with clarithromycin at the same concentration [12] The aromatic rings of these drugs could allow tighter ribosomal subunit binding by

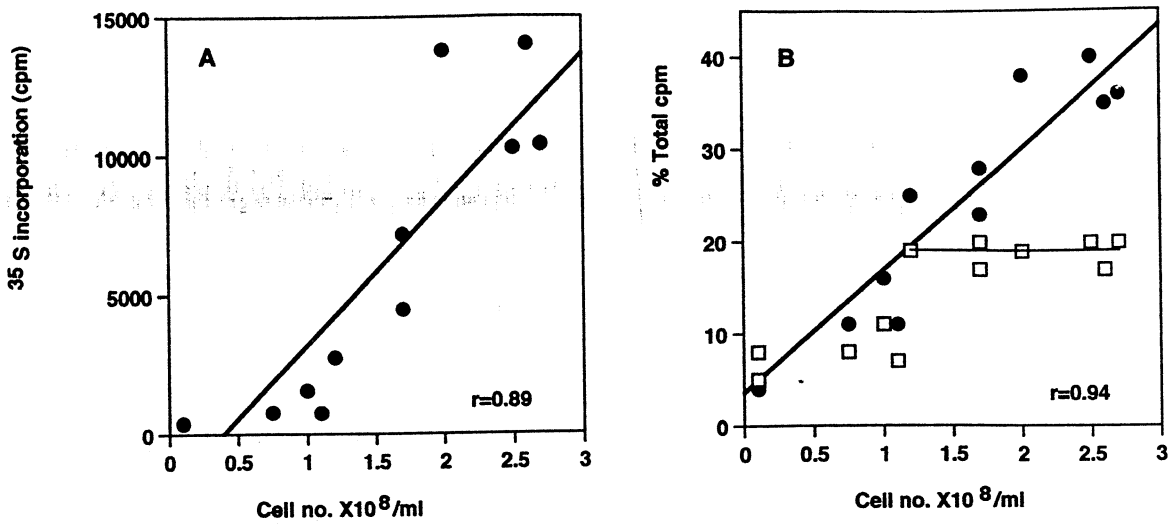

Fig 4 Correlation of decline in cell numbers with decline in (A), protein synthesis rates (●) and (B), 50S (●) and 30S (□) subunit formation for each ketolide antibiotic The least squares best fit lines are shown

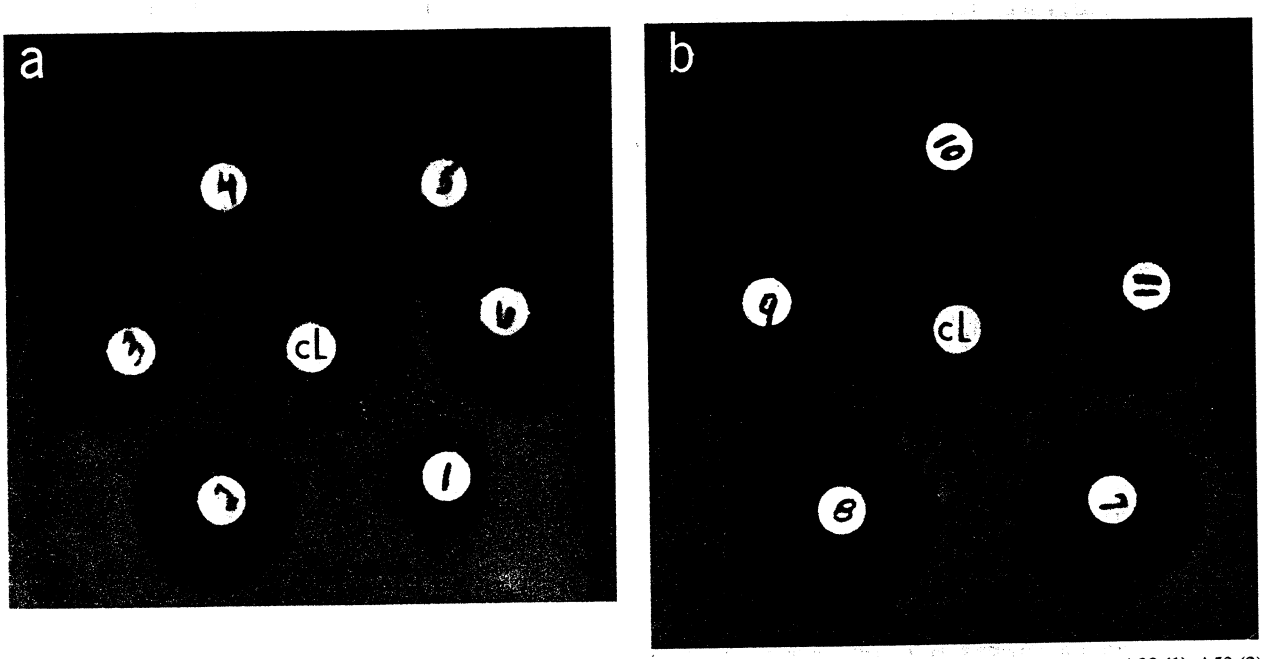

Fig 5 Ketolide induction assay (a) Disks containing 10 µg of each ketolide or clarithromycin (cl) are shown Ketolides tested were A22 (1), A53 (2), A51 (3), A11 (4), A23 (5), and A52 (6) (b) Ketolides tested were A24 (7), A54 (8), A55 (9), HMR3004 (10), and HMR3647 (11)

intercalation of the aromatic ring into stacked RNA bases [29] or by shared hydrogen bonding to aromatic amino acid residues in ribosomal proteins [19, 21].

The maximum inhibitory effect observed with A55 is unique It is an 11,12-carbonate structure with no aromatic side chains, unlike the other ketolides examined It is a strong, effective antimicrobial agent comparable to the aromatic substituted carbamates tested It has been shown to be a potent inhibitor of cell viability and growth but with surprisingly little effect on cell-free protein synthesis [5] A macrolide analog of this compound, 11,12-carbonate, 3-deoxyclarithromycin is also an effective antimicrobial agent and is particularly inhibitory to the synthesis of the 50S subunit [12] These results suggest additional features of the ketolides to be tested for inhibitory activity N-substituted aromatic rings and other 11,12-carbonate derivatives are the best candidates for future studies

A significant difference between the ketolide and macrolide compounds is the lack of induction of 23S rRNA methylase activity by the former [7] The noninducibility of *ermC* gene expression by these compounds

suggest that they hold the promise for clinical use against MLS-resistant organisms [6, 28] Our results suggest that there may be three related binding sites for macrolide antibiotic–like compounds on the 50S ribosomal subunit. A primary site exists for binding macrolides and ketolides to a functioning 50S ribosome, which impairs its translational activity A second site presumably exists on a precursor to the subunit which leads to assembly inhibition and subsequent degradation of the incomplete particle, as our model would suggest [10, 11]. A third site on the particle may hold macrolides but not ketolides as a part of the induction mechanism for gene expression from antibiotic-stalled ribosomes [31] As examples, erythromycin, clarithromycin, and azithromycin affect all three functions, ketolides generally affect only translation and assembly and a 3-deoxy 11,12-carbonate clarithromycin derivative inhibits assembly but not translation [12]. Additional studies using macrolide and ketolide compounds with additional well defined modifications should help distinquish between these ribosomal targets

ACKNOWLEDGMENTS

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Low Dosage and Long Treatment Duration of β-Lactam

Risk Factors for Carriage of Penicillin-Resistant *Streptococcus pneumoniae*

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Context.—The spread of drug-resistant *Streptococcus pneumoniae* in the community is a public health problem in developed and developing nations, but whether antibiotic use is responsible for the increase in drug resistance is not known.

Objective.—To analyze the relationship between penicillin-resistant *S pneumoniae* (PR*Sp*) pharyngeal carriage and characteristics of β-lactam use.

Design.—Observational study of children attending 20 randomly sampled schools.

Setting.—The Loiret, in the center of France.

Participants.—A total of 941 children, 3 to 6 years old.

Main Outcome Measure(s).—Pharyngeal carriage of *S pneumoniae*, antibiotic use, and medical events during the preceding 30 days. Pneumococcal penicillin G sodium minimal inhibitory concentrations and serotyping were performed.

Results.—Medical illnesses and the use of antibiotics were not associated with PR*Sp* carriage. However, oral β-lactam use was associated with an increased risk of PR*Sp* carriage (odds ratio [OR], 3.0; 95% confidence interval [CI], 1.1-8.3; P=.03). Children treated by low daily doses of an oral β-lactam (defined as lower than clinical recommendations) had an increased risk of PR*Sp* carriage, as compared with children who did not (OR, 5.9; 95% CI, 2.1-16.7; P=.002). A treatment of long duration (>5 days) with a β-lactam was associated with an increased risk of PR*Sp* carriage (OR, 3.5; 95% CI, 1.3-9.8; P=.02).

Conclusions.—Our results suggest that a low daily dose and a long duration of treatment with an oral β-lactam contribute to the selective pressure in promoting pharyngeal carriage of PR*Sp*.

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THE SPREAD of drug-resistant *Streptococcus pneumoniae* in the community poses a major challenge for clinicians and microbiologists. It is now a public health problem in both developing and developed countries.

Streptococcus pneumoniae is a major cause of community-acquired pneumonia, bacteremia, meningitis, and acute otitis media. It accounts for over 1 million deaths each year around the world in children younger than 5 years.[1] The increase in penicillin-resistant *S pneumoniae* (PR*Sp*) complicates treatment of these infections[2,3] and risks to increase morbidity and mortality from pneumococcal infection.[1]

For some areas in the United States, 25% to 30% of invasive pneumococcal isolates were found to have either intermediate or high-level resistance.[4] A report from Spain, which has a high prevalence of drug-resistant pneumococci, showed that between 1979 and 1994, 57% of more than 5000 isolates were resistant to 1 or more antibiotics.[5] For over a decade in France, the frequency of PR*Sp* isolates in the National Reference Center for Pneumococci increased from 0.5% in 1984 to 32% in 1994.[6]

For editorial comment see p 394.

Many authors have suggested that the dominant factor in the spread of bacterial resistance in the community is the increasing use of antibiotics[7,8]; however, the chain of causality is not clear. Ecologic correlations have been found between invasive PR*Sp* or erythromycin-resistant group A streptococci and antibiotic use in the community.[9,10] There is also time concordance between invasive *Moraxella catarrhalis* and sales of cephalosporins.[11] Several studies have shown in vitro that β-lactams may promote PR*Sp*.[12,13] More recently, a study has shown that antibiotic use increases the carriage rate of PR*Sp* in children.[14] These studies do not explain how antimicrobial drug use is a risk factor for human colonization by PR*Sp*.

The lack of adequate community studies has prevented the development of epidemiologic models, which would predict the evolution of antimicrobial-drug resistance. As a result, policies regarding antibiotic treatment of outpatients have been hindered.

High carriage rates of PR*Sp* in the community have been shown to result in an increased incidence of clinical infection.[15] To test the hypothesis that PR*Sp* carriage is related to β-lactam use, we conducted a survey for pharyngeal carriage of *S pneumoniae* and antimicrobial use in children.

METHODS

Survey Design

We surveyed oropharyngeal carriage of *S pneumoniae* in healthy 3- to 6-year-old schoolchildren in the Loiret, an administrative department in the center of France with 600 000 inhabitants, where more than 99.5% of these children are enrolled at school. This area is similar to the rest of France in terms of sociodemographic characteristics, medical activities of nonhospital practitioners, and Social Security coverage. The choice of the population (3- to 6-year-old children) was based on the possibility to recruit a randomized population sample of children. The survey was conducted over a 5-week period from April 10, 1995, to May 16, 1995.

Assuming a ratio of 50:1 non-PR*Sp* carriers to PR*Sp* carriers, and that 2% of non-PR*Sp* carriers were treated by low doses, our sample size enabled us to detect whether PR*Sp* carriage was associated with a low dosage of β-lactam with an odds ratio (OR) of 2.0 with $\alpha = .05$ and power close to 80% with a 2-tailed test.[16]

The survey was stratified for rural/urban and socioeconomic status of the school area. Since there were not any schools with low socioeconomic status in a rural area, 3 strata were used. Twenty schools were selected at random, with equal sampling fraction from the following strata: fewer than 5000 inhabitants; at least 5000 inhabitants and low socioeconomic school level; and at least 5000 inhabitants and high socioeconomic school level. The socioeconomic school level was defined according to National Ministry of Education criteria.

Children were included in this study if they were registered for school at the beginning of the year, if the parents gave informed consent, and if the children gave oral consent for the throat screening.

Thirty days before the date planned for the throat screening, we asked the parents to complete a short questionnaire on family size, physician consultation, and diagnosis as stated by the practitioner and drug consumption (including type of drug, duration of treatment and number of daily doses).

This study was approved by the Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale of the Kremlin-Bicêtre hospital and the Commission Nationale de l'Informatique et des Libertés.

Sample Collection

We used an oropharyngeal bacterial screening procedure because of better acceptability by the children. A swab from the oropharynx was immediately plated onto 5% sheep blood-agar with an optochin disk. The plates were incubated at 37°C in 5% carbon dioxide for 24 hours. Children were weighed at screening.

Microbiological Methods

α-Hemolytic colonies were identified as pneumococci by their typical colonial morphology and susceptibility to optochin, stored frozen at −80°C in brain-heart infusion with 15% glycerol, and then sent to the National Reference Center for Pneumococci. *Streptococcus pneumoniae* isolates were identified using standard methods.[17] The penicillin G and cefotaxime sodium minimal inhibitory concentrations (MICs) for all *S pneumoniae* isolates were determined using an agar-dilution method. An inoculum of 10^4 minus 10^5 colony-forming units per spot was delivered with a Steers replicator onto Müller-Hinton agar plates (Sanofi Diagnostic Pasteur, Marne la Coquette, France) supplemented with 5% horse blood and appropriate antimicrobial concentration, which were incubated overnight at 37°C with carbon dioxide supplementation. The MIC was defined as the lowest concentration of antimicrobial agent that completely inhibited bacterial growth after incubation for 18 hours. Two *S pneumoniae* strains were used as controls (Collection Institut Pasteur, Nos. 104 485 and 104 471). Penicillin resistance was defined as penicillin G MIC of at least 0.1 μg/mL according to the recommendations of the National Committee for Clinical Laboratory Standards.[18] Isolates were serotyped with latex agglutination.

Descriptive and Analytic Methods

Characteristics of *S pneumoniae* noncarriers, carriers, and PR*Sp* carriers were compared using Kolmogorov-Smirnov 2-tailed tests for quantitative variables and the χ^2 test or Fisher exact test for binary variables.

The daily dose in milligrams per kilogram was calculated for the last-used antimicrobial generic drug and coded as a high or low daily dose as follows. For amoxicillin, the recommended daily dose ranges between 20 and 100 mg/kg according to disease, authors, and countries.[19-21] As many authors recommend an increase in daily dose to 80 to 100 mg/kg in otitis, we considered 50 mg/kg a reasonable cutoff to define low daily dose. For oral cephalosporins, we used the dosing range for children as recommended in the fourth edition of *Principles and Practice of Infectious Diseases*[20]: cefaclor, 40 mg/kg per day; cefatrizine, cefadroxil, and cefuroxime axetil, 30 mg/kg per day; and cefpodoxime proxetil and cefixime, 8 mg/kg per day. For each generic drug, the low daily dose was defined as less than or equal to the above limits. While recent studies have suggested efficacy in community respiratory infectious diseases with an antibiotic given for 5 days or less,[22-25] we strictly considered more than 5 days a long duration of treatment.

Relations between PR*Sp* carriage and antibiotic consumption were quantified by unadjusted ORs (UORs).[26] To take into account a possible association between upper and lower respiratory tract infectious events (otitis, common cold, bronchitis, and pharyngitis) and PR*Sp* carriage, as well as possible interactions between predictive variables, these variables and their interactions were tested. An analysis was performed excluding children who had an otitis media during the previous 30 days. The Fisher exact test was used for the univariate analysis, and 95% confidence intervals (CIs) for the ORs were calculated by the logit method.[27] Multivariate analyses were performed to verify the lack of diminution of UORs when adjusted for factors associated with *S pneumoniae* carriage. Adjusted ORs (AORs) were calculated using logistic regression models[28] for school strata and school prevalence of the pneumococcal carriage as a quantitative variable.

Furthermore, we calculated the percentile of daily dose for each generic antibiotic and defined 2 classes of daily dosage in reference to the median (more or less than the median). The Fisher exact test was used to compare penicillin G susceptibility according to these classes. Calculations were performed using the Statistical Package for the Social Sciences program.[29]

RESULTS

Characteristics of Participation Rate of Children

Of the 1168 eligible subjects, 941 participated. Nonparticipation was due to parents refusing (5.8%), children refusing (2.9%), children absent from the school because of holidays (2.4%), afternoon nap at home (2.4%), chickenpox (1.9%), other reasons (1.1%), and un-

Table 1.—*Streptococcus pneumoniae* and Penicillin-Resistant *S pneumoniae* (PR*Sp*) Carriage According to School

School	Strata*	No. of Children	*S pneumoniae* Carriage, %	PR*Sp* Carriage, %
1	C	39	7.7	7.7
2	A	12	0	0
3	A	25	20	4
4	A	57	5.3	3.5
5	C	101	4	0
6	C	61	8.2	0
7	C	45	0	0
8	C	86	4.7	0
9	A	49	0	0
10	A	19	0	0
11	C	102	4.9	2
12	C	59	0	0
13	C	26	19.2	7.7
14	A	17	5.9	5.9
15	A	30	3.3	0
16	B	56	10.7	3.6
17	B	52	9.6	1.9
18	C	20	0	0
19	C	40	7.5	2.5
20	A	45	11.1	2.2
Total		941	5.7	1.7

*A indicates fewer than 5000 inhabitants; B, at least 5000 inhabitants and low socioeconomic school level; and C, at least 5000 inhabitants and high socioeconomic school level.

Table 2.—Sensitivity of the 55 *Streptococcus pneumoniae* Isolates

Drug	Minimal Inhibitory Concentration, µg/mL	*S pneumoniae* Isolates, No. (%)	Total No. (%) Resistant
Penicillin G	≤.06	39 (71)	16 (29)
	0.1-1	13 (24)	
	≥2	3 (5)	
Cefotaxime sodium	≤0.5	49 (89)	6 (11)
	1	5 (9)	
	≥2	1 (2)	

known reasons (0.8%). The median age was 4.9 years, and the median body weight was 17.5 kg.

S pneumoniae Carriage

The frequency of pneumococci carriage differed among schools, ranging from 0% to 20% of the children (Table 1). Fifty-five *S pneumoniae* isolates were identified. One child carried 2 different pneumococcal isolates. Among the *S pneumoniae* identified, the rate of penicillin resistance was 29% and the rate of cefotaxime sodium resistance was 11% (Table 2).

There was no significant difference in age, weight, sex, number of children in the family, and demographic level of the school between *S pneumoniae* carriers and noncarriers, or between PR*Sp* carriers and non-PR*Sp* carriers (Table 3). The percentage of PR*Sp* carriers was significantly higher in 2 of the schools (schools 1 and 13) compared with the others (7.7% vs 1.3%, $P=.003$). These schools were both urban and of high socioeconomic level, but there were no differences in β-lactam use in comparison with the other schools.

Three PR*Sp* isolates were nontypable and the 13 others fell into group/type 6A, 9V, 14, 15, 15C, 23A, and 24 (Table 4). Furthermore, 40% of the pneumococcal isolates and 44% of PR*Sp* isolates had a serotype not included in the pneumococcal vaccine.

PR*Sp* Carriage and Antibiotic Use

No medical event could be identified as a risk factor for PR*Sp* carriage. The use of any antibiotic was not a risk factor for PR*Sp* carriage.

During the previous 30 days, 161 children used at least 1 β-lactam: aminopenicillin only (n=97), cephalosporin only (n=55), or aminopenicillin and cephalosporin (n=9). The β-lactams used were amoxicillin (with or without clavulanic acid), cefaclor, cefadroxil, cefatrizine, cefuroxime axetil, cefpodoxime proxetil, and cefixime. Six of the 16 children with PR*Sp* reported β-lactam use. Both β-lactam and, in particular, aminopenicillin use were associated with an increased risk of PR*Sp* carriage (UOR, 3.0; 95% CI, 1.1-8.3; and UOR, 4.4; 95% CI, 1.5-13; respectively) (Table 5).

Daily Doses

The number of daily doses was not found to be associated significantly with a risk for PR*Sp* carriage. For amoxicillin, the most frequent β-lactam used during the previous 30 days, there were 2 PR*Sp* among 39 children who used amoxicillin with 2 daily doses or less and 14 PR*Sp* among 886 children with no amoxicillin or amoxicillin with 3 daily doses or more (number of missing data=16); the difference in PR*Sp* carriage was 3.3%. However, given the small sample sizes, it is difficult to show a statistically significant difference for the number of daily doses of amoxicillin.

Thirteen children used a β-lactam more than once a month. None of these children was a *S pneumoniae* carrier.

The last β-lactam used was a low daily dose in 52.2% of the children treated, which is in 8.9% of the children. As compared with no use, low daily doses of the last β-lactam were associated with an increased risk of PR*Sp* carriage (UOR, 5.9; 95% CI, 2.1-16.7). The association was not diminished when adjusted for strata and the school prevalence of pneumococcal carriage (Table 6) and persisted even after exclusion of children with otitis media in whom PR*Sp* might have been involved in β-lactam use (UOR, 5.5; 95% CI, 1.8-16.6). In contrast, PR*Sp* carriage was never identified with high doses of β-lactam.

Furthermore, in *S pneumoniae* carriers, as compared with no β-lactam treatment, low daily dose of β-lactam was associated with an increased risk of PR*Sp* carriage (UOR, 4.8; 95% CI, 1.1-20.5).

As compared with no use, low daily doses of the last aminopenicillin or cephalosporin were associated with an increased risk of PR*Sp* carriage (UOR, 6.7; 95% CI, 2.2-19.9; and UOR, 4.9; 95% CI, 1.1-22.9) (Table 6).

The median daily dose for amoxicillin was 46.2 mg/kg; for cefaclor, 31.8 mg/kg; cefadroxil, 43.5 mg/kg; cefatrizine, 41.6 mg/kg; cefuroxime axetil, 23.4 mg/kg; cefpodoxime proxetil, 8.4 mg/kg; and cefixime, 8.9 mg/kg. Seventy-seven percent of *S pneumoniae* isolated from children who had not taken a β-lactam had a penicillin G MIC lower than 0.1 µg/mL. All the *S pneumoniae* isolated from children who had taken a daily dose of β-lactam lower than the median (n=6) had a penicillin G MIC higher than 0.1 µg/mL. In contrast, all *S pneumoniae* isolated from children who had a daily dose of β-lactam higher than the median (n=8) had a penicillin G MIC lower than 0.1 µg/mL ($P=.003$). These 2 groups did not have different mean durations of treatment or different mean numbers of daily doses.

Duration of Treatment

The last β-lactam used was a treatment of long duration in 85.7% of treated children, which represents 14.7% of children. A long duration of treatment with β-lactam increased the risk of PR*Sp* carriage (UOR, 3.5; 95% CI, 1.3-9.8, in comparison with no use) (Table 6).

Daily Doses and Duration of Treatment

Children were grouped according to their combined value for daily dose and

Table 3.—Characteristics of *Streptococcus pneumoniae* Noncarriers, *S pneumoniae* Carriers, and Penicillin-Resistant *S pneumoniae* (PR*Sp*) Carriers

Characteristics	*S pneumoniae* Noncarriers (Non-*Sp*, n=887)	*S pneumoniae* Carriers: Penicillin Susceptible (PS*Sp*, n=38)	*S pneumoniae* Carriers: Penicillin Resistant (PR*Sp*, n=16)	Non-*Sp* vs PS*Sp* + PR*Sp* *P* Value	PS*Sp* vs PR*Sp* *P* Value
Median age, y*	4.9	4.6	5.5	.9	.9
Median weight, kg	17.5	17.8	18.3	.8	.8
Male, %†	50.0	59	50	.4	.7
Mean No. of children in family*	2.4	2.3	2.2	.9	.9
School strata, %†					
Urban and high socioeconomic area (n=579)	62.1	53.8	50.0		
Rural and high socioeconomic area (n=254)	27.0	25.6	31.3	.1	.9
Urban and low socioeconomic area (n=108)	10.9	20.5	18.8		

*Based on results using the Kolmogorov-Smirnov 2-tailed test.
†Percent calculated with χ^2 test.

Table 4.—Serotypes of *Streptococcus pneumoniae* Isolates

Serotype	No. of Isolates	No. Penicillin Resistant*
3	3	0
4	1	0
6A	4	1
6B	1	0
9N	1	0
9V	5	3
10A	1	0
11A	3	0
14	2	2
15	2	1
15A	1	0
15C	1	1
16	3	0
19A	7	0
19F	4	0
23A	4	1
23F	3	3
24	4	1
35C or 42	1	0
38	1	0
Nontypable	3	3
Total	**55**	**16**

*Defined as minimal inhibitory concentration of at least 0.1 μg/mL.

Table 5.—Odds Ratio for Penicillin-Resistant *Streptococcus pneumoniae* (PR*Sp*) Carriage by Antimicrobial Drug Use and by Medical Events During the 30 Preceding Days

Variable	No. of Children	Frequency, % (n=941)	Unadjusted Odds Ratios (95% Confidence Interval)*	*P* Values
Antimicrobial Drugs				
Any antimicrobial drug use	203	21.6	2.6 (0.9-7.3)	.1
β-Lactams	161	17.1	3.0 (1.1-8.3)	.03
Aminopenicillin	106	11.3	3.7 (1.3-10.9)	.01
Penicillin V	7	0.7	...	.9†
Cephalosporin	64	6.8	1.9 (0.4-8.9)	.4
First generation	45	4.8	1.3 (0.2-10.3)	.6†
Second generation	5	0.5	...	.9†
Third generation	15	1.6	4.3 (0.5-35.1)	.2†
Macrolides	41	4.3	1.8 (0.2-14.1)	.4
Medical Events				
Common cold	65	6.9	0.9 (0.1-6.8)	.9
Otitis	28	3	2.2 (0.3-17.3)	.4
Gastroenteritis	21	2.2	...	.8†
Bronchitis	21	2.2	...	.8†
Pharyngitis	40	4.3	...	.7†

*Ellipses indicate that odds ratio was close to zero because there were no PR*Sp* isolates for the exposed cases.
†The association, tested with a 2-tailed Fisher exact test, was not statistically significant.

duration of treatment for aminopenicillin and cephalosporin or the last β-lactam they had taken. The percentage of low dose with a long duration was 46.6%; high dose with a short duration, 39.1%; and missing data on dose, 14.3%. The rate of PR*Sp* carriage in low dose with a long duration was different than in high dose with a short duration, 8.0% and 0.0%, respectively (P=.03).

COMMENT

We found that a low daily dose and a long treatment duration of an oral β-lactam are risk factors for PR*Sp* carriage. The number of daily doses was not a risk factor for PR*Sp* carriage, but the power of this study was low.

The oropharyngeal bacterial sampling procedure is specific but probably weakly sensitive in identifing pneumococcus. Thus, the 6% prevalence of *S pneumoniae* carriage, the 2% prevalence of PR*Sp* carriers, and the calculated ORs may be underestimates. Nevertheless, this is unlikely to introduce a bias either in the 29.6% rate of penicillin-resistance among carriers or in the conclusion that a low daily dose and a long treatment duration of an oral β-lactam are risk factors for PR*Sp*.

The parents' information was not validated with physician records. This is unlikely to induce a bias in the association we observed for the following reasons. Questionnaires were distributed 1 month before the throat screening. When parents completed the questionnaire, they did not know whether their child was a PR*Sp* carrier. Furthermore, neither *S pneumoniae* carriage nor PR*Sp* carriage was associated with acute otitis media and the associations persisted even after exclusion of children with otitis media in whom PR*Sp* might have been involved in β-lactam use.

Associations between the recent use of oral antibiotics and drug-resistant pneumococcal pharyngeal carriage have already been described.[14, 30-32] The relation between dosage, duration of antibiotic treatment, and spread of PR*Sp* in the community has been suggested,[33] but has never been proven in clinical studies. Our results support the hypothesis that a low daily dose and a long treatment of β-lactam are major factors contributing to PR*Sp* carriage. To our knowledge, this is the first such clinical demonstration. As discussed above, the effect of the number of daily doses remains to be clarified in a study with more statistical power.

Carriage of PR*Sp* is the precondition for interindividual transmission. Two main causes for the spread of PR*Sp* in the community are antibiotic selective-pressured and interindividual transmission.[30,34,35] Several factors could help to explain the antibiotic selective pressure: bacterial antagonism in regulating the bacterial flora of the human pharynx,[36-39] horizontal gene transfer,[40] or the selection of mutants of *S pneumoniae* due to low tissue concentration to antibiotics.[13] Recently, bacteriological findings have suggested that a reduced exposure to antibiotics may not necessarily lead to a significant decrease in the frequency of resistant bacteria,[41] but this conclusion was only based on in vitro observations

Table 6.—Odds Ratios for Penicillin-Resistant *Streptococcus pneumoniae* (PR*Sp*) Carriage According to Daily Dose and Duration of the Last Antibiotic Used During the Previous 30 Days*

Variable	No. of Children	No. of PR*Sp* Carriers	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Last β-lactam						
Daily dose						
No use†	780	10	1.0		1.0	
Low†	84	6	5.9 (2.1-16.7)	.002	7.5 (2.5-22.8)	<.001
High	54	0	NA	.9	NI	
Missing‡	23	0	NA	.9	NI	
Duration of treatment						
No use†	780	10	1.0		1.0	
Long†	138	6	3.5 (1.3-9.8)	.02	3.9 (1.4-11.2)	.01
Short	23	0	NA	.9	NI	
Last aminopenicillin						
Daily dose						
No use†	835	11	1.0		1.0	
Low†	61	5	6.7 (2.2-19.9)	.003	9.6 (2.9-31.5)	<.001
High	30	0	NA	.9	NI	
Missing	15	0	NA	.9	NI	
Duration of treatment						
No use†	835	11	1.0		1.0	
Long†	91	5	4.4 (1.5-12.8)	.01	5.2 (1.5-18.1)	.003
Short	15	0	NA	.9	NI	
Last cephalosporin						
Daily dose						
No use†	877	14	1.0		1.0	
Low†	27	2	4.9 (1.1-22.9)	.08	5.4 (1.3-25.8)	.04
High	27	0	NA	.9	NI	
Missing	10	0	NA	.9	NI	
Duration of treatment						
No use†	877	14	1.0		1.0	
Long†	53	2	2.4 (0.5-10.9)	.2	2.3 (0.5-10.7)	.3
Short	11	0	NA	.9	NI	

*Each category for each variable is compared with no use. The unadjusted odds ratios (ORs) did not use the logistic model but were directly calculated. *P* values were calculated using a 2-tailed Fisher exact test; 95% CI denotes 95% confidence interval. Multivariate logistic regression model was adjusted for school strata and the school prevalence of pneumococcal carriage. NA indicates not applicable; NI, variable not included. The association tested with a 2-tailed Fisher exact test was not statistically significant.

†Groups included in multivariate logistic models.

‡Missing values for children who used an aminopenicillin or a cephalosporin, but for whom there was no information on the daily dose.

for *Escherichia coli*. Pharmacoepidemiologic studies are required to understand how these factors are involved in the spread of PR*Sp* and to assess the possibility of reversing the increase in PR*Sp* in the community by improving antimicrobial-drug prescription.

The brief period of this study (a 5-week period in late spring 1995) only provides a snapshot of what is happening with regard to *S pneumoniae* colonization. The duration of *S pneumoniae* carriage is likely to be an important factor in interindividual transmission. We can hypothesize that the epidemiologic advantage of PR*Sp* vs nonresistant *S pneumoniae* may be related to different durations of carriage according daily doses and durations of treatment with antimicrobials. A longer period of follow-up would be needed if durations of carriage vary with daily doses and duration of β-lactam treatment.

Nearly half of the PR*Sp* serotypes found in our study are not included in the pneumococcal vaccine currently used in the United States and Europe. Further, as currently used pneumococcal vaccines are effective in preventing pneumococcal infection but not pneumococcal carriage[42] even if conjugate pneumococcal vaccines may be shown to reduce pneumococcal carriage,[43] it is unlikely that these vaccines would limit, in the near future, the spread of PR*Sp*. Furthermore, it is not possible to limit interindividual transmission of resistant bacteria in the community. To reverse the trend of the spread of PR*Sp*, there is no choice but to reduce the antibiotic selection pressure.

Modeling the spread of antimicrobial drug resistance is essential to anticipate its evolution in the community. Epidemiologic models of antibiotic resistance have only taken into account exposure to antibiotics through the fraction of the population using antibiotics.[44] Our results indicate that studies should also take into consideration the daily dosage, the duration of treatment, and, but this remains to be established, the number of daily doses.

In developed countries, most antimicrobials are prescribed to outpatients. A reduction in the use of antibiotics has recently been proposed to forestall the problem of antibiotic resistance.[45] To control drug-resistant *S pneumoniae*, community-wide education programs for clinicians and the general public are important. These programs should focus on appropriate use of antibiotics and aim to encourage higher daily doses and shorter treatment with β-lactams.

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The macrolide–ketolide antibiotic binding site is formed by structures in domains II and V of 23S ribosomal RNA

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Summary

The macrolide antibiotic erythromycin interacts with bacterial 23S ribosomal RNA (rRNA) making contacts that are limited to hairpin 35 in domain II of the rRNA and to the peptidyl transferase loop in domain V. These two regions are probably folded close together in the 23S rRNA tertiary structure and form a binding pocket for macrolides and other drug types. Erythromycin has been derivatized by replacing the L-cladinose moiety at position 3 by a keto group (forming the ketolide antibiotics) and by an alkyl-aryl extension at positions 11/12 of the lactone ring. All the drugs footprint identically within the peptidyl transferase loop, giving protection against chemical modification at A2058, A2059 and G2505, and enhancing the accessibility of A2062. However, the ketolide derivatives bind to ribosomes with widely varying affinities compared with erythromycin. This variation correlates with differences in the hairpin 35 footprints. Erythromycin enhances the modification at position A752. Removal of cladinose lowers drug binding 70-fold, with concomitant loss of the A752 footprint. However, the 11/12 extension strengthens binding 10-fold, and position A752 becomes protected. These findings indicate how drug derivatization can improve the inhibition of bacteria that have macrolide resistance conferred by changes in the peptidyl transferase loop.

Introduction

The majority of clinically useful antibiotics function by inhibiting protein synthesis by bacterial ribosomes (Vázquez, 1979; Gale *et al*, 1981). The main target site of each of these drugs is generally a conserved ribosomal structure that is associated with an essential step in protein synthesis. Despite the considerable diversity in the structure of antibiotics, the number of such ribosomal target sites is quite modest and includes the peptidyl transferase and GTPase-associated centres of the 50S subunit and the decoding region of the 30S subunit (Cundliffe, 1986; 1990) Present evidence indicates that the specificity of an antibiotic for a target site is determined by direct interaction between the drugs and the ribosomal RNA (rRNA) (Noller, 1984; 1991) The inhibitory characteristics of each of these drugs are presumably determined by a combination of the ability of the drug to gain access to its target site on the ribosome, its binding affinity at that site and its effect on perturbing or blocking access to the rRNA structure

The peptidyl transferase centre is the site of interaction of macrolide, lincosamide and streptogramin B (MLS) antibiotics and of chloramphenicol and puromycin (reviewed by Vázquez, 1979; Gale *et al*, 1981). More recently, other drug types including amicetin (Leviev *et al.*, 1994) and sparsomycin (Lázaro *et al.*, 1996) have been added to this list. Although this is a chemically diverse group of antibiotics, all these drugs have been shown to interact with an internal loop structure within domain V of bacterial 23S rRNA, termed the peptidyl transferase loop (reviewed by Cooperman *et al.*, 1990; Douthwaite, 1992a; Rodriguez-Fonseca *et al.*, 1995). Erythromycin A is a macrolide antibiotic with a 14-member lactone ring with 3-cladinose and 5-desosamine sugars (Gale *et al.*, 1981) Erythromycin shows high specificity and affinity for the bacterial 50S ribosomal subunit, having a dissociation constant of approximately 10^{-8} M, as measured by equilibrium dialysis (Pestka and Lemahieu, 1974) and footprinting (Douthwaite and Aagaard, 1993) Like other macrolides, the primary site of erythromycin interaction is at the 23S rRNA peptidyl transferase loop (Moazed and Noller, 1987; Sigmund *et al*, 1988; Tenson *et al*, 1996). However, the footprinting pattern of erythromycin in this loop is distinctive and different from macrolides with a 16-member lactone ring, and also different from lincosamides, streptogramins and chloramphenicol (Moazed and Noller, 1987; Egebjerg and Garrett, 1991; Douthwaite, 1992b, Rodriguez-Fonseca *et al.*, 1995)

Erythromycin has been derivatized in numerous ways

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with a range of effects on its binding (e.g. Pestka and Lemahieu, 1974). Some of the most extensive modification of the macrolide structure is exhibited in the ketolide drugs, which are characterized by substitution of the cladinose sugar for a 3-keto (Griesgraber *et al.*, 1996; Agouridas *et al.*, 1997a; Elliott *et al.*, 1997; Schülin *et al.*, 1997). In some ketolides, the 11/12 positions of the lactone ring are extended with an alkyl-aryl chain from a carbamate group (Fig. 1). These derivatized ketolides are reputed to interact with higher affinity than erythromycin to the bacterial ribosome, and to be more effective in inhibiting growth of macrolide-resistant strains (Agouridas *et al.*, 1997b; Ednie *et al.*, 1997; Jamjian *et al.*, 1997). To determine whether there is a molecular basis for this assertion, we compared macrolide and ketolide binding to ribosomes by chemical footprinting. The relative binding affinities of the drugs were measured, and differences in the ketolide interaction with the rRNA were uncovered that can account for the altered binding properties of these drugs

Results

Cell growth in antibiotics

Escherichia coli was chosen to compare the minimal inhibitory concentrations (MICs) of the different drugs, as ribosomes from this bacterium were to be used for identifying the sites of drug interaction with rRNA. The MIC of erythromycin for *E. coli* strain DH1 is 30 $\mu g\ ml^{-1}$. The drugs derivatized at the 11/12 position (Fig. 1) inhibit growth at approximately one-tenth of this concentration: MICs for HMR 3004 and RU 66252 are 3 $\mu g\ ml^{-1}$; the MIC for HMR 3647 is 4 $\mu g\ ml^{-1}$. RU 56006 is relatively poor at inhibiting cell growth, with a MIC of 200 $\mu g\ ml^{-1}$.

Sites of drug interaction with 23S rRNA

Chemical footprinting was carried out on *E. coli* ribosomes to compare the binding of erythromycin with its derivatives depicted in Fig. 1. To determine sites of drug interaction,

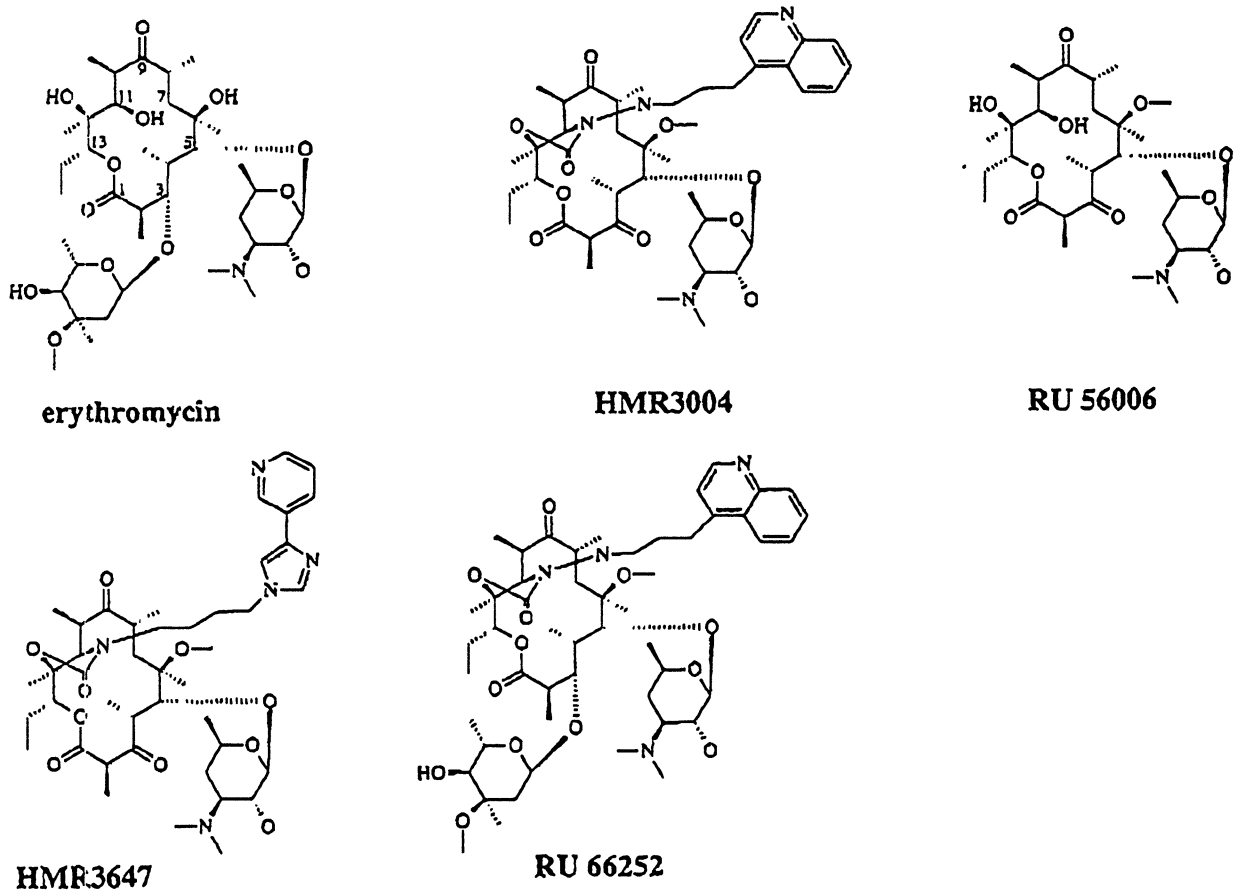

Fig. 1. Structures of the macrolide erythromycin A and ketolide antibiotics used in the study. All the drugs are based on a 14-member lactone ring structure The ring numbering is shown for erythromycin. Ketolides are semi-synthetic derivatives of erythromycin and are characterized by the substitution of a 3-keto group (in HMR 3004, HMR 3647 and RU 56006) where erythromycin has cladinose. By this definition, RU 66252 is a modified macrolide The derivatives (with the exception of RU 56006) additionally have an alkyl-aryl extension from a cyclic hydrazonocarbamate modification at the 11/12 positions (Agouridas *et al*. 1997a,b)

ribosomes were complexed with erythromycin, or with its derivatives, at drug concentrations several orders of magnitude above the K_{diss} to ensure that the binding sites were fully occupied After chemical modification with DMS or kethoxal, the entire 23S rRNA structure was screened by primer extension.

In the peptidyl transferase loop, protection at two adenines 2058 and 2059 that are accessible to DMS was identical for both macrolide and ketolides (Fig. 2). The HMR derivatives and erythromycin enhance the accessibility of the neighbouring adenine at 2062, although the effect is less obvious for erythromycin (Table 1) and has been missed in previously published studies. Kethoxal modifies at positions G2061 and G2505 in the peptidyl transferase loop. No drug effects were seen at G2061, despite the fact that this position is within a group of adenines with altered reactivities. However, G2505 was protected by all the drugs and to the same extent (Table 1).

A striking different in drug binding is apparent in hairpin 35 of domain II. Here, ketolide derivatives with the 11/12 extension (HMR 3004 and 3647) protect nucleotide A752, whereas the accessibility of this position is enhanced by erythromycin The same observation has been made independently by Xiong *et al.* (1998). The difference in the A752 modification raised the question of whether it is caused by the ketolide extension at the 11/12 position of the lactone ring or their lack of a 3-cladinose. This was resolved by footprinting the interactions of RU 66252 (HMR 3004 with 3-cladinose) and RU 56006 (a ketolide that lacks the 11/12 extension). RU 66252 gives A752 protection that is identical to that observed for HMR 3004 and HMR 3647 (Fig. 3), whereas RU 56006 produces no footprint at this position (not shown). Thus, the 11/12 extension in the ketolide lactone ring produces the dominant effect in protecting position A752. However, the lack of A752 footprint with RU 56006 indicates that the cladinose moiety in erythromycin also influences this position to promote the enhancement observed with DMS.

Kethoxal and DMS modification sites throughout the entire the 23S rRNA were assessed from 17 primers. No other drug footprinting effects were found apart from those depicted in the secondary structure models in Fig. 4

Binding affinities of the drugs

The DMS protection sites at A752, A2058 and A2059 were used to determine the relative binding affinities of macrolides and ketolides. Drug binding on wild-type ribosomes was probed in the 1 nM to 1 mM range. Protection effects are discernible at 1 nM drug concentrations and are already pronounced at 10 nM, as shown for HMR 3647 and erythromycin in Fig 5 The degree of protection is taken to correspond to the proportion of ribosomes binding the drugs. The protection effects are most reproducibly precise at

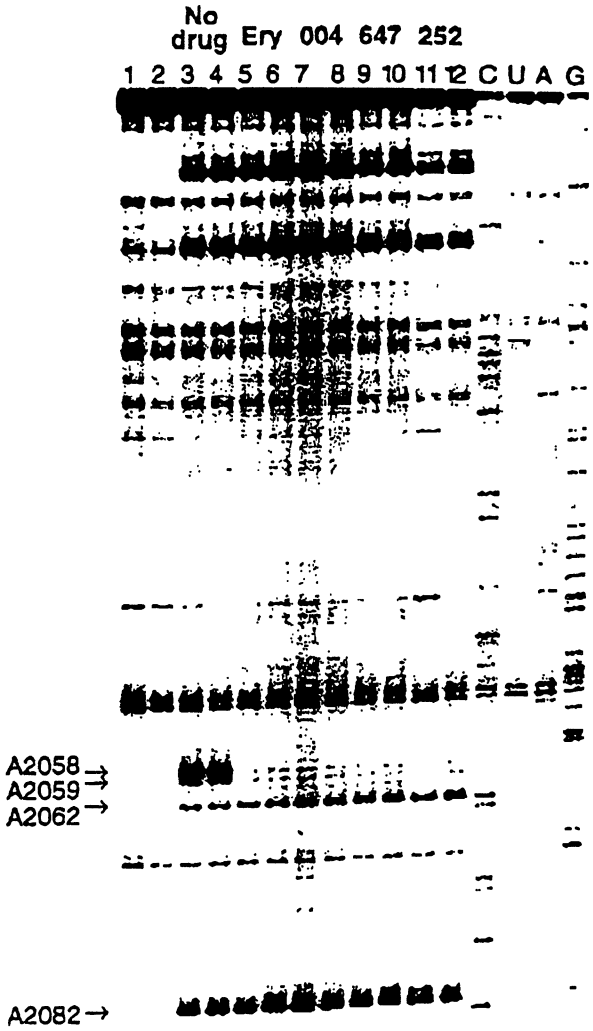

Fig. 2. Footprints at saturating drug concentrations. DMS footprints were analysed from a primer complementary to nucleotides 2099–2115 in 23S rRNA. Brief experimental details: *E. coli* ribosomes were at 100 nM for each sample Drugs were added at 250 μM to duplicate samples (lanes 5–12) Samples 3–12 were modified with DMS. RNA was extracted from the ribosomes, ^{32}P-labelled primer was hybridized to the RNA and extended with reverse transcriptase and dNTPs Resulting cDNAs were run on denaturing polyacrylamide sequencing gels and visualized by autoradiography. Gel lanes 1 and 2 are duplicated unmodified controls: lanes 3 and 4, no drug; lanes 5 and 6, erythromycin; lanes 7 and 8, HMR 3004; lanes 9 and 10, HMR 3647; lanes 11 and 12, RU 66252. Dideoxy sequencing lanes are shown Quantification was by phosphorimaging of the sequencing gels Background values in lanes 1 and 2 were subtracted from the corresponding positions for the bands at A2058, A2059, A2062 and A2082 in each of the lanes 3–12 Comparison with other bands between positions 1930 and 2110 shows that the A2082 is not affected by drug binding. A2082 was therefore used to normalize the intensities of A2058, A2059 and A2062 within each lane These normalized values are then compared with the modified control lanes with no drugs (lanes 3 and 4) These relative values are given in Table 1.

Table 1. Nucleotides in 23S rRNA, the accessibilities of which are affected by drug binding

	No drug	Erythromycin	HMR 3004	HMR 3647	RU 66252	RU 56006
A752	1.00	1 57 (± 0 24)	0 18 (± 0.10)	0 36 (± 0 15)	0 35 (± 0 11)	0.98 (± 0.07)
A2058	1 00	0 08 (± 0.03)	0 08 (± 0.02)	0.08 (± 0 03)	0.07 (± 0 02)	0.09 (± 0.02)
A2059	1 00	0 16 (± 0.04)	0.18 (± 0 05)	0 15 (± 0 02)	0.18 (± 0 04)	0.19 (± 0.05)
A2062	1.00	1.21 (± 0 09)	1.63 (± 0 18)	1 55 (± 0.16)	1.80 (± 0 25)	1.30 (± 0.12)
G2505	1.00	0.28 (± 0 12)	0 34 (± 0.14)	0.31 (± 0 18)	0 21 (± 0.12)	ND

Drugs at saturating concentrations (100 μM to 1 mM) were bound to wild-type ribosomes at 100 nM in experiments as shown in Figs 2 and 3. The only positions shown here are those in which binding of the drugs alters the base reactivities Each data point is from between three and eight independent experiments. Standard deviations are shown in parentheses ND, not determined

A2058 and A2059, and these data were used in the drug binding curves in Fig. 6. The dissociation constants of the ketolides and macrolides were calculated from these data (Table 2) The graphs for protection by the ketolides at A752 (not shown) are the same as the protection at A2058/59. However, A752 is less reactive to DMS than A2058 and A2059, and the ketolide protection data for this nucleotide thus have a lower signal-to-noise ratio The A752 data were, therefore, not used in the final dissociation constant calculations in Table 2.

The K_{diss} for erythromycin was measured previously as 10^{-8} M by footprinting (Douthwaite and Aagaard, 1993). The value calculated here, K_{diss} for erythromycin of 1.4 $(\pm 0.2) \times 10^{-8}$ M, was from a larger number of binding measurements that were quantified by a more accurate means (phosphor-imager scanning of gels instead of autoradiography). The ribosome binding of the modified macrolide RU 66252 is about fivefold tighter than erythromycin. The binding of the ketolides HMR 3004 and HMR 3647 is even stronger and is approximately 10-fold better than erythromycin. However, the loss of the cladinose in the absence of the 11/12 extension (in RU 56006) lowers the binding considerably (Table 2)

Determination of the number of ribosomal binding sites for the drugs

Ribosomes at 100 nM were incubated with HMR 3647 at concentrations of 1 nM to 1 μM (in 10-fold increments) and probed with DMS. Owing to the excess of ribosomes, protection at A752 and A2058 first became apparent at 100 nM drug concentration (data not shown) At this concentration, A752 and A2058 were protected 76% and 89%, respectively, of the maximum effects shown in Table 1 and Fig 6. This is consistent with the notion that hairpin 35 and the peptidyl transferase loop are part of the same single drug binding site.

Discussion

The footprinting patterns of macrolide and ketolide antibiotics on rRNA have been compared to investigate the molecular mechanism of the improved antibacterial effectiveness of ketolide derivatives. The protection effects on 23S rRNA at A2058 and A2059, together with the partial protection at G2505 and the enhancement at A2062, are similar and appear to be characteristic for macrolides and the ketolides with 14-member lactone rings. However, the footprints at A752 are quite distinct for the different drugs, indicating that the derivatization affects the mode of interaction with hairpin 35.

These footprinting effects are caused either by direct drug–RNA contact or by drug-induced allosteric changes from a distance. Although an unambiguous conclusion is difficult to draw from footprinting data, the most straightforward explanation for protection is by direct drug contact

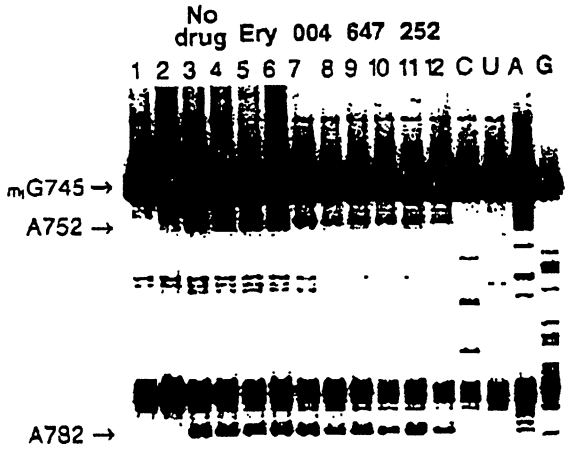

Fig. 3. Footprints in hairpin 35. DMS footprints were analysed from a primer complementary to nucleotides 888–906 in 23S rRNA. Samples were treated in the same manner as in Fig. 2. Quantification was by phosphor-imaging of the sequencing gels. Background values in lanes 1 and 2 were subtracted from the corresponding positions for the bands at A751, A752 and A782 in each of the lanes 3–12. Comparison with other bands between positions 800 and 850 shows that the A782 is not affected by drug binding. A782 was therefore used to normalize the intensities of A751 and A752 within each lane These normalized values are then compared with the modified control lanes with no drugs (lanes 3 and 4). There is a significant enhancement at the A752 position by erythromycin, whereas the derivatives (with the exception of RU 56006, not shown) protect this position (Table 1). There is no change at A751

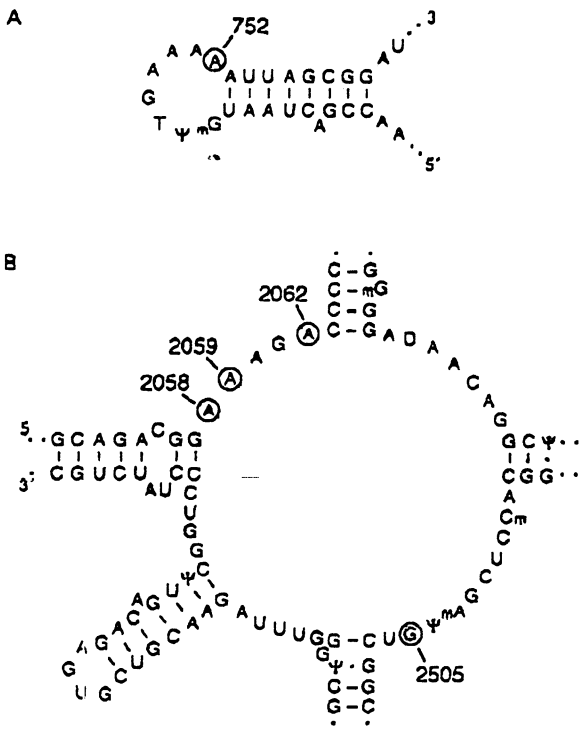

Fig. 4. Structures of 23S rRNA in (A) hairpin 35, and (B) the peptidyl transferase region. Nucleotides at which the ketolide and macrolide drugs interact are circled. The drug-induced changes in accessibility of these nucleotides to the chemical probes have been quantified in Table 1. These rRNA regions are redrawn from the secondary structure model of *E. coli* 23S rRNA (Noller, 1984; Gutell *et al*., 1994).

at that nucleotide. Thus, we infer that A2058, A2059 and G2505 are contacted by chemical groups that are common to both the macrolide and ketolide antibiotics, whereas A752 is in contact with a structure that is unique to the derivatized antibiotics. This latter contact is shown here to be facilitated via the alkyl-aryl extension at the 11/12 position of the lactone ring.

The protection effects were used to estimate the drug binding affinities on ribosomes. This approach has been used previously to measure the dissociation constants of lincosamide antibiotics (Douthwaite, 1992a) and erythromycin (Douthwaite and Aagaard, 1993), and gave values that are in good agreement with estimates from other methods (reviewed by Gale *et al*., 1981). The ketolide (HMR 3004 and HMR 3647) dissociation constants are in the nanomolar range, a binding affinity that is approximately 10-fold stronger than that for erythromycin. The improvement in binding is not quite as great when the 3-cladinose is present (in RU 66252). There are no immediately obvious qualitative differences in the footprints of HMR 3004 and HMR 3647 compared with RU 66252 to explain this effect. However, further comparison with the erythromycin and RU 56006 footprints (Table 1) indicates that the 3-cladinose and the 11/12 alkyl-aryl extension are promoting mutually exclusive effects at A752. The influence of the 11/12 extension is predominant and improves binding by enabling drugs to anchor firmly at hairpin 35 in addition to their interaction at the peptidyl transferase loop.

This prompts the question as to whether hairpin 35 and the peptidyl transferase loop are two distinct binding sites that each bind a ketolide molecule, or whether one ketolide molecule interacts simultaneously with both regions. Ketolide interaction at A2058/59 (Fig. 6) and A752 (not shown) show similar protection curves. This suggests that there is only one binding site. However, these data do not rule out the formal possibility of two sites of identical affinity or two sites that are co-operatively linked. These alternative explanations have been tested (and excluded) by titrating in HMR 3647 in the presence of a molar excess of ribosomes. The appearance of the footprint at A752 is accompanied by the footprint at A2058, and both footprints near

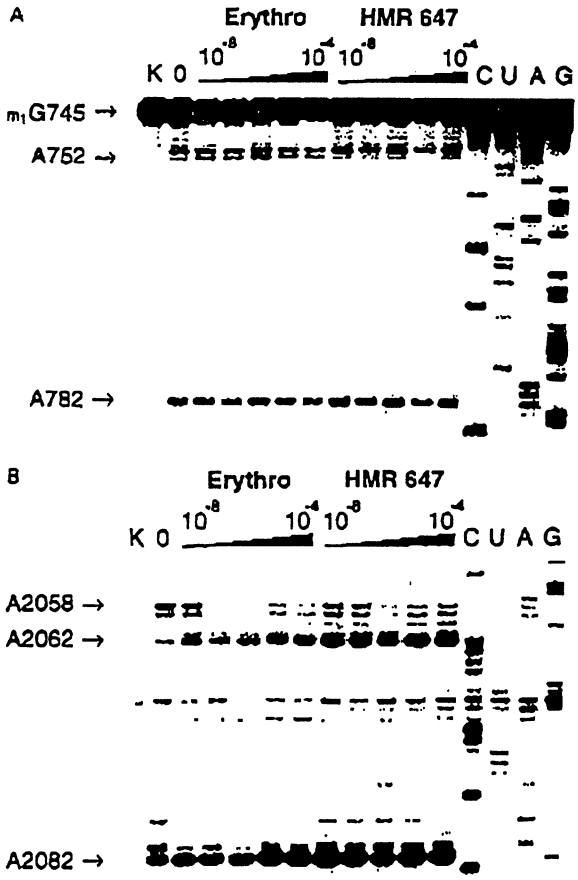

Fig. 5. Footprints of drugs at lower concentrations to estimate their binding affinities. Erythromycin and HMR 3647 were bound over a concentration range of 10^{-8}–10^{-4} M (in 10-fold increments) to ribosome samples at 1 nM. Bands were analysed as described in the legends to Figs 2 and 3.

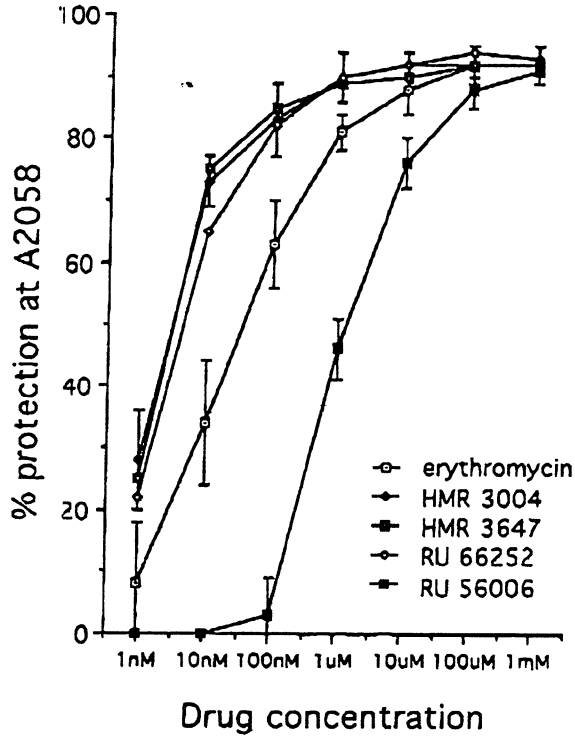

Fig. 6. Binding curves for erythromycin and derivatives The proportion of ribosomes binding the drugs (measured as the protection of A2058 against DMS modification) is plotted against the drug concentrations. Each point is a mean derived from between three and eight independent experiments. For clarity, standard deviations are shown only for erythromycin, HMR 3004 and RU 56006. These values, together with the near identical values for the DMS protection at A2059, were used to calculate the drug dissociation constants shown in Table 2.

saturation at a drug:ribosome stoichiometry that is consistent with a single drug binding site on the ribosome.

The case for a single site also fits with evidence from other types of study. One molecule of erythromycin binds per 50S subunit (reviewed by Vázquez, 1979), which would suggest that the same is true for ketolides. Furthermore, it appears that 23S rRNA folds within the 50S subunit, so that regions of domains II and V are proximal: Ψ746 has been shown to co-vary with the G2057-C2611 basepair, suggesting that these three nucleotides are involved in a base–triplet interaction (Gutell *et al*, 1994); and a zero-length cross-link between hairpin 35 and the sequence around A2614 has been formed by UV irradiation (reviewed by Baranov *et al.*, 1998) These observations suggest that hairpin 35 and the peptidyl transferase loop are in contact, and thereby form the drug binding site.

Within the binding site, the enhanced modification effects give a sensitive indication of drug interaction. As with the protection effects, the cause of the enhanced base reactivity is not unambiguous. The enhancement at A752 is promoted by the cladinose moiety of erythromycin, although it is unlikely that the cladinose contacts the N-1 position of A752 directly, as this would presumably block access to the DMS probe. Erythromycin could interact with another point of this nucleotide or with neighbouring nucleotides to bring the adenine N-1 position into a more accessible orientation. Alternatively, the drug could influence the local hydrophobicity, making the base more reactive to DMS. Similar arguments can be made for the enhancement at A2062 by both ketolides and macrolides. At A2062, the enhancement effect is apparent at lower drug concentrations than the neighbouring protection effects at A2058 and A2059. This is illustrated by the erythromycin footprint pattern at drug concentrations below the dissociation constant (10^{-8} M in Fig. 5), at which protection at A2058 and A2059 is slight, although the enhancement at A2062 has reached a maximum. The enhancement effect at A2062 is also evident when ribosomes are in excess relative to the drug. These observations probably reflect differences in the protection and enhancement phenomena. For protection to be complete, the drug has to remain bound throughout the course of the modification reaction, whereas enhancement can be a hit-and-run effect. Once modification at A2062 has been induced, the position stays modified irrespective of whether the drug remains bound The modification kinetics at A2062 in the presence of drug appear to be quiet rapid, and this suggests the intriguing possibility that a transitory rRNA conformation is being observed upon drug association with or dissociation from the ribosome.

In addition to ketolides and macrolides, the binding pocket is the site of interaction of several other chemically disparate drug groups, some of which are summarized in Table 3. One of these drugs from the streptogramin B group, vernamycin, has also been shown to interact with domains II and V of the rRNA (Moazed and Noller, 1987). The chemical dissimilarity of the drugs in Table 3 suggests

Table 2. Dissociation constants for erythromycin and derivatives on *E coli* ribosomes

	Erythromycin	HMR 3004	HMR 3647	RU 66252	RU 56006
K_{diss} (M)	$1.4 (\pm 0.2) \times 10^{-8}$	$1.6 (\pm 0.3) \times 10^{-9}$	$1.3 (\pm 0.2) \times 10^{-9}$	$2.9 (\pm 0.2) \times 10^{-9}$	$9.8 (\pm 1) \times 10^{-7}$

The values are derived from the DMS protection data at A2058 and A2059 in 23S rRNA. These data are illustrated in Fig. 6. At saturating drug concentrations, all the drugs give a maximum protection of approximately 92% at A2058, and 82–85% protection at A2059 (the inverse of the accessibilities shown in Table 1). These values are taken to represent complete binding site occupancy

that the binding pocket is flexible and probably subject to perturbation on drug binding. As discussed above, such perturbation is possibly indicated by the enhancement effects in the footprinting patterns Despite the interaction at mainly the same 23S rRNA nucleotides, each drug type in Table 3 has a characteristically different footprinting pattern.

Changes in the rRNA structure by either methylation (Skinner *et al*, 1983; Weisblum, 1995) or mutation (Vester and Garrett, 1987; Sigmund *et al.*, 1988) at or around A2058 in the 23S rRNA domain V confer resistance to MLS drugs and chloramphenicol. In the accompanying paper, a novel mutation at position 754 (U to A) in domain II is reported that confers macrolide and ketolide resistance (Xiong *et al.*, 1999). These mutations within or adjacent to the drug binding pocket probably perturb the rRNA structure, and thereby reduce drug binding with resulting resistance. Such a mechanism has been shown for some of the domain V mutations (Douthwaite and Aagaard, 1993) Presumably, the resistance conferred by Erm methyltransferase modification at A2058 (Skinner *et al*, 1983; Weisblum, 1995) functions in a similar manner. It will now be interesting to establish whether drug resistance caused by 23S rRNA changes in either the domain II or the domain V side of the binding pocket can be counteracted by drug derivatization that improves the interaction on the other side of the pocket.

Experimental procedures

Bacterial strain and growth conditions

E. coli strain DH1 (Sambrook *et al.*, 1989) was used throughout the study. Cell cultures for the preparation of ribosomal particles were grown in LB medium (Sambrook *et al*, 1989) The minimal inhibitory concentrations (MICs) of the different antibiotics that were required to stop cell growth were established on agar plates. Samples of 50 μl of a 10^{-5} dilution of overnight cultures were spread onto LB agar plates containing between 0 and 50 μg ml^{-1} erythromycin (in 10 μg ml^{-1} steps), or HMR 3004, 3647 or RU 66252 (Hoechst Marion Roussel) at between 0 and 10 μg ml^{-1} (in 1 μg ml^{-1} steps), or RU 56006 at between 0 and 300 μg ml^{-1} (in 50 μg ml^{-1} steps). The plates were incubated at 37°C and scored after 24 h. The MIC values given in the results indicate that no growth was detected at that drug concentration after 24 h incubation at 37°C, whereas cells grew at the next lower drug concentration, forming approximately the same number of colonies as on control plates with no drug.

Preparation of ribosomal particles

Cultures of DH1 were grown to an A_{450} of 0.4 in the absence of antibiotics. Cells were harvested by centrifugation, washed and resuspended in TMN buffer (50 mM Tris-HCl, pH 7.8, 10 mM $MgCl_2$, 100 mM NH_4Cl). The cells were lysed by sonication, and cell debris was removed by centrifugation. Ribosomes were pelleted from the cell supernatants by centrifugation at 20 000 r p m. for 16 h at 4°C in a Beckman Ti50 rotor. 70S ribosomes and subunits were fractionated as described previously (Douthwaite *et al.*, 1989).

Binding of antibiotics and probing of complexes

Ribosomes at 1–100 nM were incubated alone or with 1 nM to 1 mM antibiotics in 100 μl of 50 mM potassium cacodylate, pH 7 2, 10 mM $MgCl_2$, 100 mM NH_4Cl and 5 mM dithiothreitol (DTT) for 30 min at 37°C The antibiotics were in molar excess relative to ribosomes In all the qualitative probing experiments and the experiments to determine dissociation constants. In one series of experiments, aimed at determining the number of drug binding sites, drug concentrations of 1 nM to 1 μM were titrated to ribosomes at 100 nM. Ribosomes were probed at 37°C for 10 min with dimethyl sulphate (DMS) (2 μl of a 1:6 dilution in 96% ethanol) or with kethoxal [3 μl of a 66 mg ml^{-1} solution in 30% (v/v) ethanol]. DMS modifies the N-1 position of adenines and the N-3 of cytosines; kethoxal modifies the N-1 and N-2 positions in guanines. These chemical reagents have been shown previously to be two of the most versatile probes for detecting drug–RNA interactions (e.g. Moazed and

Table 3. Comparison with footprinting effects for drugs in other categories.

	Nucleotide positions in 23S rRNA					
Antibiotics	A752	A2058	A2059	A2062	A2451	G2505
HMR 3004 and 3647	P	P	P	E	–	P
RU 66252	P	P	P	E	–	P
RU 56006	–	P	P	e	ND	ND
Erythromycin	E	P	P	e	–	P
Carbomycin	–	p	p	P	P	P
Clindamycin	–	P	p	–	P	P
Vernamycin	P	e	–	P	p	P
Chloramphenicol	–	e	p	p	P	P

Footprinting patterns from comparable drug binding experiments Erythromycin and HMR derivatives (this study); carbomycin (Moazed and Noller, 1987) is a macrolide with a 16-member lactone ring; clindamycin (Douthwaite, 1992b) belongs to the lincosamide group; vernamycin (Moazed and Noller, 1987) is a streptogramin B antibiotic Puromycin showed no detectable footprint pattern (Moazed and Noller, 1987), even though this drug has been cross-linked to the peptidyl transferase centre (Cooperman *et al*, 1990) P, strong protection; p, partial protection; E, strongly enhanced; e, slightly enhancement; –, no change; ND, not determined.

Noller, 1987). Reactions were stopped (Stern *et al.*, 1988), and the rRNA was recovered from ribosomal particles by extracting twice with phenol, once with chloroform and precipitating with ethanol before redissolving in TE (10 mM Tris-HCl, pH 7.8, 1 mM EDTA).

Analysis of chemical footprinting by primer extension

The site of modification in the rRNA was analysed by primer extension with reverse transcriptase. The entire *E. coli* 23S rRNA structure was screened by a series of reverse transcriptase extensions using primers complementary to the sequences 228–245, 417–433, 617–635, 888–906, 1009–1026, 1169–1187, 1347–1363, 1510–1528, 1687–1703, 1906–22, 2099–2115, 2141–2157, 2275–2291, 2500–2515, 2677–2694, 2795–2812 and 2888–2904 (Noller, 1984). The 5'-[^{32}P]-end-labelled primers were extended with AMV reverse transcriptase (Life Sciences) as described by Stern *et al.* (1988). Extension products were run on 6% polyacrylamide/7 M urea gels alongside sequencing reactions performed on an unmodified rRNA template. Gels were autoradiographed and quantified by scanning with a Molecular Dynamics Storm 840 phosphor-imager.

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Issue of the Day

Overview of Issues Related to Medical Compliance with Implications for the Outpatient Management of Infectious Diseases

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Summary: Noncompliance with therapeutic drug regimens is a public health problem with major health and economic implications. Reported rates of noncompliance for all types of drugs range from 13% to 93% among adults and from 25% to 82% among children. In recent years, sophisticated techniques for evaluating noncompliance have evolved, as has our understanding of factors associated with noncompliance. A key factor is the prescribed dosing schedule for a drug. Studies indicate that there is a direct relationship between frequency of dose and compliance. A study of compliance with short-term regimens of oral antibiotic therapy found mean compliance rates of 80%, 69%, and 38% for administration once a day (QD), twice a day (BID), and three times a day (TID), respectively. Pharmacoeconomic analyses of dose-related compliance have demonstrated that significant savings can be achieved with QD dosing of antihypertensive medication. Although similar analyses have not been performed for drug regimens used in the treatment of infectious diseases that are usually treated on an outpatient basis, it is probable that comparable savings will be attained when economic analyses of dose/compliance relationships in short-term antibiotic therapy for such common disorders as sinusitis, pharyngitis, otitis media, urinary tract infections, and community-acquired pneumonia are undertaken. Key Words: Antibiotics, administration and dosage—Drug administration schedule—Drug monitoring—Health economics—Patient compliance.

Since the mid-1940s and the emergence of such medications as broad-spectrum antibiotics, antituberculosis drugs, and phenothiazine tranquilizers, the therapeutic impact of patient compliance and noncompliance has been a topic of increasing concern among health-care professionals (22,33).

Compliance with therapeutic drug regimens is often defined as the extent to which the time history of a patient's dosing corresponds to the prescribed treatment regimen (33). Noncompliance is known to have major health and economic implications. Many studies have associated noncompliance with increases in hospital admissions, length of stay, and health-care expenditures (28). Both undercompliance and overcompliance may have a direct effect on pharmaceutical development, as undetectable errors in medication administration during clinical trials may lead to an underestimation of the efficacy of the compound or to a high rate of adverse effects and drug toxicity (15). Undercompliance with oral antibiotic regimens may be associated with recurrent disease and the development of complications.

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whereas overcompliance may result in adverse effects such as nausea, vomiting, diarrhea, abdominal cramps, and, with longer-term administration, superinfection.

Patient compliance has become an especially important concern for children in light of today's increasing stress on selecting the most effective first-line therapies. At a time of growing emphasis upon the most efficient use of health-care professionals' time and the avoidance of the human and economic costs associated with preventable treatment failure, it is important for physicians to weigh the factors that have been demonstrated to enhance patient compliance when they are deciding which of the available agents to prescribe for the treatment of common infections.

This article summarizes reports of compliance patterns in adults and children, methods of evaluating compliance, consequences of noncompliance, and predictors of compliance. It reviews some particularly important investigations of the relationship between dosing schedules and patient compliance. Finally, it considers the economic implications of noncompliance, noting issues related to noncompliance with short-term oral antibiotic therapy and suggesting investigations that might be undertaken to determine the direct and indirect costs of noncompliance with typical drug regimens for infectious diseases that are normally treated on an outpatient basis.

COMPLIANCE PATTERNS IN ADULTS AND CHILDREN

Noncompliance with therapy is common. In a review of the literature, Bond and Hussar (5) found that rates of noncompliance among adults ranged from 13% to 93%, with an average rate of 40%. Rates in children are almost as high, with a reported range of 25% to 82% (1,23). Among children who are asymptomatic for a diagnosed condition, there is a greater than 50% chance that the course of treatment will not be completed (23). Extensive research has shown that antibiotics prescribed for an acute infection are rarely taken for the stipulated number of days (33). Noncompliance among children receiving oral penicillin for an acute illness has been reported to occur in 25%–75% of patients (1).

A typical instance of compliance patterns among children can be seen in a study undertaken by Bergman and Werner (3), who evaluated compliance with a 10-day, three-times-per-day (TID) regimen of oral penicillin in pediatric patients suspected to have streptococcal pharyngitis, acute otitis media, or skin infections throughout to be caused by streptococci. They found that more than half the patients had stopped taking the drug by the third day, 71% had stopped by day 6, and 82% had stopped by day 9.

METHODS OF EVALUATING COMPLIANCE

Although patient compliance has been a serious concern for more than four decades, the true magnitude of the problem has become evident as more accurate means of measuring compliance have become available (33). The ideal method of assessing compliance would measure accuracy of dose-taking and dose-timing with perfect sensitivity and specificity (5). While direct observation of patients taking their medication satisfies this definition, it is impractical. Accordingly, a number of direct and indirect methods for measuring compliance have been developed (Table 1). Although a significant body of literature addressing the relative value of the different techniques is gradually developing, reliable accuracy rates for these methods have yet to be established.

Direct assays to determine the presence of the drug are often said to be the most objective measures of compliance, but such measurements can also be misleading (1). Because patients tend to become more compliant when a visit to the physician is imminent, these assays have limited utility unless they are conducted with a marker compound that has a long half-life, such as phenobarbital or digoxin (5,25,33). Furthermore, since drug concentrations are affected by individual variations in pharmaco-

TABLE 1. *Common methods for evaluating compliance*

Indirect methods (1,5)
Self-report (17)
Patient interview (3,8,10,12,17)
Interpretation of therapeutic outcome (12)
Pill count (3,9,12,16,25)
Medication refill rate (17)
Computerized compliance monitors that record each medication container opening (e.g., Medication Event Monitoring System [MEMS] bottle cap) (8,9,12,16)
Direct methods (1,5)
Biological markers (e.g., drug serum concentrations, measurement of glycosylated hemoglobin in paients with diabetes mellitus) (8,9,12)
Tracer compounds (e.g., low-dose administration of phenobarbital) (17,25)
Biological assays of body fluids (e.g., *Sarcina lutea* method for detection of penicillin in urine) (3,7)

kinetics, the timing of blood sampling may not coincide with measurable drug concentrations (9,17). In many cases, precise "normal" ranges for marker compounds are still being determined (25).

Although interviews and self-reports are common, easily implemented methods of estimating compliance, comparison with the results of direct assays indicates that these indirect methods usually overestimate compliance, even when the interviewer is highly skilled or the self-report form carefully design (12). Pill counts may provide an inaccurate measure of compliance because they do not indicate whether medication was taken at prescribed intervals and because patients may discard their medication before a visit to the physician. In a study of antacid consumption by patients with ulcers, for example, pill counts indicated a 36% higher rate of compliance than did measurement of a tracer compound (17). In a study involving patients with type II diabetes mellitus in which compliance was monitored by both pill count and phenobarbital marker levels, pill count identified only 13% of the noncompliant individuals by phenobarbital levels (25).

The use of drug vials, boxes, and blister packs equipped with microcircuitry has made indirect monitoring of compliance increasingly accurate (8,16). The advent of these types of electronic container has enabled investigators to obtain a record of the date and time of each opening of the package and, thus, each opportunity for the patient to take the prescribed medication. Although the counting of each lid opening may exaggerate compliance, since it cannot verify whether the medication was actually taken or measure the size of the dose, comparative studies suggest that this method tends to be considerably more accurate than pill counts and most patient interviews (8,9,16,33).

CONSEQUENCES OF NONCOMPLIANCE

Noncompliance is a serious issue because it can be associated with treatment failure that may have serious and sometimes long-term effects on the patient's health (33). Furthermore, noncompliance-related treatment failure may foster heightened noncompliance when the patient is subsequently treated with an extended course of the first medication or with a different drug (9). In addition, an apparent treatment failure may be attributed to poor drug efficacy when the actual cause is noncompliance. The economic consequences of noncompliance are only beginning to be methodically explored, but it is clear that the associated costs greatly exceed the cost of an additional course of treatment with the original drug or even with a more costly agent (14,33).

Compliance with treatment regimens for oral antibiotics has been shown to be particularly poor. As Urquhart (33) has explained, this probably occurs because fever and other symptoms of an acute infection often subside before the pathogens have been eradicated. A compliance rate of 57% is often cited as typical for short-term antibiotic therapy (20). In addition to its influence on the therapeutic outcome in an individual patient, inadequate antibiotic therapy may also have broader ramifications, such as encouraging the development of resistant strains of organisms (23,33).

As the literature indicates, not all failures to comply with antibiotic treatment regimens are clinically significant (6,17,26,27). Nevertheless, evidence exists to suggest that noncompliance can be associated with significant health risks and concomitant expense. A case in point is the work of Daschner and Marget (13), who studied 105 pediatric patients with a history of recurrent urinary tract infections who were receiving long-term antibiotic therapy (for an average of 24.3 months) to reduce the frequency of infections. Patients were prescribed a TID regimen of one of the following antibiotics: ampicillin, cephalexin, chloramphenicol, gentamicin, nalidixic acid, nitrofurantoin, or sulfamethoxazole. The investigators found that the 30 children (32.2%) who complied with the treatment regimen had an average of 3.9 infections per year. The 36 patient (48.7%) who showed limited compliance averaged 4.8 infections per year, whereas the 27 (19.1%) who failed to take medication had an average of 7.2 infections per year.

Similarly, Jordan (21) compared compliance and failure rates in male patients with gonococcal urethritis who were treated with tetracycline 500 mg four times a day (QID) for 5 days or doxycycline 300 mg stat and 200 mg once a day (QD) for 4 days. Of the 214 patients who received tetracycline, 82 (38%) were found to be noncompliant; of the noncompliant patients, 15% were culture-positive 7 days after the start of treatment, whereas 0.8% of compliant patients were culture-positive. Of the 158 patients who received doxycycline, 34 (21%) were noncompliant; of those patients, 3% remained culture-positive 7 days after the start of treatment, whereas 0% of compliant patients failed treatment.

In view of the potentially severe complications of streptococcal pharyngitis, Green et al. (18) investigated the relationship between noncompliance and recurrence rate in 222 children with a suspected diagnosis of streptococcal pharyngitis. Patients were prescribed a 10-day course of therapy with penicillin given twice a day (BID) (body weight <80 lb) or TID (body weight ≥80 lb). Compliance was evaluated on day 9 by means of the *Sarcina lutea* urine culture method; of the 114 assessable patients, 83 (73%) were judged to have been compliant and 31 (27%) were judged noncompliant. When throat cultures were taken at 3 weeks, 32% of the noncompliant patients had positive cultures for beta-hemolytic streptococci, whereas only 12% of compliant patients had positive cultures. Thus the data show a 1 in 8.3 chance of recurrence in compliant patients and a 1 in 3 chance among those who did not comply with the treatment program.

OVERVIEW OF PREDICTORS ASSOCIATED WITH COMPLIANCE

Research has consistently shown that, although they are aware that failure to comply with treatment programs is a significant public health problem, physicians are poor predictors of which patients will prove to be noncompliant (7,17). Accordingly, many studies have been undertaken to identify the factors most commonly associated with compliance among adults and children (4,10,11,20). As summarized in Table 2, compliance in adults involves attitudes and behaviors of the prescribing physician, the nature of the disorder being treated, the available treatment regimens for the condition, the characteristics of the patient, and the patient's perceptions about the severity of the illness and the acceptability of the treatment regimen. Although many of the factors that affect compliance among adults also influence compliance in children, who generally receive medication from their parents, additional predictors of compliance have been defined for pediatric populations (Table 2).

COMPLIANCE AND DOSAGE FREQUENCY

Duration and frequency of treatment have been shown to be important factors in patient compliance (5,10,11,17,20). Patients are more likely to be compliant with a short course of drug therapy than with prolonged treatment. In both acute and long-term pharmacotherapy, patients are more likely to achieve acceptable levels of compliance with drugs that must be taken once or twice a day than with those that must be taken three or four times a day. Many studies have also shown that compliance increases with once-daily as opposed to twice-daily dosing, though the observed differences between these regimens have not always been statistically significant (12,16,19,25).

An extensive review of compliance and medication dosing by Greenberg (19) included more than 100 published papers and book chapters. Reports of QD dosing reflected a range of 42%–93% compliance, with a mean of 73% ± 6%; the range for BID dosing was 50%–94%, with a mean of 70% ± 6%; that for TID dosing was 18%–89%, with a mean of 52% ± 7%; and that for QID dosing was 11%–66%, with a mean of 42%±5%.

An important investigation that demonstrates the relationship between patient compliance and daily dose frequency is that of Eisen et al. (16). In that study, researchers evaluated the compliance of 105 patients who were receiving antihypertensive medication using data obtained from microprocessor-equipped pill containers that recorded the date and time of medication removal. Compliance was 59.0% for a TID regimen, 74.9% for a BID regimen, and 83.6% for a QD regimen. On the basis of these results, the investigators suggested that probably the simplest and single most important action that health-care providers can take to improve compliance is to select medications that permit the lowest possible daily dose frequency.

In another study that utilized microprocessor-equipped medication containers, Cramer et al. (12) evaluated patient compliance with antiepileptic medications prescribed in frequencies of one to four times per day. Compliance was 87% for a QD regimen, 81% for a BID regimen, 77% for a TID regimen, and 39% for a QID regimen.

Pullar et al. (25) used low-dose phenobarbital as a pharmacological indicator to compare compliance with oral hypoglycemic drugs to be taken once, twice, or three times per day in 179 patients with type II diabetes mellitus. Mean (±SD) compliance by tablet count was 100.4% ± 9.3% for QD dosing, 95.3% ± 14.5% for BID dosing, and 95.2% ± 10% for TID dosing. However, analysis of phenobarbital level/dose ratios (LDRs) showed a very different picture of patient compliance. By this method of evaluation, compliance rates were 63% for QD dosing, 57.2% for BID dosing, and 36.6% for TID dosing.

TABLE 2. *Major factors associated with patient compliance with therapeutic drug regimens in adults and children*

Factor associated with compliance	Reported in adults	Reported in children
Physician characteristics		
Long-term relationship with patient	X (4,20)	X (1,7,23)
Reasonably young, in practice for a comparatively short time	X (10)	—
Patient/parent characteristics		
Not a child, an adolescent, or an elderly person	X (4,20)	X (4,20)
Without chronic illness or disability	X (4,5)	X (1)
Presence of clearly delineated or serious symptoms that disrupt normal routines	X (4,5)	X (1,3,7,23)
Presence of family support	X (4,17)	X (23)
Absence of a risk-taking, obsessional, paranoid, or hypochondriacal personality	X (4)	—
Possession of intact mental faculities	X (20)	—
Employed	X (10)	—
Characteristics of treatment regimen		
Low daily dosage frequency (QD or BID)	X (5,9–11,14,19,20,25)	X (1,19,
Dosage that can be tailored to patient's schedule	X (5,10,17,20)	X (1,20,23)
Regimen not unusually complex	X (4,5,17,20)	X (1,23)
Prolonged course of treatment not required	X (5,10,17,20)	X (1)
Therapy not unusually costly	X (5,17,20)	—
Palatability of liquid or chewable formulations; tablets easily swallowed	—	X (1,4,23)
Associated with low incidence of serious adverse effects	X (4)	—
Physician attitudes and behaviors		
Displays empathetic behavior	X (17)	X (1,4,23)
Meets patient's/parent's expectations of the medical visit	X (20)	X (1,23)
Provides extensive information about the nature of the illness, purpose of the medication, and potential side effects	X (5,17,20)	X (1,20,23
Gives explicit instructions about how and when to take the medication	X (5,17)	X (23)
Explains the risks associated with noncompliance	X (4)	—
Reinforces oral instructions with written materials, such as medication cards or follow-up telephone calls	X (5,17,20)	X (3,23)
Perceives the mother of a pediatric patient as responsible, reliable, and intelligent	—	X (7)
Patient/parent attitudes and behaviors		
Believes that the disorder is serious or potentially serious	X (4,5,20)	X (1,7,23)
Believes that drug therapy will alleviate the condition	X (4,5,20)	—
Has a positive attitude toward physicians and the health-care system	X (17)	—
Feels satisfied with initial physician visit	X (17)	X (1,4,23)
Sees self as an active member of the team involved in his or her care	X (5,20)	—
Thinks that medication-related adverse effects are tolerable	X (4,5)	—
Does not display assertiveness, anger, or unfriendliness during physician visit	X (10)	—

In two reports of a multicenter study of the factors that lead to noncompliance with short-term antibiotic therapy, Cockburn et al. (10,11) investigated the behavior of 232 adult patients treated for community-acquired infections. Of the 148 patients for whom sufficient data were available for a complete analysis, 111 (75%) were classified as compliers and 37 (25%) as noncompliers. Compliance rates were 80% for the QD regimen, 69% for the BID regimen, and 38% for the TID regimen. Further statistical analysis undertaken at the conclusion of patient interviews indicated that the variables that had the strongest association with compliance were the physician's years in general practice, patient's employment state, dosage schedule, and the patient's health status. Logistic regression indicated that an increase in frequency of one dose per day increased by 72% the probability of noncompliance. In discussing the implications of that finding, the investigators suggested that the dosage schedules of any alternative treatments should always be noted when the physician is considering the most appropriate treatment for a patient and that the least complex treatment should be prescribed when there is no therapeutic difference between two treatments.

ECONOMIC IMPLICATIONS OF NONCOMPLIANCE

Pharmacoeconomic research has established that the cost of noncompliance is staggeringly high. Bond and Hussar (5) pointed out that noncompliance is associated with an increase in clinic and

emergency room visits, hospital admissions, and admissions to nursing homes. They also noted that 125,000 deaths and several hundred thousand hospitalizations per year have been attributed to noncompliance among patients with cardiovascular disease and that in 1984 the U.S. Chamber of Commerce estimated the annual cost of treating noncompliance-related problems to be $13–$15 billion.

Several recent studies have addressed the economic implications of dosage-related compliance in patients with hypertension. Skaer et al. (31) undertook a 1-year retrospective analysis to determine the economic utility of providing prescription coverage for the sustained-release (SR) formulation of the calcium channel antagonist verapamil under the Florida Medicaid program. The study population comprised 274 ambulatory patients with a diagnosis of hypertension who had been prescribed either the SR or immediate-release (IR) formulation of verapamil.

Multivariate regression analysis was used to discern the incremental influence of selected demographic characteristics, use of medical services preceding the diagnosis of hypertension, and prescribed formulation of verapamil on health-care expenditures 1 year postdiagnosis. As part of the multivariate analysis, a Medication Possession Ratio (MPR) was calculated for each patient. The MPR was defined as the number of days' supply of medication obtained throughout the 360-day postperiod. Thus the optimal outcome would result in a ratio of 1:1 (a 360-day supply of medication obtained over a 360-day period); a less desirable outcome would be a ratio of less than 1:1. It was found that patients who had been prescribed the SR formulation achieved a significant ($p \leq 0.05$) increase in the MPR of 0.87 % 0.13 in contrast to patients who were prescribed the IR formulation (0.56 ± 0.10). Administration of verapamil in the SR formulation was associated with a reduction of $110.14 ($p \leq 0.05$) in aggregate health-care expenditures during the study period. Although administration of the SR formulation was associated with an increase in expenditures for antihypertensive therapy ($117.83), it was also associated with reduced financial commitments for physician ($50.42), hospital ($153.61), and laboratory ($23.94) services (all $p \leq 0.05$).

In a related study of the costs associated with SR and IR formulations of verapamil among beneficiaries of South Carolina's Medicaid program, comparable savings were realized (29,32). Patients who had been prescribed the SR formulation achieved a significant ($p \leq 0.05$) increase in MPR of 0.72 ± 0.08 in contrast to patients who were prescribed the IR formulation (0.59 ± 0.13). Receipt of verapamil in the SR formulation was associated with a significant ($p \leq 0.05$) reduction in aggregate health-care expenditures of $182.49 per patient during the study period. Although administration of the SR formulation was associated with a significant increase in expenditures for antihypertensive therapy ($92.71, $p \leq 0.05$), it was also associated with reduced financial commitments for physician ($63.52), hospital ($173.96), and laboratory ($39.52, all $p \leq 0.05$) services.

To date, the economic implications of noncompliance with short-term antibiotic therapy have not been explored with the same thoroughness that has characterized the study of hypertension. As Davey and Parker (14) have pointed out, a full assessment of the cost-effectiveness of QD oral antibiotic therapy awaits a more complete definition of the costs of treatment failure. Some of the costs that should be examined in detail are presented in Table 3 (2, 14,15,24,30).

As noted in the survey of the consequences of noncompliance with oral antibiotic regimens presented previously in this review, Daschner and Marget (13) determined that among 105 pediatric patients with a history of recurrent urinary tract infections, those who were compliant with the treatment regimen (32.2%) had an average of 3.0 infections per year, those who showed limited compliance (48.7%) averaged 4.8 infections, and those who failed to take medication (19.1%) averaged 7.2 infections per year. Although this study did not include a pharmacoeconomic component, it is probable that the total costs of physician visits and antibiotic therapy were significantly higher for patients who demonstrated limited compliance or

TABLE 3. *Potential costs of treatment failure associated with short-term oral antibiotic therapy*

Use of another, potentially more expensive oral antibiotic for primary therapy
Use of additional support medication (e.g., bronchodilators)
Switch to parenteral antibiotic(s) administered at home
Hospitalization for parenteral antibiotic therapy
Additional diagnostic tests
Additional visits to primary-care physician
Travel to physician
Lost wages
Visits to physician specialist for long-term complications

See references 2,14,15,24,30.

noncompliance than for those who adhered to the treatment regimen. Similarly, in the study of the relationship between compliance and recurrence of streptococcal pharyngitis reported by Green et al. (18) it is likely that after the 3-week evaluation the total direct expenses of the 32% of noncompliant patients who continued to show positive cultures were significantly higher than those of the 88% of compliant patients whose cultures were negative.

It would now be appropriate to undertake a series of carefully controlled studies to establish the direct and indirect costs of noncompliance with therapeutic regimens involving QD, BID, TID, and QID dosing used to treat common infectious diseases normally treated on an outpatient basis. Such disorders might include bacterial sinusitis, community-acquired pneumonia, sinusitis, streptococcal pharyngitis, and urinary tract infections. Since some investigations of noncompliance have indicated that failure of initial therapy may lead to disillusionment and heightened noncompliance during subsequent courses of treatment, analyses of the economic consequences of recurrent cycles of noncompliance and treatment failure in patients with common infectious diseases should also be conducted (9).

CONCLUSION

A review of the medical literature indicates a direct relationship between less frequent dosing and improved patient compliance. Given the extent of noncompliance with therapeutic regimens and today's emphasis on the use of the most efficacious and cost-effective first-line therapies, a drug that requires the least frequent dosing should be prescribed whenever possible. It is probable that pharmacoeconomic analyses of short-term oral antibiotic therapy will demonstrate that significant savings are associated with QD dosing regimens. Controlled data evaluating the economic benefits associated with QD dosing are needed.

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Article

Trovafloxacin versus High-Dose Amoxicillin (1 g Three Times Daily) in the Treatment of Community-Acquired Bacterial Pneumonia

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Abstract Once-daily trovafloxacin 200 mg was compared with high-dose amoxicillin, 1 g three times daily, given for 7 to 10 days. At end of treatment (day 10), the response was clinically successful (cure + improvement) in 93% of 152 clinically evaluable trovafloxacin patients and in 89% of 160 amoxicillin patients. At study end (day 35), respective rates were 91% and 81% (95% confidence interval: 1.6, 17.6; $P=0.01$). In evaluable patients with positive baseline radiographs, 93% of trovafloxacin and 88% of amoxicillin patients demonstrated radiological resolution at end of treatment. *Streptococcus pneumoniae* and *Haemophilus influenzae* eradication rates were comparable at end of treatment in both treatment groups, but at study end *Streptococcus pneumoniae* eradication rates were higher in trovafloxacin patients (100% vs 81%). At study end, all four trovafloxacin patients with baseline penicillin-resistant *Streptococcus pneumoniae* were clinically cured with pathogen eradication, whereas two of five amoxicillin patients with baseline penicillin-resistant *Streptococcus pneumoniae* were clinical failures with pathogen persistence. For patients in whom no pathogen was identified, trovafloxacin was significantly more effective at end of treatment ($P=0.096$) and study end ($P=0.013$). Treatment-related adverse events were comparable; the most common were headache, vomiting and dizziness in trovafloxacin patients, and diarrhoea, headache and abdominal pain in amoxicillin patients.

Introduction

Treatment of bacterial community-acquired pneumonia continues to be complicated by the failure to define the cause in about one-half of patients [1–3]. An empirical framework for initial therapy of community-acquired pneumonia has been recommended by the British Thoracic Society [4], which recommends first-line treatment of community-acquired pneumonia with β-lactam/β-lactamase inhibitors. However, the Infectious Disease Society of America recently recommended macrolides or newer-generation fluoroquinolones for the added coverage of atypical pathogens. Thus, the treatment recommendations for community-acquired pneumonia differ, depending on the relative importance placed on specific pathogens.

For non-immunocompromised outpatients with community-acquired pneumonia without co-existing illnesses, the most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella* species and *Chlamydia pneumoniae* [5]. Although most outpatient instances of community-acquired pneumonia are caused by single pathogens, infections with more than one pathogen are common among patients requiring hospitalization; these pathogens include anaerobes and *Legionella* [6]. In patients with severe community-acquired pneumonia, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Legionella pneumophila* have been

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identified as the most common causative pathogens, with mortality rates of between 10% and 25% [7].

Trovafloxacin, a new-generation fluoroquinolone, has a broad spectrum of activity against gram-positive, gram-negative, anaerobic and atypical respiratory pathogens [8–14]. Due to trovafloxacin's excellent in vitro activity against all key respiratory tract pathogens, including potent activity against penicillin- and cephalosporin-resistant strains of *Streptococcus pneumoniae* [15–17], the present randomized, multicentre, double-blind study of patients with community-acquired pneumonia was undertaken. The study compared trovafloxacin 200 mg given orally once daily for 7–10 days with amoxicillin 1 g administered orally three times daily for 7–10 days, a treatment of choice in French consensus guidelines (Fourth Consensus Conference on Anti-infectious Therapy. Respiratory Tract Infections, Lille, 18 October 1991). The study was designed to enroll specifically patients likely to have bacterial pneumonia (*Streptococcus pneumoniae*, *Haemophilus influenzae*) by including those patients with lobar infiltrates, body temperature greater than 38 °C and a bronchopneumonia or lobar pneumonia pattern on baseline radiograph.

Materials and Methods

Between 5 July 1995 and 26 October 1996, 344 patients were randomized and 342 patients were treated in the study at 44 centres throughout Europe (France 83 patients, 18 centres; Italy 86 patients, 13 centres; Spain 31 patients, 4 centres; Netherlands 12 patients, 1 centre; Lithuania 2 patients, 1 centre), South Africa (90 patients, 6 centres) and Costa Rica (40 patients, 1 centre). Patients were eligible if they were 16 years of age, or older, with a medical history and clinical and radiological findings consistent with community-acquired bronchopneumonia or lobar pneumonia appropriate for oral therapy. Patients were required to have a new infiltrate on chest radiograph, body temperature higher than 38 °C, or evidence of fever (shivers/rigors) within the preceding 24 h. Patients were also required to have at least one of the following signs and symptoms: cough or increasing severity of coughing; acute changes in sputum; rales or evidence of pulmonary consolidation on auscultation; leucocytosis (blood leucocyte count >10 000/mm^3 or >15% bands); or acute (≤24 h) onset of signs and symptoms of pneumonia.

Patients were excluded if they developed pneumonia while hospitalized, were treated with systemic antibiotics for at least 24 h within 72 h prior to the baseline visit, or had pneumonia requiring initial intravenous antibiotic therapy or requiring antibiotic therapy for longer than 10 days. Patients were excluded if they were pregnant, breast-feeding, had acquired immunodeficiency syndrome (patients could be HIV-positive) or suspected *Pneumocystis carinii* pneumonia, cavitary lung disease, known lung cancer, aspiration pneumonia, cystic fibrosis, or a high probability of an atypical pneumonia. Also excluded were patients with neutropenia, those undergoing immunosuppressive therapy, or those having significant gastrointestinal disease that may have affected study drug absorption. Individuals with a history of epilepsy, seizure, or recent drug or alcohol abuse were excluded as well. Written informed consent was obtained from all patients, and the study was approved by the Ethics Committee of all participating centres.

Patients were randomly assigned to receive, in a double-blind, double-dummy manner, either trovafloxacin 200 mg once daily or amoxicillin 1 g three times daily for 7–10 days. Blinding was maintained by providing all drugs in blister packs, with matching placebo tablets for patients assigned to trovafloxacin treatment. All medications were taken orally without regard to food intake. On days 1, 4, 10 (end of treatment) and 35 (end of study), clinical signs and symptoms were assessed, chest radiographs (posterior-anterior and lateral views) were performed (except for day 4). Freshly expectorated purulent sputum samples were examined macroscopically for consistency and colour, and microscopically (presence of >25 polymorphonuclear leucocytes and 10 squamous cells per low-power field of Gram-stained specimen). For patients who were unable to provide a satisfactory specimen of expectorated sputum, induction of sputum was carried out with nebulized saline or physiotherapy. If unsatisfactory, other lower respiratory secretions (transtracheal aspirate, bronchial brushings or biopsy material, obtained by bronchoscopy) were evaluated. Blood samples were also obtained from all patients. Susceptibility testing was performed by disk microdiffusion and broth microdilution at a central laboratory. Tentative criteria for susceptibility of trovafloxacin were based on projections from pharmacokinetic data and in vitro susceptibility testing at a central laboratory; NCCLS criteria were applied for amoxicillin susceptibility testing. Pretreatment serum samples were tested at a central laboratory for antibodies to *Mycoplasma pneumoniae*, *Chlamydia psittaci* and *Chlamydia pneumoniae*. Urine samples were tested for *Legionella* antigen. A fourfold or greater rise in titre was taken as evidence of baseline pathogen.

In addition, standard panels of haematology, blood chemistry, culture and urinalysis were performed at each visit. Healthcare utilization (concomitant medications, diagnostic and therapeutic procedures) was documented at each visit.

The primary efficacy endpoints were clinical and bacteriological responses at end of treatment. Clinical response was based on resolution or improvement of radiological findings; clinical signs of infection, such as fever, purulent sputum production, dyspnoea, cough and leucocytosis; and the patient's general physical condition. Bacteriological response was based on the presence or absence of baseline pathogens. The secondary efficacy endpoint was bacteriological response at study end. Clinical outcomes were defined as follows: cure – resolution of signs and symptoms of pneumonia, improved or resolved findings on chest radiograph, and no need for further antibiotic therapy; improvement – resolution of fever and improvement of other signs and symptoms, improvement or resolution of chest radiograph findings, and no further need for antibiotic therapy; failure – lack of resolution of chest radiograph findings, signs and symptoms, and/or requirement for additional antibiotics for inadequate response; relapse – clinical cure or improvement at treatment end with failure at a subsequent visit, or clinical cure or improvement at treatment end but receipt of additional antibiotic therapy for the primary disease before study end. Clinical success included clinical outcomes of cure and improvement, and clinical failure included failure and relapse.

Bacteriological response was based on the presence or absence of baseline pathogens at the end of the treatment period and at the end of the study, and were defined as follows: eradication – follow-up cultures with no growth of baseline pathogen; presumed eradication – clinical success with no follow-up culture material obtained; persistence – baseline pathogen present in any post-therapy culture; presumed persistence – clinical failure with no follow-up culture material obtained; relapse – reappearance of the baseline pathogen at the end of the study after a negative culture at the end of treatment; colonization – appearance of any organism post-baseline from the site of infection not associated with signs and symptoms of active infection and not requiring antibiotic therapy. The presence of atypical pathogens was defined by a fourfold serological rise or a positive urinary antigen

for *Legionella*. Eradication was presumed if there was an improvement in clinical symptoms.

For treatment group comparisons, 95% confidence intervals (CI) for differences in clinical success rates (cure and improvement) were calculated using the normal approximation method. The Cochran-Mantel-Haenszel test, controlling for differences between centres, was also performed. Since similar clinical and bacteriological results were observed for both the intent-to-treat and evaluable cohorts, only data from the evaluable patients are reported here. Descriptive statistics were compiled for healthcare utilization data, using the intent-to-treat population. Safety results for all treated patients, including adverse events, laboratory abnormalities and recording of vital signs, were summarized using descriptive statistics.

Results

Patient age, sex, race and risk factors for all treated patients were comparable in both treatment groups (Table 1). The mean ages of both males and females were 52 years, and approximately 30% of patients were smokers. Approximately 17% of patients had bilateral pneumonia, 24% had chronic obstructive pulmonary disease and 75% were hospitalized. All evaluable patients had a positive radiograph, although in seven trovafloxacin patients and in six in the amoxicillin group, this was not obtained 1 day before the initiation of treatment. Among clinically evaluable patients with baseline chest radiograph, 121 (79%) in the trovafloxacin group and 128 (80%) in the amoxicillin group had unilateral abnormalities, and 25 (16%) in the trovafloxacin group and 29 (18%) in the amoxicillin group had bilateral abnormalities (Table 2). Each group had a similar distribution of the signs and symptoms of pneumonia (Table 3); overall, the majority of patients had moderate or severe signs and symptoms. In both treatment groups, median duration from the time of the primary diagnosis to the time of treatment was 5.3 days, and median duration of treatment was 10 days.

Of the 342 treated patients, 314 (92%) patients (153 trovafloxacin, 161 amoxicillin) were clinically evaluable, and 335 were included in the intent-to-treat analyses (166 trovafloxacin, 169 amoxicillin). The most common reasons for exclusion from the evaluable cohort clinical analyses (all exclusions were performed prior to breaking the blind) were inappropriate diagnosis at baseline [eight trovafloxacin, one amoxicillin):

Table 1 Demographic characteristics and smoking history of patients

	Trovafloxacin ($n=173$)	Amoxicillin ($n=169$)
Gender		
Male	64%	67%
Female	36%	33%
Age (in years)		
Mean	52.4	52.2
Range	16–90	16–92
Race		
White	65%	62%
Black	18%	22%
Other	17%	16%
Risk factors		
Hospitalized	75%	75%
≥65-years-old	35%	31%
Smoker	31%	28%
Bilateral pneumonia	18%	19%
COPD	23%	25%
Asthma	9%	10%
Congestive heart failure	5%	5%
Diabetes mellitus	8%	4%
Pneumococcal bacteraemia	3%	2%

COPD, chronic obstructive pulmonary disease

Table 2 Radiographic results of all patients at baseline

	Trovafloxacin ($n=153$)	Amoxicillin ($n=161$)
Unilateral abnormalities	121 (79%)	128 (80%)
Consolidation	115 (75%)	111 (69%)
Bilateral abnormalities	25 (16%)	29 (18%)
Interstitial	23 (16%)	28 (17%)
Abnormalities in ≥3 lobes	5 (3%)	6 (4%)
Mean number of lobes involved	1.2	1.2

Table 3 Baseline, end of treatment and end of study signs and symptoms in clinically evaluable patients

Sign/symptom[a]	Trovafloxacin ($n=153$)			Amoxicillin ($n=161$)		
	Baseline	End of treatment	End of study	Baseline	End of treatment	End of study
Dyspnoea	79%	23%	11%	76%	28%	21%
Fever	70%	3%	<1%	64%	1%	<1%
Chills/rigors	74%	3%	<1%	73%	4%	1%
Pleuritic chest pain	63%	12%	5%	66%	17%	6%
Cough	97%	47%	20%	96%	56%	30%
Increased sputum volume	72%	23%	9%	75%	28%	11%
Focal abnormal ausculatory findings	86%	24%	4%	90%	22%	5%
Diffuse abnormal ausculatory findings	30%	11%	7%	22%	9%	11%

[a] Not all subjects were evaluated for all signs and symptoms

lung cancer (four patients) and pulmonary tuberculosis (five patients)]; randomized but not treated or no assessments in evaluable windows (five trovafloxacin, three amoxicillin); insufficient therapy (four trovafloxacin, three amoxicillin); and use of prior antibiotics or concomitant antibiotics for intercurrent illnesses unrelated to community-acquired pneumonia (seven trovafloxacin, five amoxicillin). At the end of treatment, 157 (73 trovafloxacin, 84 amoxicillin) of the clinically evaluable patients were bacteriologically evaluable. Patients could have more than one reason for exclusion from the analysis of efficacy. Treatment was discontinued due to lack of efficacy in 8 (5%) trovafloxacin and in 13 (8%) amoxicillin patients.

Clinical Response. At treatment end, a successful clinical response was reported for 144/152 (93%) trovafloxacin- and 142/160 (89%) amoxicillin-treated patients (95% CI: −2.4, 10.4; Table 4). At study end, a successful clinical response was reported for 125/138 (91%) trovafloxacin- and 119/147 (81%) amoxicillin-treated patients (95% CI: 1.6, 17.6; $P=0.01$). At this same period, 11 (8%) patients receiving trovafloxacin failed treatment and 2 (1%) relapsed, whereas 24 (16%) amoxicillin patients failed treatment and 4 (3%) relapsed. Most patients in both groups showed improvement or complete resolution of baseline radiograph findings at the end of treatment (93% trovafloxacin, 89% amoxicillin) and at study end (96% trovafloxacin, 94% amoxicillin). Incidences of other signs and symptoms at treatment and study end are summarized in Table 3.

Bacteriological Response. Among bacteriologically-evaluable patients, eradication rates for the most frequently isolated baseline pathogens are found in Table 5. Eradication rates for *Streptococcus pneumoniae* [20/20 (100%) with trovafloxacin, 22/24 (92%) with amoxicillin] and *Haemophilus influenzae* [17/17 (100%) with trovafloxacin, 15/17 (88%) with amoxicillin] were comparable at end of treatment. However, at study end, a trend towards a higher eradication rate for *Streptococcus pneumoniae* in the trovafloxacin group [20/20 (100%)] was evident, compared with the amoxicillin group [17/21 (81%)] (95% CI: 2.3, 35.8). No persistence of *Streptococcus pneumoniae* or *Haemophilus influenzae* was apparent in trovafloxacin patients at the end of treatment or end of study, whereas three patients in the amoxicillin group demonstrated persistence of these pathogens. In the clinically evaluable treatment group, colonizing organisms were isolated from 13 (8%) patients who received trovafloxacin and

Table 4 Clinical response in evaluable patients

Response	No. (%) of patients					
	End of treatment (day 10)			End of study (day 35)		
	Trovafloxacin ($n=152$)	Amoxicillin ($n=160$)	95% CI	Trovafloxacin ($n=138$)	Amoxicillin ($n=147$)	95% CI
Success (cure and improvement)	141 (93)	142 (89)	(−2.4, 10.4)	125 (91)*	119 (81)	(1.6, 17.6)
Cure	87 (57)	85 (53)		122 (88)	115 (78)	
Improvement	54 (36)	57 (36)		3 (2)	4 (3)	
Failure	11 (7)	18 (11)		11 (8)	24 (16)	
Relapse				2 (1)	4 (3)	

* $P=0.01$ versus amoxicillin

Table 5 Eradication rates for the most frequently isolated baseline pathogens

Pathogen	No. (%) of pathogens[a]			
	End of treatment		End of study	
	Trovafloxacin	Amoxicillin	Trovafloxacin	Amoxicillin
Streptococcus pneumoniae	20/20 (100)	22/24 (92)	20/20 (100)	17/21 (81)
Haemophilus influenzae	17/17 (100)	15/17 (88)	14/15 (93)	14/16 (88)
Klebsiella pneumoniae	5/5 (100)	1/3	5/5 (100)	1/3
Chlamydia pneumoniae[b]	18/22 (82)	24/26 (92)	17/22 (77)	24/26 (92)
Mycoplasma pneumoniae[b]	14/15 (93)	14/15 (93)	15/16 (94)	12/14 (86)
Legionella pneumophila	5/5 (100)	3/6 (50)	6/6 (100)	3/6 (50)
Chlamydia psittaci[b]	2/2	1/1	2/2	1/1
Total	81/86 (94)	80/92 (90)	79/86 (92)	72/87 (83)

[a] Percentage not calculated when number of patients less than five
[b] Eradication presumed based on clinical response

Table 6 Clinical success at study end by baseline pathogen for clinically and bacteriologically evaluable patients

	No. (%) of patients	
	Trovafloxacin ($n=69$)	Amoxicillin ($n=77$)
Streptococcus pneumoniae	20 (95)	21 (86)
Haemophilus influenzae	15 (100)	16 (88)
Mycoplasma pneumoniae	16 (94)	14 (86)
Chlamydia pneumoniae	22 (77)	26 (92)
Legionella pneumophila	6 (100)	6 (50)

from 33 (20%) patients who received amoxicillin. The majority of organisms were *Haemophilus* species (5 trovafloxacin, 22 amoxicillin).

In the bacteriological intent-to-treat population, all four trovafloxacin patients with penicillin-resistant *Streptococcus pneumoniae* [minimum inhibitory concentration (MIC) ≥ 1 mg/l] at baseline were classified as clinically cured at study end with bacteriological eradication or presumed eradication. In the amoxicillin group at study end, two of five patients with penicillin-resistant *Streptococcus pneumoniae* at baseline had a clinical failure and a bacteriological outcome of persistence. Eradication rates for *Mycoplasma pneumoniae* were comparable in both treatment groups, although a trend towards a high eradication rate for *Chlamydia pneumoniae* was apparent in the amoxicillin group. At both end of treatment and study end, 100% of trovafloxacin patients and 50% of amoxicillin patients with *Legionella pneumophila* had an outcome of bacteriological eradication (Table 5).

Clinical success by baseline pathogen for bacteriologically evaluable patients is shown in Table 6. For *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* and *Legionella pneumoniae,* there were trends towards improved clinical response in the patients treated with trovafloxacin. For *Chlamydia pneumoniae*, a non-significant trend towards improved clinical response favoured those patients treated with amoxicillin.

For patients in whom a pathogen was not identified, there was a statistically significant clinical difference in favour of trovafloxacin at end of treatment ($P=0.096$) and study end ($P=0.013$).

Eight treated patients (four trovafloxacin, four amoxicillin) had positive blood cultures of *Streptococcus pneumoniae* with at least one follow-up culture, but no *Haemophilus influenzae* bacteraemia was detected. All of these patients had a clinical response of cure and a bacterial response of eradication. Two of the patients treated with trovafloxacin had penicillin-resistant *Streptococcus pneumoniae* (MIC = 0.5 and 0.12 mg/l).

Healthcare Utilization. Among patients receiving concomitant medications, 26 (16%) treated with trovafloxacin received 44 different systemic antibiotics for a total of 402 treatment days (median, 7.5 days) compared with 39 (23%) patients treated with amoxicillin, who received 64 different systemic antibiotics for a total of 656 days (median, 8 days). Therapeutic procedures were performed in 39 (24%) trovafloxacin patients and 44 (26%) patients given amoxicillin. The most common procedures were respiratory therapy or nebulizer treatments, which were used 12 times in the trovafloxacin group (total, 118 days; median, six days) and 13 times in the amoxicillin group (total, 209 days; median, 12 days).

Safety. Treatment-related adverse events were reported by 29 (17%) patients receiving trovafloxacin and 18 (11%) of those receiving amoxicillin. The majority of events were of mild or moderate intensity. In the trovafloxacin group, the most frequently reported treatment-related adverse events were headache (4%), vomiting (3%) and dizziness (3%). In the amoxicillin group, abdominal pain (2%), diarrhoea (2%) and headache (2%) were the most frequent.

Serious adverse events (hospitalization, prolongation of hospitalization, cancer and life-threatening events) were recorded for 44 patients (23 trovafloxacin, 21 amoxicillin) between day 0 and day 35 of the study. No patient had a serious adverse event considered by the investigators to be related to the study medication. Eight trovafloxacin and two amoxicillin patients had serious adverse events related to their baseline conditions of tuberculosis, *Pneumocystis carinii* pneumonia, or lung cancer: 15 trovafloxacin and 19 amoxicillin patients were hospitalized or had prolonged hospitalization related to their pneumonia. Seven patients (four trovafloxacin, three amoxicillin) died between day 1 and day 35 of the study. None of the deaths was considered treatment related by the investigators. The causes of death for the four trovafloxacin patients were carcinoma of the lung (two patients), acute myocardial infarction (one patient) and pneumothorax with cardiac failure (one patient). The causes of death for the three amoxicillin patients were small-bowel perforation/respiratory insufficiency (one patient) and worsening of pneumonia with shock (two patients).

Premature Discontinuations. Discontinuation due to treatment-related adverse events occurred in four (2%) trovafloxacin patients (vomiting, dermatitis, gastrointestinal intolerance, dyspepsia) and one (1%) amoxicillin patient (diarrhoea). Eight (5%) patients treated with trovafloxacin discontinued treatment prematurely due to insufficient response compared with 13 (8%) in the amoxicillin treatment group. In four (2%) trovafloxacin and five (3%) amoxicillin patients, treatment discontinuations were unrelated to study drug (including non-treatment-related adverse events, loss to follow-up, protocol violation, withdrawal of consent).

Discussion

Pneumonia is a public health problem worldwide. Each year in the UK approximately 50 000 patients are admitted to hospital with community-acquired pneumonia [4]. Of the approximately three million people in the USA who develop community-acquired pneumonia each year, 500 000 require hospital admission and approximately 50 000 die [18]. Despite the steady flow of information afforded by extensive published data and treatment recommendations [4], alternative antibiotic treatment modalities for community-acquired pathogens are still needed [19, 20].

The present double-blind study has demonstrated, both clinically and bacteriologically, in predominantly hospitalized patients (75%), that trovafloxacin 200 mg administered orally once daily for 7–10 days was more effective, at the end of study, than amoxicillin 1 g administered orally three times daily for 7–10 days. At study end, a successful clinical response was reported for 91% of trovafloxacin and 81% of amoxicillin patients. At the end of treatment, a successful clinical response was determined in 93% of trovafloxacin and 89% of amoxicillin patients.

Trovafloxacin was highly effective against *Streptococcus pneumoniae*, including penicillin-resistant strains, *Haemophilus influenzae, Mycoplasma pneumoniae* and *Legionella pneumophila*. Eradication rates for *Streptococcus pneumoniae* and *Haemophilus influenzae* were comparable in both groups at the end of treatment, whereas at study end, patients treated with trovafloxacin demonstrated a trend towards a higher eradication rate for *Streptococcus pneumoniae* compared with amoxicillin patients. Of the four patients given trovafloxacin who had penicillin-resistant *Streptococcus pneumoniae* at baseline, each had favourable clinical and bacteriological outcomes. In the amoxicillin group, one of five patients with penicillin-resistant *Streptococcus pneumoniae* at baseline had a clinical outcome of failure and a bacteriological outcome of presumed persistence of the organism (because of the clinical failure) at study end. Another amoxicillin-treated patient with penicillin-resistant *Streptococcus pneumoniae* showed persistence of *Streptococcus pneumoniae* both at end of treatment and end of study, and was determined a clinical failure. The remaining three subjects had favourable clinical (cure or improvement) and bacteriological (eradication or presumed eradication) outcomes at the end of treatment and study. Other than infection with penicillin-resistant *Streptococcus pneumoniae*, no high-risk factors were identified in these patients.

Overall, despite similarities in the severity of baseline disease, treatment with other systemic antibiotics and non-pharmacological therapeutic procedures was less frequent in the trovafloxacin than the amoxicillin group. Thus, even when clinical and bacteriological efficacies are comparable, other factors – some of which have cost implications – may differentiate between medications.

Both treatments were well tolerated, and overall percentages of treatment-related adverse events were comparable. The most commonly reported treatment-related adverse events were headache, vomiting and dizziness in patients given trovafloxacin, and diarrhoea, headache and abdominal pain in the amoxicillin group.

Trovafloxacin, a new-generation fluoroquinolone, with its broad spectrum of activity and excellent pharmacokinetic properties, offers an attractive alternative in the empirical treatment of community-acquired pneumonia. The in vitro activity against *Streptococcus pneumoniae* (MIC_{90} 0.12 mg/l) is high, regardless of whether the strain is resistant to penicillin or a cephalosporin [15, 16]. *Haemophilus influenzae* (MIC_{90} 0.008 mg/l), another common pathogen in community-acquired pneumonia, is also highly susceptible to trovafloxacin [21]. In addition, trovafloxacin is active against *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae* (respective MIC_{90} 0.25 mg/l, $\leq$0.004 mg/l and 0.12 mg/l), the organisms implicated in atypical community-acquired pneumonia [12–14].

The possibility of resistance developing is a common problem with the excessive and inappropriate use of any antibiotic. A surveillance program (ARTEMIS) is under way to monitor worldwide susceptibilities of common pathogens to fluoroquinolones. Initial findings of this project are reported in this issue [22]. In vitro evidence suggests that trovafloxacin has a reduced potential compared with other agents (e.g. ciprofloxacin) to stimulate the fluoroquinolone resistance mechanism in *Streptococcus pneumoniae* [23], *Staphylococcus aureus* [24] and *Pseudomonas aeruginosa* [25].

The efficacy of an antibacterial agent is dependent not only on its activity against the infecting organism and its pharmacokinetic profile, but also on patient compliance. In a study by Eisen et al. [26], it was shown that compliance improved when frequency of dosing was reduced. Thus, trovafloxacin's once-daily dosing schedule particularly benefits elderly patients or those on multidrug regimens. In addition, from the perspective of potential drug–drug interactions with potential concomitant medications, trovafloxacin has no effect on plasma theophylline levels [27].

In conclusion, trovafloxacin's clinical efficacy, broad antimicrobial spectrum against the common (*Streptococcus pneumoniae* and *Haemophilus influenzae*) and less common (atypical) causative agents of community-acquired pneumonia, its efficacy against penicillin-resistant strains of *Streptococcus pneumoniae* and its

favourable pharmacokinetic profile support its use in the treatment of community-acquired pneumonia.

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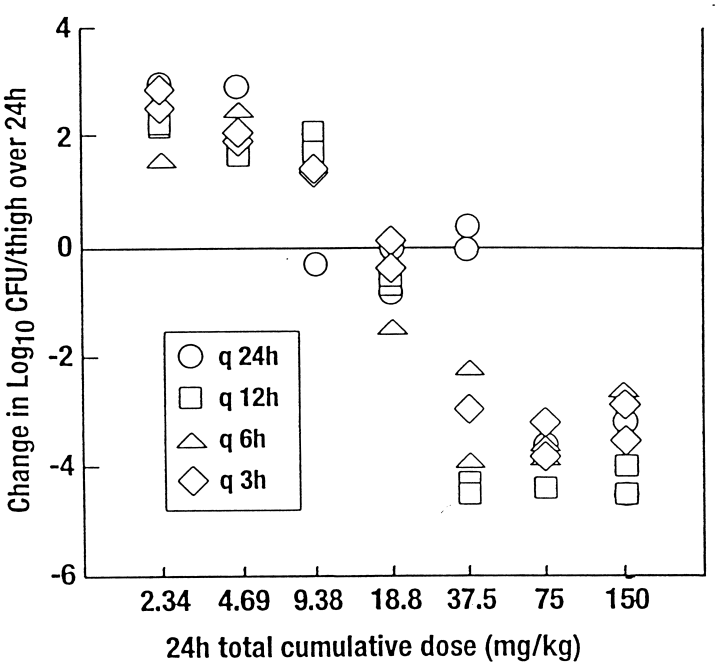
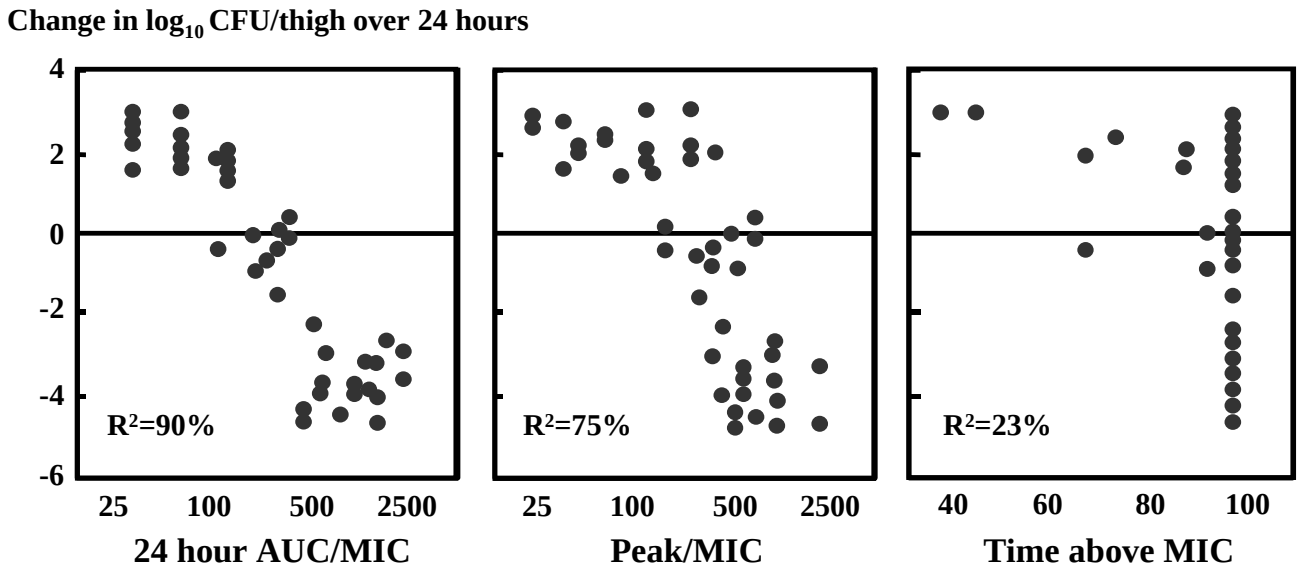
Appendix 2. Dose response

Dose-response curves for telithromycin given at different dosing intervals against *S. pneumoniae*



Relationship between efficacy and individual pharmacokinetic/pharmacodynamic parameters for total drug



Appendix 3. Schedule of efficacy assessments

Schedule of efficacy assessments

Indication Assessment/procedure	Pretherapy/ entry (Visit 1) Day 1	On-therapy (Visit 2) Days 3-5	End-of-therapy [a] (Visit 3) Days 11-13	Posttherapy/ TOC [b] (Visit 4) Days 14-21	Late posttherapy [c] (Visit 5) Days 31-36
Community-acquired pneumonia (CAP) (Studies 3000, 3001, 3006, 3009, 3009OL, ad 3010)					
Clinical assessments					
Infection-related signs and symptoms	X	X	X	X	X
Chest X-ray (PA & lateral views) [g]	X			X	
Clinical outcome				X	X
Bacteriological assessments [f]					
Gram stain [g]	X	X		X	
Respiratory secretion culture [g]	X	X		X	
Susceptibility test [g]	X	X		X	
Blood culture [h]	X				
Serology – atypical	X			X	X
PCR testing [d] – atypical	X				
Pharmacokinetic assessment [e, f]	X	X	X		

[a] Days 8-11 in Studies 3009 and 3009OL. Days 8-10 in Study 3010.
[b] TOC = test of cure. Visit 4 = Days 17-21 in CAP (Studies 3009OL and 3010), in acute sinusitis (Study 3011), and in tonsillitis/pharyngitis (Studies 3004 and 3008).
[c] CAP Study 3010 did not have a late posttherapy visit. AECB (Studies 3003 and 3007) and tonsillitis/pharyngitis (Studies 3004 and 3008) required that late posttherapy assessments were permitted via either telephone or at the study site. Visit 5 = Days 38-45 in tonsillitis/pharyngitis (Studies 3004 and 3008).
[d] PCR = polymerase chain reaction testing; performed in only in US protocols (Studies 3006 and 3009).
[e] Pharmacokinetic assessment was performed in all studies except Studies 3004 and 3009.
[f] Respiratory samples collected if obtainable.
[g] Performed at other visits only in cases of clinical deterioration and/or failure or at the investigator's discretion.
[h] In CAP (Studies 3000, 3001, 3006, and 3009), blood cultures were required at baseline. In AECB (Studies 3003 and 3007), blood cultures were only required at the baseline visit if the subject was febrile. Blood cultures were requested at subsequent visits if the subject had persistent fever or no clinical improvement.
[i] Performed only at Visit 1 and 2 in Study 3000.
[j] Sinus puncture obtained only at selected centers in Study 3005. In Study 3011, sinus puncture was performed at US sites only, sinus endoscopy was perfumed at non-US sites.
[k] Performed on paired GABHS isolates for subjects who had documented unsatisfactory bacteriological outcome.

Schedule of efficacy assessments (continued)

Indication Assessment/procedure	Pretherapy/ entry (Visit 1) Day 1	On-therapy (Visit 2) Days 3-5	End-of-therapy [a] (Visit 3) Days 11-13	Posttherapy/ TOC [b] (Visit 4) Days 14-21	Late posttherapy [c] (Visit 5) Days 31-36
Acute exacerbation of chronic bronchitis (AECB) (Studies 3003 and 3007)					
Clinical assessments					
Infection-related signs and symptoms	X	X	X	X	X
Chest X-ray (PA & lateral views) [g]	X				
Clinical outcome					
Bacteriological assessments					
Gram stain [g]	X			X	
Respiratory secretion culture [g]	X			X	
Susceptibility test [g]	X			X	
Blood culture [h]	X			X	
Serology – atypical	X				X
Pharmacokinetic assessment	X	X	X		

[a] Days 8-11 in Studies 3009 and 3009OL. Days 8-10 in Study 3010.
[b] TOC = test of cure. Visit 4 = Days 17-21 in CAP (Studies 3009OL and 3010), in acute sinusitis (Study 3011), and in tonsillitis/pharyngitis (Studies 3004 and 3008).
[c] CAP Study 3010 did not have a late posttherapy visit. AECB (Studies 3003 and 3007) and tonsillitis/pharyngitis (Studies 3004 and 3008) required that late posttherapy assessments were permitted via either telephone or at the study site. Visit 5 = Days 38-45 in tonsillitis/pharyngitis (Studies 3004 and 3008).
[d] PCR = polymerase chain reaction testing; performed in only in US protocols (Studies 3006 and 3009).
[e] Pharmacokinetic assessment was performed in all studies except Studies 3004 and 3009.
[f] Respiratory samples collected if obtainable.
[g] Performed at other visits only in cases of clinical deterioration and/or failure or at the investigator's discretion.
[h] In CAP (Studies 3000, 3001, 3006, and 3009), blood cultures were required at baseline. In AECB (Studies 3003 and 3007), blood cultures were only required at the baseline visit if the subject was febrile. Blood cultures were requested at subsequent visits if the subject had persistent fever or no clinical improvement.
[i] Performed only at Visit 1 and 2 in Study 3000.
[j] Sinus puncture obtained only at selected centers in Study 3005. In Study 3011, sinus puncture was performed at US sites only, sinus endoscopy was perfumed at non-US sites.
[k] Performed on paired GABHS isolates for subjects who had documented unsatisfactory bacteriological outcome.

Schedule of efficacy assessments (continued)

Indication Assessment/procedure	Pretherapy/ entry (Visit 1) Day 1	On-therapy (Visit 2) Days 3-5	End-of-therapy [a] (Visit 3) Days 11-13	Posttherapy/ TOC [b] (Visit 4) Days 14-21	Late posttherapy [c] (Visit 5) Days 31-36
Acute sinusitis (Studies 3002, 3005, and 3011)					
Clinical assessments					
Infection-related signs and symptoms	X	X	X	X	X
Sinus X-ray [g]	X			X	
Clinical outcome				X	X
Bacteriological assessments					
Sinus secretion culture [g, j]	X				
Susceptibility test [g, j]	X				
Pharmacokinetic assessment	X	X	X		

[a] Days 8-11 in Studies 3009 and 3009OL. Days 8-10 in Study 3010.
[b] TOC = test of cure. Visit 4 = Days 17-21 in CAP (Studies 3009OL and 3010), in acute sinusitis (Study 3011), and in tonsillitis/pharyngitis (Studies 3004 and 3008).
[c] CAP Study 3010 did not have a late posttherapy visit. AECB (Studies 3003 and 3007) and tonsillitis/pharyngitis (Studies 3004 and 3008) required that late posttherapy assessments were permitted via either telephone or at the study site. Visit 5 = Days 38-45 in tonsillitis/pharyngitis (Studies 3004 and 3008).
[d] PCR = polymerase chain reaction testing; performed in only in US protocols (Studies 3006 and 3009).
[e] Pharmacokinetic assessment was performed in all studies except Studies 3004 and 3009.
[f] Respiratory samples collected if obtainable.
[g] Performed at other visits only in cases of clinical deterioration and/or failure or at the investigator's discretion.
[h] In CAP (Studies 3000, 3001, 3006, and 3009), blood cultures were required at baseline. In AECB (Studies 3003 and 3007), blood cultures were only required at the baseline visit if the subject was febrile. Blood cultures were requested at subsequent visits if the subject had persistent fever or no clinical improvement.
[i] Performed only at Visit 1 and 2 in Study 3000.
[j] Sinus puncture obtained only at selected centers in Study 3005. In Study 3011, sinus puncture was performed at US sites only, sinus endoscopy was perfumed at non-US sites.
[k] Performed on paired GABHS isolates for subjects who had documented unsatisfactory bacteriological outcome.

Schedule of efficacy assessments (continued)

Indication Assessment/procedure	Pretherapy/ entry (Visit 1) Day 1	On-therapy (Visit 2) Days 3-5	End-of-therapy [a] (Visit 3) Days 11-13	Posttherapy/ TOC [b] (Visit 4) Days 14-21	Late posttherapy [c] (Visit 5) Days 31-36
Tonsillitis/pharyngitis (Studies 3004 and 3008)					
Clinical assessments					
Infection-related signs and symptoms	X	X	X	X	X
Clinical outcome				X	X
Bacteriological assessments					
Rapid Strep A test	X				
Throat culture [g]	X	X		X	X
Serotyping [k]	X	X		X	X
Susceptibility test	X	X		X	X
Pharmacokinetic assessment [e]	X	X	X		

[a] Days 8-11 in Studies 3009 and 3009OL. Days 8-10 in Study 3010.
[b] TOC = test of cure. Visit 4 = Days 17-21 in CAP (Studies 3009OL and 3010), in acute sinusitis (Study 3011), and in tonsillitis/pharyngitis (Studies 3004 and 3008).
[c] CAP Study 3010 did not have a late posttherapy visit. AECB (Studies 3003 and 3007) and tonsillitis/pharyngitis (Studies 3004 and 3008) required that late posttherapy assessments were permitted via either telephone or at the study site. Visit 5 = Days 38-45 in tonsillitis/pharyngitis (Studies 3004 and 3008).
[d] PCR = polymerase chain reaction testing; performed in only in US protocols (Studies 3006 and 3009).
[e] Pharmacokinetic assessment was performed in all studies except Studies 3004 and 3009.
[f] Respiratory samples collected if obtainable.
[g] Performed at other visits only in cases of clinical deterioration and/or failure or at the investigator's discretion.
[h] In CAP (Studies 3000, 3001, 3006, and 3009), blood cultures were required at baseline. In AECB (Studies 3003 and 3007), blood cultures were only required at the baseline visit if the subject was febrile. Blood cultures were requested at subsequent visits if the subject had persistent fever or no clinical improvement.
[i] Performed only at Visit 1 and 2 in Study 3000.
[j] Sinus puncture obtained only at selected centers in Study 3005. In Study 3011, sinus puncture was performed at US sites only, sinus endoscopy was perfumed at non-US sites.
[k] Performed on paired GABHS isolates for subjects who had documented unsatisfactory bacteriological outcome.

Appendix 4. ITT analyses

All indications: Clinical Outcome at posttherapy/TOC – ITT population

	Clinical cure						95% Confidence Intervals
	Telithromycin			Comparators			
	N	n	(%)	N	n	(%)	
CAP							
Study 3001	199	171	(85.9)	205	161	(78.5)	[-0.5; 15.3]
Study 3006	224	161	(71.9)	225	171	(76.0)	[-12.6; 4.4]
Study 3009	110	82	(74.5)	112	89	(79.5)	[-16.9; 7.0]
Study 3000	240	191	(79.6)				
Study 3009OL	221	182	(82.4)				
Study 3010	432	357	(82.6)				
AECB							
Study 3003	163	130	(79.8)	161	125	(77.6)	[-7.4; 11.6]
Study 3007	183	142	(77.6)	193	138	(71.5)	[-3.2; 15.4]
Acute sinusitis							
Study 3002 – 5 days	168	139	(82.7)				
– 10 days	168	147	(87.5)				[-13.0; 3.4]
Study 3005 – 5 days	245	160	(65.3)				[-5.8; 11.9]
– 10 days	257	177	(68.9)	252	157	(62.3)	[-2.1; 15.2]
Study 3011	260	211	(81.2)	125	89	(71.2)	[0.1; 19.8]
Tonsillitis/pharyngitis							
Study 3004	198	170	(85.9)	197	169	(85.8)	[-6.5; 8.4]
Study 3008	232	193	(83.2)	231	192	(83.1)	[-7.1; 7.3]

Appendix 5. Number of telithromycin-treated subjects in populations by study

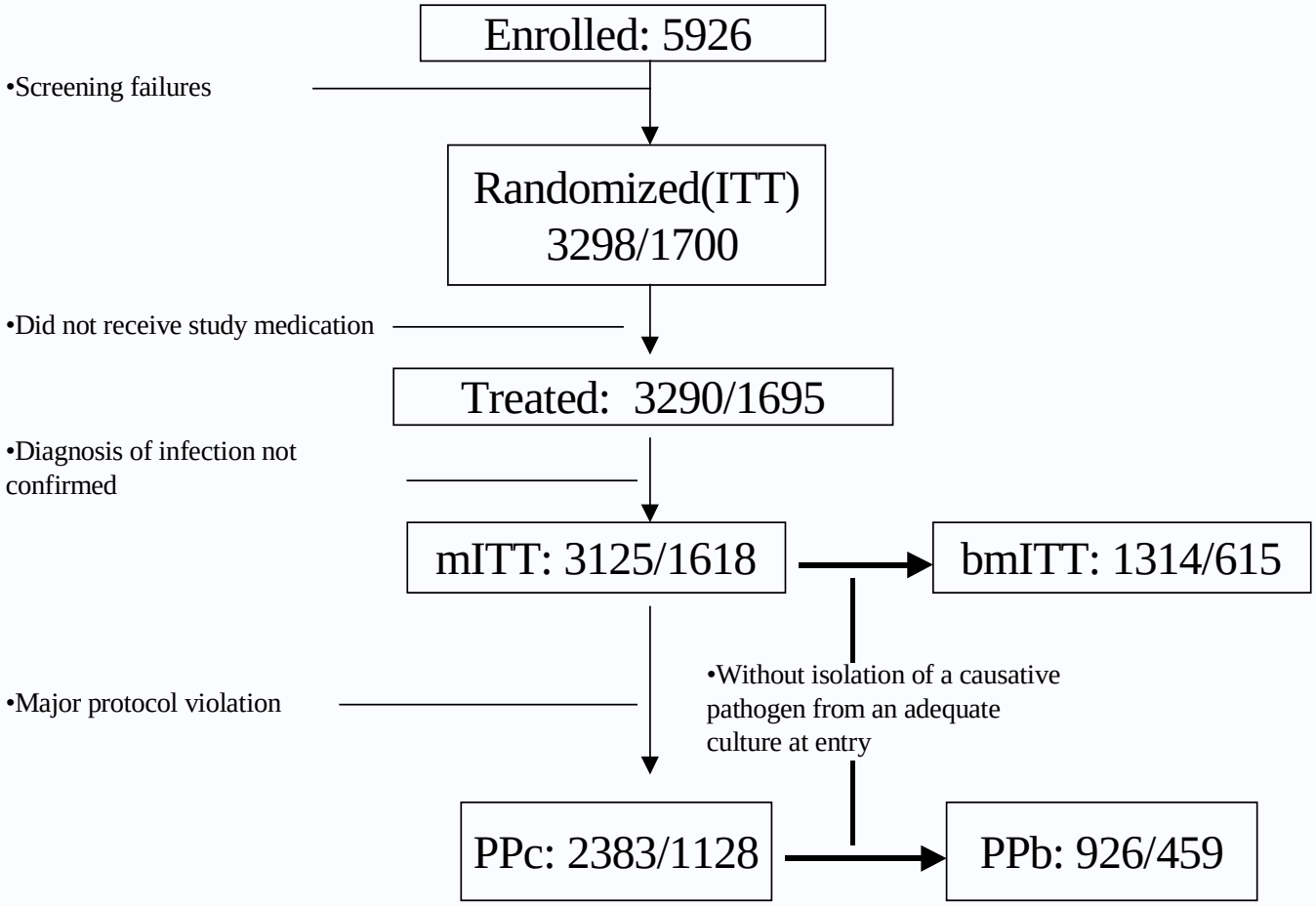
Telithromycin-treated populations

Population	Randomized	Treated	mITT	PPc	bmITT	PPb
CAP (Total)	1427	1427	1373	1132	562	344
Study 3001	199	199	199	149	62	40
Study 3006	224	224	204	162	48	28
Study 3009	111	111	100	80	32	14
Study 3000	240	240	240	197	67	45
Study 3009OL	221	221	212	187	98	68
Study 3010	432	432	418	357	255	149
AECB (Total)	346	343	342	255	82	64
Study 3003	163	161	160	115	50	39
Study 3007	183	182	182	140	32	25
Acute sinusitis (Total)	1095	1090	980	731	345	253
Study 3002 – 5 days	170	168	167	123	97	70
–- 10 days	171	168	168	133	104	69
Study 3005 – 5 days	245	245	201	146	9	7
–- 10 days	257	257	204	140	9	7
Study 3011	252	252	240	189	126	100
Tonsillitis/pharyngitis (Total)	430	430	430	265	325[a]	265
Study 3004	198	198	198	115	138	115
Study 3008	232	232	232	150	187	150
Total (All studies)	3298	3290	3125	2383	1314	926

[a]There was no PPc population defined in these studies, number reflects the bmITT population.

Appendix 6. Flow chart of Phase III subject disposition

Subjects in 13 Phase III Clinical Trials (Pooled): All Indications



Note: In Study 3005, subjects treated with degraded study medication were also excluded from the mITT population

Appendix 7. Key inclusion/exclusion criteria

Table Key inclusion diagnostic criteria

Indication [a]	Protocols	Criteria
CAP	HMR3647A/3006 HMR3647A/3009 HMR3647A/3001 HMR3647A/3000 HMR3647A/3009OL HMR3647A/3010	• Clinical diagnosis of CAP in protocols HMR3647A/3006, HMR3647A/3009, and HMR3647A/3000 based on at least two of the following clinical signs/symptoms including: [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/mm^3 or >15% immature neutrophils; and [7] a positive Gram stain on an adequate sputum sample (optional in HMR3647A/3006 and HMR3647A/3009). At least three clinical signs/symptoms of CAP were required in protocol HMR3647A/3001 including at least two from 1-4 listed above and at least one from 5-7 listed above. In Study 3009 OL, consolidation on chest X-ray was required. In Study 3010, at least one criterion from 5-7 above was required. • 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.
AECB	HMR3647A/3007 HMR3647A/3003	• 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. • FEV_1/FVC<70% based on lung function tests within the previous 12 months (HMR3647A/3003 only). • Clinical diagnosis of AECB based on at least two (HMR3647A/3007) or three (HMR3647A/3003) 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.

Table Key inclusion diagnostic criteria

Indication [a]	Protocols	Criteria
Sinusitis	HMR3647A/3005 HMR3647A/3002 HMR3647A/3011	• Clinical diagnosis of acute maxillary sinusitis based on at least one 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.
TONS/PHAR	HMR3647A/3008 HMR3647A/3004	• Clinical diagnosis of acute pharyngitis or tonsillitis based on the following clinical signs/symptoms including sore throat and at least one of the following including fever; erythema of the uvula and pharynx or tonsils; edema of these tissues; exudate; or cervical lymphadenopathy. • Positive streptococcal antigen (rapid diagnosis) test from an adequate specimen obtained within 24 hours prior to initiation of study treatment required for inclusion.[d] • Throat swab specimen obtained for bacteriological assessment at inclusion.

a CAP=community-acquired pneumonia, AECB=acute exacerbation of chronic bronchitis, TONS/PHAR=tonsillitis/pharyngitis.

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: occipitomental, occipitofrontal, and lateral views obtained in HMR3647A/3005; occipitomental view obtained in HMR3647A/3002.

d Subjects with throat cultures positive for *Streptococcus pyogenes* were included in HMR3647A/3004 prior to the availability of susceptibility results.

Selected CAP exclusion criteria

Subjects who had CAP requiring either intensive care unit admission, parenteral antibiotic treatment or who had at least one 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 ≥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% O_2 saturation (by pulse oximetry) or PaO_2 <60 mm Hg
- Total peripheral white blood cell count <4,000/mm^3
- 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

Chest X-ray score (Study 2105)

The following scoring was used as an inclusion criterion in Study 2105.

Chest X-ray: <6 points(between 5 points [shadow over about one-third of one lung field] and 7 points [shadow over about two-thirds of one lung field]).

Pneumonia score	Extension of pneumonia shadow
0	No abnormal shadow
1	Extremely slight shadow stays within the two adjacent costa
2	Between scores 1 and 3
3	Shadow overspreads approximately 1/10 of a single lobe
4	Between scores 3 and 5
5	Shadow overspreads approximately 1/3 of a single lobe
6	Between scores 5 and 7
7	Shadow overspreads approximately 2/3 of a single lobe
8	Shadow overspreads almost an entire single lobe
9	Between scores 8 and 10
10	Shadow overspreads approximately the entire bilateral lobes

Add one extra point for an extremely dark shadow.
If multiple shadows exist, add up all the scores.

Appendix 8. Narratives for subjects with *S. pneumoniae* from single or mixed pathogen infections at entry who failed therapy

Narratives for subjects with S. pneumoniae single pathogen infections at entry who failed therapy

CAP

- Subject 3009OL/0369/105 (37-year-old female, Fine score II, hypoalbuminemia) presented at pretherapy/entry with bilateral pneumonia, including consolidation in one lobe. *S. pneumoniae* (*mef*E genotype) isolated from the sputum were resistant to penicillin G (MIC of 2 µg/mL) and erythromycin A (MIC of 4 µg/mL), but were 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). On Day 4 the subject's symptoms were unchanged. *S. pneumoniae* susceptible to telithromycin (MIC of 0.5 µg/mL) were isolated from a blood culture. On Day 5 the subject's symptoms had not improved sufficiently and she was treated with intravenous penicillin G (1.2 million units every 6 hours) and cefoxitin (1 g every 8 hours). The clinical outcome after this subsequent antimicrobial treatment was cure.

- Subject 2105/15/15-1 was classified as a failure at one week after treatment because the investigator prescribed an additional antibiotic (clarithromycin, 200 mg bid, 6 days) even though clinical symptoms and C-reactive protein had normalized. This case was categorized as a treatment failure because the investigator confirmed that the additional antibiotic was prescribed to prevent relapse. The subject had a *S. pneumoniae* that was resistant to clarithromycin.

Acute sinusitis

- Subject 3002/504/002 - Baseline: 34 year-old male with no relevant medical history. Sinus X-ray, total opacity right side and mucosal thickening left side. Sinus puncture culture *S. pneumoniae* resistant to erythromycin. On day 3, the subject was clinically improved. Eleven days after the end of treatment, the clinical condition improved. Sinus X-ray showed disappearance of right side total opacity and presence of bilateral mucosal thickening. However the investigator started him on subsequent antibiotic. No repeat sinus puncture was performed and the baseline *S. pneumoniae* was presumed persistent.

- Subject 3011/604/007 – a 36-year-old white female with single infection at pretherapy/entry of *S. pneumoniae* sensitive to telithromycin (MIC 0.120 µg/mL) and resistant to penicillin G (MIC 2.000 µg/mL), erythromycin A (MIC 4.000 µg/mL), and cefuroxime (MIC 4.000 µg/mL). Relevant medical history included 2 AMS episodes in the 12 months prior to study entry that required antibiotic treatment, allergic rhinitis treated with Flonase® (fluticasone) on days -3 to 2, and the subject is a current tobacco smoker. On day 13, at the end-of-therapy visit this subject showed improvement in facial/maxillary pain symptoms but still had mild to moderate purulent symptoms of nasal and postnasal discharge. The sinus x-ray showed improvement compared to pretherapy/entry with resolution of mucosal thickening ≥10 mm on the right side. A second sinus puncture to obtain a culture specimen was not done. The *S. pneumoniae* was presumed persistent and the subject was given subsequent antimicrobial therapy of Augmentin® (amoxicillin + clavulanic acid) for 7 days with a sinusitis outcome of cure.

- Subject 3011/659/018: a 50-year-old white female with single infection at pretherapy/entry *of S. pneumoniae* sensitive to telithromycin (MIC 0.060 µg/mL) and resistant to penicillin G (MIC 2.000 µg/mL), erythromycin A (MIC 2.000 µg/mL), and cefuroxime (MIC 4.000 µg/mL). Relevant medical history included allergic rhinitis treated with Zyrtec® (cetirizine) and the subject is a current tobacco smoker. On day 5 at the on-therapy visit, this subject showed

improvement in both purulent (from severe to moderate and mild) and facial/maxillary pain symptoms (from moderate to absent). The subject was contacted by telephone on day 13 for the end-of-therapy visit. On day 20 at the posttherapy/TOC visit, the subject showed further improvement in purulent nasal discharge and all facial/maxillary pain was absent. The sinus x-ray had improved compared to pretherapy/entry from mucosal thickening ≥10 mm to mucosal thickening <10 mm. A second sinus puncture to obtain a culture specimen was not done. The *S. pneumoniae* was presumed persistent and the subject was given subsequent antimicrobial therapy of Tequin® (gatifloxacin) with a sinusitis outcome of failure.

Narratives for subjects with S. pneumoniae mixed infections at entry who failed therapy

CAP:

- 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 two 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 added for the presence of *S. aureus* in the urine.
- Subject 3001/1002/027 (age 71, Fine score IV, with consolidation on the pretherapy/entry chest x-ray), with a history of COPD, presented with lobar consolidation on chest X-ray, *S. pneumoniae* susceptible to telithromycin (MIC of 0.03 μg/mL) isolated from respiratory specimen, associated with two other causative pathogens isolated from respiratory specimens *H. influenzae* and *S. aureus* susceptible to telithromycin by MIC testing. This subject had a low blood pressure at entry (95/70 mm Hg), and after worsening of the symptoms on day 2 leading to the prescription of intravenous antibiotics. The subject died on day 4 from a severe multiorgan failure considered not related to the study medication by the investigator. The exclusion criteria used in the protocol were based on the American Thoracic Society and the British Thoracic Society criteria for severity of CAP (systolic blood pressure ≤90 mm Hg considered as shock) as well as the judgment of the investigator. *A posteriori* although this subject could not be excluded based on the criteria above, the subject should have received intravenous treatment at entry given the association of low blood pressure, age (>65 years), and CAP.

Appendix 9. Listing of subjects with resistant *S. pneumoniae* – bmITT not PPb population

Penicillin G resistant *S. pneumoniae* treated with telithromycin – bmITT not PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
3000/101/1365	CAP	Blood	Single		S	S	S	S	S	R	R	Indeterminate	Indeterminate
3001/0111/010	CAP	Blood	Single		S	S	S	S	S	R	R	Indeterminate	Indeterminate
3001/902/002	CAP	Sputum	Single		S	S	S	S	S	R	I	Failure	Eradication
3010/0473/009	CAP	Sputum	Mixed	*mef*E	I	R	R	S	R	R	R	Indeterminate	Indeterminate
3010/0526/002	CAP	Sputum	Single		S	S	S	S	R	R	R	Cure	Presumed eradication
3005/0153/001	AS	Sinus s.	Single		S	S	S	S	S	R	S	Cure	Presumed eradication
3011/0649/006	AS	Sinus s.	Single	*mef*E	S	R	R	S	R	R	R	Cure	Presumed eradication
3011/0675/006	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	R	Cure	Presumed eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole

Penicillin G Intermediate *S. pneumoniae* treated with telithromycin – bmITT no PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
3000/605/1090	CAP	Sputum	Single	*erm*B	S	R	R	R	R	S	S	Cure	Eradication
3001/1001/005	CAP	Sputum	Single		S	S	S	S	S	S	S	Indeterminate	Indeterminate
3006/42/025	CAP	Sputum	Single		S	S	S	S	S	S	S	Indeterminate	Indeterminate
3009OL/365/127	CAP	Sputum	Mixed		S	S	S	S	S	S	S	Indeterminate	Indeterminate
3010/0470/001	CAP	Sputum	Single		S	S	S	S	S	R	S	Cure	Presumed eradication
3010/0494/026	CAP	Sputum	Mixed	*erm*B	S	R	R	R	R	S	S	Cure	Presumed eradication
3011/0706/001	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	I	R	Indeterminate	Indeterminate
3011/0733/004	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	R	Cure	Presumed eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Erythromycin A-resistant *S. pneumoniae* treated with telithromycin – bmITT not PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
3000/605/1090	CAP	Sputum	Single	*erm*B	S	R	R	R	R	S	S	Cure	Eradication
3010/0473/009	CAP	Sputum	Mixed	*mef*E	I	R	R	S	R	R	R	Indeterminate	Indeterminate
3010/0494/026	CAP	Sputum	Mixed	erm B	S	R	R	R	R	S	S	Cure	Presumed eradication
3002/701/012	AS	Sinus s.	Single	*mef*E	S	R	R	S	R	S	I	Indeterminate	Indeterminate
3011/0649/006	AS	Sinus s.	Single	*mef*E	S	R	R	S	R	R	R	Cure	Presumed eradication
3011/0675/006	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	R	Cure	Presumed eradication
3011/0706/001	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	I	R	Indeterminate	Indeterminate
3011/0733/004	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	R	Cure	Presumed eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Appendix 10. Listing of subjects with resistant *S. pneumoniae* treated with active comparators – PPb and bmITT not PPb populations

Penicillin G resistant *S. pneumoniae* treated with active comparators – PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
Augmentin													
3003/606/005	AECB	Sputum	Single	*erm*B	S	R	R	R	R	R	R	Failure	Eradication
Cefuroxime													
3007/0062/001	AECB	Sputum	Mixed	*mef*E	S	R	R	S	R	R	S	Failure	Presumed persistence
3011/0626/001	AS	Sinus s.	Mixed		S	S	S	S	S	R	R	Cure	Presumed eradication
3011/0658/001	AS	Sinus s.	Single	*mef*E	S	R	R	S	R	R	R	Cure	Presumed eradication
3011/0675/007	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	S	Cure	Presumed eradication
3011/0682/017	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	R	Cure	Presumed eradication
Clarithromycin													
3006/0008/032	CAP	Sputum	Single		S	S	S	S	S	R	R	Cure	Eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Penicillin G intermediate *S. pneumoniae* treated with active comparators – PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
Amoxicillin													
3001/1001/006	CAP	Sputum	Single		S	S	S	S	S	S	S	Cure	Eradication
Cefuroxime													
3007/0067/036	AECB	Sputum	Mixed		S	S	S	S	S	R	R	Failure	Presumed persistence
3007/0068/001	AECB	Sputum	Single	*erm*B	S	R	R	R	R	R	I	Cure	Presumed eradication
3011/0704/008	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	S	S	Cure	Presumed eradication
3011/0707/035	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	R	I	Cure	Presumed eradication
Clarithromycin													
3006/0013/001	CAP	Sputum	Single	*mef*E	S	R	I	S	I	R	R	Cure	Eradication
Trovafloxacin													
3009/0283/009	CAP	Sputum	Single		S	S	S	S	S	S	R	Cure	Eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Erythromycin A resistant *S. pneumoniae* treated with active comparators – PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
Amoxicillin													
3001/1004/011	CAP	Sputum	Mixed	*erm*B	S	R	R	R	R	S	R	Cure	Eradication
Augmentin													
3003/606/005	AECB	Sputum	Single	*erm*B	S	R	R	R	R	R	R	Failure	Eradication
Cefuroxime													
3007/0062/001	AECB	Sputum	Mixed	*mef*E	S	R	R	S	R	R	S	Failure	Presumed persistence
3007/0068/001	AECB	Sputum	Single	*erm*B	S	R	R	R	R	R	I	Cure	Presumed eradication
3011/0658/001	AS	Sinus s.	Single	*mef*E	S	R	R	S	R	R	R	Cure	Presumed eradication
3011/0675/007	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	S	Cure	Presumed eradication
3011/0682/017	AS	Sinus s.	Mixed	*erm*B	S	R	R	R	R	R	R	Cure	Presumed eradication
3011/0704/008	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	S	S	Cure	Presumed eradication
3011/0707/035	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	R	I	Cure	Presumed eradication
Clarithromycin													
3006/0013/001	CAP	Sputum	Single	*mef*E	S	R	I	S	I	R	R	Cure	Eradication
3006/0037/014	CAP	Sputum	Single	*erm*B	S	R	R	R	R	S	I	Cure	Eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Penicillin G resistant *S. pneumoniae* treated with active comparators – bmITT not PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
Augmentin													
3005/0176/023	AS	Sinus s.	Single		S	S	S	S	S	R	R	Failure	Presumed persistence
Cefuroxime													
3011/0675/010	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	R	S	Indeterminate	Indeterminate
Clarithromycin													
3006/0032/014	CAP	Sputum	Single	*mef*E	S	R	R	S	R	R	R	Cure	Eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Penicillin G intermediate *S. pneumoniae* treated with active comparators – bmITT not PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
Trovafloxacin													
3009/0298/010	CAP	Sputum	Single		S	S	S	S	S	S	R	Indeterminate	Presumed persistence

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Erythromycin A resistant *S. pneumoniae* treated with active comparators – bmITT not PPb population

Subject	Indica-tion	Source	Mixed or single	Resistance								Clinical outcome	Eradication
				Genotype	Phenotype								
					Tel	Ery	Cla	Cli	Azi	Cef	Cot		
Cefuroxime													
3011/0675/010	AS	Sinus s.	Single	*erm*B	S	R	R	R	R	R	S	Indeterminate	Indeterminate
Clarithromycin													
3006/0032/014	CAP	Sputum	Single	*mef*E	S	R	R	S	R	R	R	Cure	Eradication

Tel=Telithromycin; Pen=Penicillin; Cla=Clarithromycin; Cli=Clindamycin ;Azi=Azithromycin; Cef= Cefuroxime; Cot=Cotrimoxazole. Sinus s. = sinus secretion

Appendix 11. Narratives for subjects with *S. pneumoniae* positive blood cultures who failed therapy

Narratives for subjects with *S. pneumoniae* positive blood cultures who failed therapy

CAP:

- 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 two 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 (also described in Appendix 10) (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 two 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 (also described in Appendix 10) (age 37, Fine score II, with bilateral pneumonia and consolidation in one 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 0.120 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 12. Listing of subjects with pneumococcal bacteremia – bmITT but not PPb population

Listing of subjects with pneumococcal bacteremia – bmITT but not PPb population

Study No./ Investigator No./ Subject No.	Reason excluded from PPb population	Clinical outcome		Bacteriological outcome	
		at TOC	at LPTV	at TOC	at LPTV
3000/101/1364	Inability to determine bacteriologic outcome at TOC because of an adverse event leading to discontinuation.	Failure	Failure	Indeterminate	Indeterminate
3000/101/1365	Met laboratory exclusion at entry (impaired renal function)	Indeterminate	Indeterminate	Indeterminate	Indeterminate
3001/0110/007	Wrong entry diagnosis (entry chest x-ray showed empyema)	Indeterminate	Indeterminate	Indeterminate	Indeterminate
3001/0111/010	Insufficient treatment duration, received concomitant antimicrobial therapy	Indeterminate	Indeterminate	Indeterminate	Indeterminate
3001/0608/001	Insufficient treatment duration (subject did not complete the first 5 days with 100% treatment and did not reach an overall 70% active drug intake).	Cure	Cure	Pres. erad.	Pres. erad.
3001/1004/006	Met laboratory exclusion at entry (WBC <4000 mm^3)	Indeterminate	Indeterminate	Indeterminate	Indeterminate
3006/0012/004	Received prophylactic Bactrim for *Pneumocystis carinii* pneumonia between end of treatment and TOC.	Indeterminate	Indeterminate	Indeterminate	Indeterminate
3006/0012/007	Sample outside the TOC window. No sample collected at TOC.	Failure	Failure	Indeterminate	Indeterminate
3009/0315/003	Wrong entry diagnosis (CAP requiring parenteral antibiotic)	Indeterminate	Indeterminate	Indeterminate	Indeterminate

Appendix 13. Clinical cure rates without indeterminate responses – mITT and bmITT populations

Clinical cure rate without indeterminate responders for telithromycin *vs* active comparators for all studies – mITT population

	Clinical cure						
	Telithromycin			Comparators			
	N	n	(%)	N	n	(%)	CI[1]
CAP							
Study 3001							
mITT without indeterminate	184	171	(92.9)	183	161	(88.0)	[-1.6; 11.5]
Study 3006							
mITT without indeterminate	184	161	(87.5)	195	171	(87.7)	[-7.4; 7.0]
Study 3009							
mITT without indeterminate	92	82	(89.1)	95	89	(93.7)	[-13.6; 4.5]
Study 3000							
mITT without indeterminate	210	191	(91.0)				
Study 3009OL							
mITT without indeterminate	195	182	(93.3)				
Study 3010							
mITT without indeterminate	385	357	(92.7)				
AECB							
Study 3003							
mITT without indeterminate	152	130	(85.5)	154	125	(81.2)	[-4.6; 13.3]
Study 3007							
mITT without indeterminate	164	142	(86.6)	166	138	(83.1)	[-4.9; 11.8]
Acute sinusitis							
Study 3002 – 5 days							
mITT without indeterminate	150	138	(92.0)				[-6.6; 6.8][4]
Study 3002 – 10 days							
mITT without indeterminate	160	147	(91.9)				
Study 3005 – 5 days							
mITT without indeterminate	187	140	(74.9)				[-10.3; 8.4][2]
Study 3005 – 10 days							
mITT without indeterminate	190	140	(73.7)	182	138	(75.8)	[-11.5; 7.2][3] [-8.2; 10.5][4]
Study 3011 – 5 days							
mITT without indeterminate	222	193	(86.9)	101	84	(83.2)	[-5.5; 13.0]
Tonsillitis/Pharyngitis							
Study 3004							
mITT without indeterminate	184	170	(92.4)	182	169	(92.9)	[-6.4; 5.4]
Study 3008							
mITT without indeterminate	218	193	(88.5)	213	192	(90.1)	[-7.9; 4.7]

[1]Pairwise comparison between telithromycin regimen and comparator regimen, unless otherwise specified.
[2]Pairwise comparison between 5-day telithromycin regimen and comparator regimen.
[3]Pairwise comparison between 10-day telithromycin regimen and comparator regimen.
[4]Pairwise comparison between 5-day and 10-day telithromycin regimens.

Clinical cure rate without indeterminate responders for telithromycin *vs* active comparators for all studies –bmITT population

	Clinical cure						
	Telithromycin			Comparators			
	N	n	(%)	N	n	(%)	CI[1]
CAP							
Study 3001							
bmITT without indeterminate	56	49	(87.5)	55	46	(83.6)	[-11.0; 18.7]
Study 3006							
bmITT without indeterminate	42	36	(85.7)	40	37	(92.5)	[-22.6; 9.0]
Study 3009							
bmITT without indeterminate	28	27	(96.4)	31	29	(93.5)	[-11.6; 17.3]
Study 3000							
bmITT without indeterminate	58	49	(84.5)				
Study 3009OL							
bmITT without indeterminate	88	81	(92.0)				
Study 3010							
bmITT without indeterminate	237	217	(91.6)				
AECB							
Study 3003							
bmITT without indeterminate	49	39	(79.6)	41	31	(75.6)	[-15.6; 23.5]
Study 3007							
bmITT without indeterminate	29	22	(75.9)	30	23	(76.7)	[-25.9; 24.3]
Acute sinusitis							
Study 3002 – 5 days							
bmITT without indeterminate	86	79	(91.9)				[-9.9; 7.5][4]
Study 3002 – 10 days							
bmITT without indeterminate	101	94	(93.1)				
Study 3005 – 5 days							
bmITT without indeterminate	9	8	(88.9)				[-26.7; 64.5][2]
Study 3005 – 10 days							
bmITT without indeterminate	9	7	(77.8)	10	7	(70.0)	[-42.1; 57.6][3] [-34.0; 56.3][4]
Study 3011 – 5 days							
bmITT without indeterminate	118	102	(86.4)	54	43	(79.6)	[-6.9; 20.6][4]
Tonsillitis/Pharyngitis							
Study 3004							
bmITT without indeterminate	133	123	(92.5)	140	129	(92.1)	[-6.7; 7.4]
Study 3008							
bmITT without indeterminate	177	156	(88.1)	162	146	(90.1)	[-9.2; 5.2]

[1]Pairwise comparison between telithromycin regimen and comparator regimen, unless otherwise specified.
[2]Pairwise comparison between 5-day telithromycin regimen and comparator regimen.
[3]Pairwise comparison between 10-day telithromycin regimen and comparator regimen.
[4]Pairwise comparison between 5-day and 10-day telithromycin regimens.

Appendix 14. TEAEs in clinical pharmacology studies

All TEAEs associated with single oral doses in clinical pharmacology studies (NDA)[a]

Coded term	Number (%) of subjects				
	Telithromycin				Placebo
	All doses (N = 526)	<800 mg (N = 83)	800 mg (N = 346)	1200 to 2400 mg (N = 97)	(N = 50)
Total subjects with TEAEs	137 (26.0)	10 (12.0)	68 (19.7)	59 (60.8)	12 (24.0)
Headache	30 (5.7)	1 (1.2)	10 (2.9)	19 (19.6)	2 (4.0)
Nausea	21 (4.0)	0 (0.0)	10 (2.9)	11 (11.3)	1 (2.0)
Diarrhea	20 (3.8)	1 (1.2)	9 (2.6)	10 (10.3)	0 (0.0)
Taste perversion	20 (3.8)	0 (0.0)	3 (0.9)	17 (17.5)	1 (2.0)
Dizziness	19 (3.6)	1 (1.2)	4 (1.2)	14 (14.4)	1 (2.0)

[a] Based on a frequency of 2.0% or more for all dose levels of telithromycin combined.

All TEAEs associated with single oral doses in clinical pharmacology studies (4-Month Safety Update Data)

Coded term	Number (%) of Subjects				
	Telithromycin				Placebo
	Total (N = 79)	800 mg (N = 31)	2400 mg (N = 24)	3200 mg (N = 24)	(N = 24)
Total subjects with TEAEs	64 (81.0%)	17 (54.8%)	24 (100.0%)	23 (95.8%)	11 (46.0%)
Taste perversion	29 (36.7%)	0 (0.0%)	13 (54.8%)	16 (66.7%)	2 (8.3%)
Enteritis	23 (29.1%)	0 (0.0%)	10 (41.7%)	13 (54.2%)	0 (0.0%)
Headache	16 (20.3%)	2 (6.5%)	8 (33.3%)	6 (25.0%)	4 (16.7%)
Diarrhea	14 (17.7%)	0 (0.0%)	9 (37.5%)	5 (20.8%)	3 (12.5%)
Gastrointestinal pain	11 (13.9%)	0 (0.0%)	6 (25.0%)	5 (20.8%)	0 (0.0%)
Blurred vision	9 (11.4%)	0 (0.0%)	5 (20.8%)	4 (16.7%)	0 (0.0%)
Vaginal moniliasis	8 (10.1%)	0 (0.0%)	5 (20.8%)	3 (12.5%)	1 (4.2%)
Nausea	8 (10.1%)	1 (3.2%)	5 (20.8%)	2 (8.3%)	0 (0.0%)

*TEAEs in Studies 1046 and 1047 based on frequency of at least 10.1% in total telithromycin column.
The N's represent dosing periods with telithromycin alone.
The numbers in each column are not additive because a subject may have had more than one TEAE.

All TEAEs associated with multiple oral doses in clinical pharmacology studies (NDA)[a]

Coded term	Number (%) of Subjects				
	Telithromycin				Placebo
	All doses (N = 244)	<800 mg (N = 69)	800 mg (N = 133)	900 to 1600 mg (N = 42)	(N = 42)
Total subjects with TEAEs	121 (49.6)	31 (44.9%)	56 (42.1%)	34 (81%)	19 (45.2)
Headache	31 (12.7)	14 (20.3)	10 (7.5)	7 (16.7)	10 (23.8)
Diarrhea	23 (9.4)	3 (4.3)	13 (9.8)	7 (16.7)	2 (4.8)
Nausea	14 (5.7)	7 (10.1)	2 (1.5)	5 (11.9)	1 (2.4)
Dizziness	13 (5.3)	1 (1.4)	5 (3.8)	7 (16.7)	1 (2.4)
Taste Perversion	12 (4.9)	3 (4.3)	8 (6.0)	1 (2.4)	2 (4.8)
Abdominal Pain	8 (3.3)	1 (1.4)	6 (4.5)	1 (2.4)	0 (0.0)
Asthenia	7 (2.9)	0 (0.0)	3 (2.3)	4 (9.5)	1 (2.4)
Rash	7 (2.9)	2 (2.9)	2 (1.5)	3 (7.1)	1 (2.4)
Flatulence	5 (2.0)	0 (0.0)	5 (3.8)	0 (0.0)	0 (0.0)
Gastrointestinal Disorder	5 (2.0)	1 (1.4)	1 (0.8)	3 (7.1)	0 (0.0)
Mouth Ulceration	5 (2.0)	5 (7.2)	0 (0.0)	0 (0.0)	1 (2.4)
Rhinitis	5 (2.0)	1 (1.4)	1 (0.8)	3 (7.1)	1 (2.4)
Somnolence	5 (2.0)	3 (4.3)	0 (0)	2 (4.8)	1 (2.4)

[a] Based on a frequency of 2.0% or more for all dose levels of telithromycin combined.

Appendix 15. Deaths and discontinuations for Phase III uncontrolled studies

Results of Uncontrolled Studies

A. Deaths and other serious adverse events in uncontrolled studies

A.1 Deaths

One death occurred in Study 3009OL and two deaths occurred in Study 3010; see *Section 7.2.5, Deaths and other serious adverse events*.

A.1 Other serious TEAEs

In uncontrolled Studies 3000 and 3002 reported in the initial NDA submission, 19 subjects (3.3%) had serious adverse events (none deaths); of these subjects, 4 had possibly related serious adverse events. All the possibly related serious adverse events occurred in CAP Study 3000 and were moderate or severe in intensity. The following table summarizes the event and outcome for the possibly related serious adverse events.

Possibly related serious adverse events in study 3000*

Study No./ Subject No	Age/sex/race	Treatment	Event/serious criterion	Outcome
3000 0101/1001	21/M/W	Telithromycin	Leukopenia Medically important	Recovered, no sequelae
3000 0502/1069	53/M/W	Telithromycin	Hepatitis Medically important/Required or prolonged hospitalization	Ongoing
3000 0803/1520	65/M/W	Telithromycin	Vasculitis Medically important/Required or prolonged hospitalization	Recovered, no sequelae
3000 0902/1389	56/M/O	Telithromycin	Gastroenteritis Medically important/Required or prolonged hospitalization	Recovered, no sequelae

Key: Sex: M = male. Race: W = white; B = black; A = Asian/Oriental; O = other races.

*There were no possibly related serious adverse events in Study 3002.

In Studies 3009OL and 3010, there were no serious adverse events that were considered possibly related to treatment by the investigator.

B. Discontinuations due to TEAEs in uncontrolled Phase III studies

As reported in the initial NDA, discontinuation of telithromycin due to a TEAE occurred in 19 of 572 subjects in Studies 3000 and 3002 irrespective of causality; 11 (1.9%) of these subjects were discontinued due to a possibly related TEAE. In CAP study 3000, 7 (2.9%) of 239 subjects had possibly related TEAEs that led to discontinuation. In the 5-day treatment group in acute sinusitis Study 3002, 3 (1.8%) of subjects had possibly related TEAEs leading to discontinuation; in the 10-day treatment group, 1 (0.6%) of 167 subjects had possibly related TEAEs leading to discontinuation.

As reported for Study 3009OL in the 4-month safety update, treatment with telithromycin was discontinued in only 1 (0.5%) of 218 subjects. This subject (369/108) had died as reported in *Section 7.2.5, Deaths and other serious adverse events*. The TEAEs leading to discontinuation were multiorgan failure and sepsis. Neither TEAE was considered related to treatment by the investigator.

In Study 3010, treatment with telithromycin had to be discontinued due to a TEAE in 11 (2.6%) of the 430 subjects. Six of these events were reported as possibly related to the study medication (allergic reaction, abdominal pain, diarrhea, vomiting, vertigo, and SGPT increased). Four of the events were serious but not considered to be related to the study medication; 2 of these serious events led to death (respiratory disorder and myocardial infarct).

Appendix 16. Narratives for deaths in the Phase III studies

Controlled CAP studies

Subject 0111/004 in Study 3001 was a 52-year-old white male who started treatment for CAP with amoxicillin on 27 July 1998. Study medication was discontinued on 3 August 1998 due to low creatinine clearance at study entry (exclusion criteria). Subsequent antimicrobial therapy with amoxicillin was started on 3 August 1998 to treat the pneumonia. On 29 August 1998, the subject experienced bronchospasm and died while being transported to the hospital. The severe asthmatic crisis, which led to the death, was reported as assessed by the investigator to be not related to study medication. No autopsy was performed. Relevant medical history included asthma since 1956 and gastritis since 1998.

Subject 1002/027 in Study 3001 was a 71-year-old white female who started treatment for CAP with 800 mg telithromycin daily on 14 September 1998. At study entry, the subject was admitted to a nursing care unit. Pretherapy chest x-ray showed single lobe consolidation on the right side. Sputum cultures were positive for *S. pneumonia*e, beta-lactamase-producing *H. influenza*e, and *S. aureus*. This subject also had low blood pressure at entry (95/70 mm Hg). On 15 September 1998, the subject's clinical condition worsened (severe lobar pneumonia, with associated hypotension, cyanosis, and altered mental state). Antimicrobial therapy with intravenous gentamicin and Rocephin (ceftriaxone) was started. On 16 September 1998, severe multiorgan failure developed, with circulatory, kidney, and respiratory failure. The subject died on 17 September 1998, with the primary cause of death reported as multiorgan failure (coded using the HARTS dictionary as "ill-defined condition"). The investigator assessed the multiorgan failure as not related to the study medication. The last dose of study medication was taken on 16 September 1998. Relevant medical/surgical history included COPD since 1990, CAD since 1994, dorsal scoliosis, and surgical intervention for squamous carcinoma of the right cheek in 1994.

Subject 1301/004 in Study 3001 was an 80-year-old white male who started treatment for CAP with 800 mg telithromycin daily on 16 December 1998. On 25 December 1998, 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. The last dose of study medication was taken on 25 December 1998. Relevant medical history included coronary artery disease since 1990, atrial fibrillation since 1990, cerebrovascular disease since 1990, diabetes mellitus since 1995, and unspecified liver disease since 1990.

Subject 0060/002 in Study 3006 was a 70-year-old white female who started treatment for CAP with clarithromycin on 17 July 1998. The subject completed 10 days of treatment with study medication on 26 July 1998. The subject died 5 months posttreatment (on 18 December 1998), with the cause of death reported as malignant bronchial neoplasm. Relevant medical/surgical history included schizophrenia since 1978, hypothyroidism since 1995, seizure disorder since 1995, COPD since 1988, constipation since 1995, intestinal pneumatosis since 1997, and small bowel resection in 1997. The subject had been a smoker since 1941, and smoked 20 cigarettes/day at the time of enrollment.

Subject 0386/018 in Study 3006 was a 43-year-old white female who started treatment for CAP with clarithromycin on 28 July 1999. Pretherapy sputum culture revealed normal flora. The subject completed 10 days of treatment with study medication on 6 August 1999. On 9 August 1999, the subject developed worsening pneumonia. Subsequent antimicrobial therapy with ceftriaxone was started on 9 August 1999 to treat the pneumonia. On 17 August 1999, the subject was hospitalized for worsening pneumonia with associated dyspnea, tachypnea, hyperventilation, increased sputum production, chest pain, nausea, increased rales and rhonchi, and mild pleural effusion. Antimicrobial therapy with clindamycin, cefotaxime, ceftazidime, and amikacin was started to treat the pneumonia.

The subject died on 26 August 1999, with the primary cause of death as pneumonia (organism not identified). Relevant medical/surgical history included diabetes mellitus since 28 July 1999 and a breast biopsy in 1994.

Subject 0301/020 in Study 3009 was a 79-year-old white female who started treatment with 800 mg telithromycin for CAP on 26 May 1999. The last dose of study medication was taken on 4 June 1999. The subject died on 22 June 1999, 18 days after the last dose of study medication. Relevant medical history included severe chronic obstructive pulmonary disease and hypertension. The investigator assessed the death as unrelated to the study medication. The reported cause of death was cardiopulmonary arrest and chronic obstructive pulmonary disease.

Uncontrolled CAP studies

Subject 0703/1466 in Study 3000 was a 57-year-old white male who started treatment for CAP with 800 mg telithromycin daily on 24 November 1998. On 25 November 1998, the subject developed gastritis with nausea and vomiting. On 26 November 1998, the onset of acute leptospirosis, confirmed by serological tests, was recorded in association with renal failure, hemolytic anemia, sepsis, and liver insufficiency. On 27 November 1998, the subject developed adult respiratory distress syndrome (ARDS), with worsening pneumonia and sepsis. Study medication was discontinued on 27 November 1998 due to the events of acute leptospirosis and ARDS. Subsequent antimicrobial therapy was started on 27 November 1998 to treat the pneumonia. The subject died on 17 December 1998, with the primary cause of death as ARDS and acute leptospirosis. Relevant medical/surgical history included hypertension and total hip replacement in 1977. The pretherapy chest x-ray showed left lower lobe consolidation with infiltrates. Retrospective serology was positive for *Chlamydia pneumonia*e.

Subject 0803/1520 in Study 3000 was a 65-year-old white male who started treatment for CAP with 800 mg telithromycin daily on 8 December 1998. Treatment with study medication was completed on 16 Dec 1998. At the end of treatment visit on 17 December 1998, the subject's clinical status had returned to the preinfection state. On 19 December 1998, the subject presented with a nonpruritic rash on upper and lower extremities, which a skin biopsy confirmed as leukocytoclastic vasculitis. Urinalysis showed microscopic hematuria and chest x-ray showed bilateral infiltrates, which were identified in the chest CT scan as pleural fluid. On December 27 1998, the posttherapy assessment of clinical outcome was cure. On this day, however, the subject became hypotensive and ECG and serum creatine kinase indicated an acute myocardial infarction. On 8 January 1999 (the posttherapy/ TOC visit), the clinical assessment was failure. The subject died on 8 January 1999, with the primary cause of death as gram-negative septicemia. Relevant medical/surgical history included stroke in 1993, COPD since 1994, hypertension since 1993, CHF since June 1998, respiratory insufficiency from 4-6 September 1998, CAD, diabetes mellitus since 1993, partial gastrectomy in 1976, thymectomy in 1996, aortobifemoral bypass on 29 May 1998, and chronic osteomyelitis of the left foot since September 1998.

Subject 0369/108 in Study 3009OL was a 37-year-old black female who started treatment for CAP with 800 mg telithromycin on 15 September 1999. Pretherapy transaminases were elevated at baseline (AST, 806 U/L; ALT, 1235 U/L; alkaline phosphatase, 326 U/L; and, GGT, 205 U/L). The last dose of study medication was taken on 21 September 1999. On 20 September 1999, the subject became clinically jaundiced and complained of painful lower legs. The next day, she became dyspneic with peripheral edema and hepatomegaly. She was withdrawn from the study and transferred to another hospital. HIV testing done on 21 September 1999 was positive. The subject died on 26 September 1999, five days after the last dose of study medication. The investigator assessed these events as unrelated to the study medication and attributed the death to the

underlying/concomitant illness. The reported cause of death was respiratory failure, cardiomyopathy, liver failure, and immunosuppression.

Subject 0473/009 in Study 3010 was a 77-year-old white male who started treatment for CAP with 800 mg telithromycin on 31 July 2000. He presented to the emergency room with increased shortness of breath, cough productive of purulent sputum, chest discomfort, and mild chills for 2 to 3 days prior. The causative agents isolated from his sputum were *S. pneumoniae, M. catarrhalis, and H. influenzae*. The subject was also diagnosed with mild renal insufficiency (reported as a serious adverse event) that was initially felt to be compromised due to the pneumonia and underlying congestive heart failure. Due to the subject's age and medical history, he was admitted to the hospital on day 1 (31 July 2000). On day 3 (02 August 2000) the subject showed improvement in clinical signs and symptoms of his pneumonia (confirmed by chest x-ray). However, renal insufficiency increased from mild to moderate, which was thought to be due to a substantial loss of fluid due to nausea, vomiting, and stools (possibly aggravated by concomitant theophylline administered for shortness of breath), with limited rehydration. On day 5 (04 August 2000), the subject was found to be experiencing labored respirations and shortness of breath secondary to acute aspiration. The subject was transferred to the intensive care unit where he died a short time later. The investigator assessed the most likely cause of death as acute aspiration; an autopsy report obtained post-database closure indicated the following:

- Severe coronary arteriosclerosis with ischemic cardiomyopathy and pericarditis
- Severe pulmonary emphysema, bilateral, with active and resolving bronchopneumonia and pulmonary congestion
- Chronic pyelonephritis and extensive fibrosis of right kidney due to previous ischemic injury
- Very mild fatty liver with passive congestion
- Postoperative status, remote abdominal surgery with extensive peritoneal adhesions.

The investigator's causal assessment was that the renal insufficiency and acute aspiration were not related to the study medication, but to an underlying or concomitant illness.

Subject 0537/009 in Study 3010 was a 44-year-old black male who started treatment for CAP with 800 mg telithromycin on 07 July 2000. He experienced a serious adverse event of acute myocardial infarction on day 1 of the study. The subject presented with pleuritic chest pain, cough, dyspnea, tachypnea, and fever; he was hospitalized and enrolled into the study. Pretherapy/entry chest x-ray revealed consolidation. No causative pathogen for CAP was isolated. Review of the pretherapy/entry ECG indicated new myocardial infarction (Q waves in leads V1-V3, ST segment elevation in leads V1-V4, and PR segment depressions in lead II [QTc of 470 ms]) and sinus tachycardia at 130 beats/min. The subject died on day 2 (08 July 2000). The investigator assessed the event as not related to the study medication, but rather to an underlying or concomitant illness (acute myocardial infarction).

Controlled tonsillitis/pharyngitis study

Subject 1306/008 in Study 3004 was a 55-year-old white female who started treatment for tonsillitis/pharyngitis with penicillin VK on 25 February 1999. The last dose of study medication was taken on 27 February 1999. On 26 February 1999, the subject had fever and weakness. Pretherapy hematology tests showed elevated leukocytes (215 $x10^9$/L). The subject was diagnosed with severe acute lymphoid leukemia. The subject was started on amoxicillin for tonsillitis on 28 February 1999. On 01 March 1999, the subject was withdrawn from the study and transferred to another hospital for treatment of acute lymphoid leukemia. On 12 April 1999, 44 days after the last dose of study medication, the subject died with the primary cause of death reported as acute lymphoid leukemia. The investigator assessed the cause of death as not related to study medication but due to the underlying/concomitant illness. Relevant medical/surgical history included mild perceptive hearing loss and splenectomy in 1997.

Appendix 17. Narratives for possibly related serious adverse events in the completed phase III studies

CAP studies

Subject 0060/039 in Study 3006 was a 76-year-old female who began treatment for CAP with telithromycin on 11 February 1999. The last dose of study medication was given on 16 February 1999. On 15 February 1999, an asymptomatic elevation of liver associated enzymes was discovered. The subject was discontinued from the study on 17 February 1999. The investigator assessed the liver injury (coded as liver damage) as possibly related to the study medication. The event, however, was asymptomatic. On 22 February 1999, ALT had decreased to 64 U/L and AST had returned to within normal limits.

Subject 0387/001 in Study 3006 was a 24-year-old white female who started treatment with telithromycin on 02 June 1999. The last dose of study medication was taken on 05 June 1999. On 03 June 1999, she experienced severe nausea, followed by severe vomiting which led to medical intervention. Study medication was discontinued on 05 June 1999. Nausea resolved after 3 days (06 June 1999), vomiting resolved the same day it occurred (05 June 1999). The subject was also diagnosed with a pulmonary abscess associated with fever and respiratory difficulty on 05 June 1999. The investigator assessed the nausea as possibly related to study medication, the vomiting as possibly related to study medication as well as to other known or suspected causes (aspirin, naproxen, and dipyrone), and the pulmonary abscess as not related to study medication. Subject was withdrawn from the study on 06 June 1999.

Subject 0608/003 in Study 3001 was a 20-year-old man who started treatment with telithromycin for CAP on 03 September 1998. The last dose of study medication was administered on 07 September 1998 when the subject presented with pruritus on the testicles, forearms and hands; these events had started on 04 September 1998. Target-shaped lesions and bullae were present and the skin disorder was diagnosed as bullous erythema multiforme of moderate intensity. On 08 September 1998, the subject was discontinued from the study and treatment with a topical corticosteroid was commenced. The event resolved on September 24, 1998 and the subject recovered without sequelae.

Subject 0106/005 in Study 3001 was a 34-year-old woman who started treatment for CAP with amoxicillin on 28 June 1998. The last dose of medication was taken on 1 July 1998 when her clinical condition worsened and she presented with facial erythema, and mild lip and palpebral edema. The investigator evaluated this as an allergic reaction related to study medication, and discontinued treatment. A few hours later, the subject contacted the investigator (by telephone) to complain that she was very scared as the edema was getting worse. The subject was brought to the casualty ward and treated with dexamethasone (2 mg x 1) iv. The subject recovered without sequelae on the same day and was thereafter lost to follow-up.

AECB studies

Subject 0603/011 in Study 3003 was a 66-year-old male who started treatment for AECB with amoxicillin/clavulanic acid on 21 July 1998. On the same day, the subject was discontinued from the study. Two hours fifteen minutes after the second (and last) dose, the subject developed a severe gastrointestinal disorder**,** with abdominal pain, and severe vomiting and diarrhea. The gastrointestinal disorder, which required hospitalization, was considered related to study medication. The subject recovered without sequelae on 22 July 1998.

Acute sinusitis studies

Subject 0188/032 in Study 3005 was a 33-year-old white female who started treatment with telithromycin on 18 February 1999 for acute sinusitis. The last dose of study medication was administered on 21 February 1999. On 19 February 1999, she experienced mild diarrhea, which over the next several days, became severe with abdominal cramping before a bowel movement and blood in the stool. On 22 February 1999, counteractive treatment started. The subject was withdrawn from the study on 23 February 1999. The investigator assessed this event as suspicious pseudomembranous colitis (unconfirmed) possibly related to study medication.

Subject 0194/012 in Study 3005 was a 30-year-old Asian/Oriental female who started treatment with telithromycin on 16 April 1999 for acute sinusitis. Her last study medication was administered on 20 April 1999. On 21 April 1999, she experienced severe gastroenteritis (with symptoms of nausea, vomiting, abdominal pain, electrolyte imbalance, and diarrhea) which was considered possibly related to treatment. The subject was seen in the emergency room on 21 April 1999 where a diagnosis of gastroenteritis was made and counteractive treatment was begun. The event resolved without sequelae on 25 April 1999. The subject was withdrawn from the study on 26 April 1999.

Subject 0174/003 in Study 3005 was a 34-year-old white female who started treatment with HMR3647 on 29 October 1998 for acute sinusitis. The last study dose was administered on the same day, 29 October 1998. The subject experienced an allergic reaction approximately 1 hour following study medication. Associated symptoms of the allergic reaction included the following: hot flashes; disorientation; one episode of emesis; severe nausea; abdominal pain; blurred vision; and rash on face, chest and arms bilaterally. The subject was taken to the emergency room and then admitted to the hospital. When the subject returned for a follow-up visit on 04 November 1998, the allergic reaction and all associated symptoms had completely resolved. The subject was permanently withdrawn from the study on 04 November 1998.

Subject 0194/008 in Study 3005 was 30-year-old white female who started treatment on 09 February 1999 with amoxicillin/clavulanic acid for acute sinusitis. Her last dose of study drug was administered on 13 February 1999 after she experienced pseudomembranous colitis of severe intensity. Symptoms included loose stools, diarrhea, and dehydration. The investigator assessed the pseudomembranous colitis as possibly related to study medication. The subject was rehydrated in the emergency room following the severe diarrhea and treated. The event resolved on 19 February 1999 and she was withdrawn from the study.

Subject 0652/004 in Study 3011 was a 72-year-old woman who started treatment on 24 August 2000 with cefuroxime axetil for acute sinusitis. She experienced severe dyspnea with onset on 25 August 2000 (day 2 of the study). The intensity of the symptoms increased over several days, and she presented at the emergency room on 31 August 2000 with severe hypoxia. She was admitted on 01 September 2000 and treated for pneumonia, bronchitis, and sinus infection and was later discharged (06 September 2000) on oxygen. The serious adverse event of dyspnea was considered by the investigator to be related to the study medication and led to its discontinuation on 29 August 2000; the subject was withdrawn from the study on 08 September 2000. The event was unresolved at withdrawal from the study, and no follow-up was considered necessary.

Tonsillitis/pharyngitis studies

Subject 0259/005 in Study 3008 was a 19-year-old white male who started treatment for tonsillitis/pharyngitis on 29 March 1999 with telithromycin. His last study drug dose was administered on 7 April 1999. On 10 April 1999, the subject was shown to have experienced liver injury, a serious adverse event, characterized by increased AST (SGOT), ALT (SGPT) and lactate dehydrogenase (LDH) levels. The subject had no associated signs or symptoms, but stated that he had ingested an excessive amount of alcohol during the previous evening. There was no counteractive treatment given. By 18 April 1999, the SGOT, SGPT, and LDH levels had decreased to near baseline values and by 28 Apr 1999 had returned to baseline values. The investigator assessed the liver injury as possibly related to study medication with other known or suspected cause of excessive alcohol intake but suspected that the excessive alcohol intake as the most probable cause of the acute liver injury. The Sponsor commented that the possibility of a causal relationship between the study drug and the reported event could not be excluded. However the history of excessive alcohol intake, and the AST/ALT ratio of 2:1 is compatible with an alcohol-related etiology. It was not known if the subject has early alcoholic liver disease or a history of chronic alcohol abuse.

Subject 0264/013 in Study 3008 was a 34-year-old white male who started treatment on 12 January 1999 for tonsillitis/pharyngitis with telithromycin. His last study drug was administered on 13 January 1999 when he reported experiencing an allergic reaction to the study medication. Approximately 30 minutes to one hour after taking half of the evening dose of study medication, the subject felt pain in his stomach which spread to his chest, he felt pressure in his chest, had trouble breathing (felt short of breath), felt his throat swelling and developed a rash on his face. All of the symptoms except the facial rash resolved after 1.5 hours. The subject sought medical attention for this event on the morning of 13 January 1999. No counteractive medication or measure was taken for this event. As a result of this event, study medication was discontinued and the subject was withdrawn from the study on 13 January 1999. The facial rash lasted 10 days following withdrawal from study medication and resolved. To the investigator's knowledge, there was no record of this subject having been previously exposed to macrolide antibiotics. The investigator requested the subject to undergo allergy testing, but the subject declined. The investigator assessed the allergic reaction as possibly related to study medication.

Appendix 18. Shift tables for ALT (SGPT)

Number of subjects (%) with normal and high values of ALT (SGPT) at entry and during treatment in CAP studies

Entry Status	During Treatment (from pretherapy through end of treatment + 7 days)					
	Normal	High				
	<ULN	>1 ULN	>2 ULN	>3 ULN	>5 ULN	>8 ULN
Controlled Studies						
Telithromycin						
Normal, N=395	309 (78.2)	72 (18.2)	10 (2.5)	3 (0.8)	1 (0.3)	0 (0.0)
High, N=101	18 (17.8)	57 (56.4)	18 (17.8)	6 (5.9)	2 (2.0)	0 (0.0)
Comparator						
Normal, N=388	317 (81.7)	64 (16.5)	4 (1.0)	2 (0.5)	1 (0.3)	0 (0.0)
High, N=96	25 (26.0)	43 (44.8)	16 (16.7)	8 (8.3)	3 (3.1)	1 (1.0)
Uncontrolled Studies						
Normal, N=671	549 (81.8)	93 (13.9)	21 (3.1)	7 (1.0)	0 (0.0)	1 (0.1)
High, N=146	20 (13.7)	71 (48.6)	27 (18.5)	25 (17.1)	1 (0.7)	2 (1.4)

Number of subjects (%) with normal and high values of ALT (SGPT) at entry and during treatment in non-CAP studies

Entry Status	During Treatment (from pretherapy through end of treatment + 7 days)					
	Normal	High				
	<ULN	>1 ULN	>2 ULN	>3 ULN	>5 ULN	>8 ULN
Controlled Studies						
Telithromycin						
Normal, N=1251	1126 (90.0)	117 (9.4)	5 (0.4)	2 (0.2)	0 (0.0)	1 (0.1)
High, N=182	31 (17.0)	115 (63.2)	22 (12.1)	12 (6.6)	1 (0.5)	1 (0.5)
Comparator						
Normal, N=936	836 (89.3)	92 (9.8)	6 (0.6)	2 (0.2)	0 (0.0)	0 (0.0)
High, N=130	25 (19.2)	74 (56.9)	19 (14.6)	9 (6.9)	1 (0.8)	2 (1.5)
Uncontrolled Studies						
Normal, N=265	241 (90.9)	24 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
High, N=34	12 (35.3)	17 (50.0)	4 (11.8)	1 (2.9)	0 (0.0)	0 (0.0)

Appendix 19. Narratives for subjects treated with telithromycin who experienced serious hepatic events

Narratives for subjects treated with telithromycin who experienced serious hepatic events.

Subject 0060/039: A 76-year-old women in Study 3006 started treatment with telithromycin on 11 Feb 1999 for treatment of pneumonia. Sputum culture at pretherapy/entry revealed colonization with *Streptococcus*, group A. On 15 Feb 1999, asymptomatic elevation of liver associated enzymes was discovered. This event led to discontinuation of the study medication and withdrawal from the study on 17 Feb 1999. Therapy was changed to Ceftin (cefuroxime) 500 mg twice daily on 16 Feb 1999. Laboratory test results are presented in the following table.

Laboratory test results for subject 0060/039

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

NR= normal range

Both investigator and sponsor assessed the liver injury (coded as liver damage) as possibly related to the study medication. The event, however, was asymptomatic, and appeared to be resolving even with continued treatment with telithromycin because the transaminase levels were appreciably lower on day 7 when the drug was discontinued, and quickly returned to normal levels thereafter.

Subject 502/1069: A 53-year-old man with a long history of asthma and diabetes mellitus was enrolled in Study 3000 on 02 Feb 1999 with CAP. The patient had been previously exposed to macrolide antibiotics without event. He received telithromycin from 3-12 Feb 1999, with an outcome of cure. Three days after the last dose (15 Feb 1999), he was exposed to family members suffering from a gastroenteritis-like illness and developed an acute illness (fever, vomiting, and diarrhea) 24 hours later. The vomiting and diarrhea resolved, but on visit 4 (22 Feb 1999) he still complained of fever. ALT, which was already elevated at baseline (81 U/L with N< 49), was 354 U/L, and CRP was elevated (68 mg/L), both measured at a local laboratory. On 25 Feb 1999, three days after visit 4, AST was significantly elevated (1529 U/L) and CRP was 170 mg/L; both were examined at a local laboratory. The subject was hospitalized with a diagnosis of hepatitis. Hepatitis A-B-C serology was negative. EBV- and CMV-serology were positive (IgG) but these results were considered consistent with past infection. Percutaneous liver biopsy performed on 02 March 1999 revealed acute hepatitis with predominantly centrilobular liver necrosis, granulomata-like structures and eosinophilic infiltration. An abdominal ultrasound examination suggested skatosis. The subject was discharged from the hospital on 10 March 1999. The table below demonstrates the trend of liver-associated enzymes and using results from the local laboratory (values were obtained outside of the clinical observation period).

Laboratory test results for subject 502/1069

Date	2Feb99	22Feb99	25Feb99	26Feb99	27Feb99	28Feb99	2Mar99	10Mar99	15Mar99	9Apr99
AST (NR<49 U/L)	38	-	-	170	-	-	-	-	-	-
ALT (NR<49 U/L)	81	354	1529	947	694	550	456	362	130	53
Alk Phos (NR 60-275 U/L)	-	-	169	164	194	260	259	251	-	169
Bilirubin (NR 2-20 μmol/l)	9	-	29	31	26	24	18	13	-	16

NR = normal range

All serology tests were negative. Concomitant medications included: Para-tabs 500 mg x 1) po for fever during 28-29Jan 1999; fluticasone inhaler dates unknown; Nasonex nasal aerosol, paracetamol (500 mg doses for a total of 6 tablets in 1 week) po for fever from 15 Feb 1999; and salbutamol (dose unknown, as needed) inhaler for asthma. The investigator assessed the serious adverse event as related to study medication. At the time the Sponsor commented that the causal relationship between the study drug and the reported event is possible.

This patient had a second episode of asymptomatic acute hepatitis in November 1999, which followed treatment with acetaminophen (no exposure to telithromycin). ALT reached 1331 U/L on 12 November and returned to 43 U/L on 3 February 2000. The IgG was 18 g/L. A liver biopsy on 27 December 1999 showed centrilobular necrosis (and fibrosis). ALT, AST, alkaline phosphatase and bilirubin were last tested 19 July 2000 and were normal. The results of antibody testing are shown in the following table.

Auto antibodies testing

		Anti nuclear antibodies ANA	Anti smooth muscle antibodies ASMA	Anti liver and kidney microsomes antibodies LKM1	Hospital Finnish = F Beaujon = B
First episode of hepatitis	2 Feb 99	NEG	NEG	NEG	B
	5 Feb 99	POS: 1/200	NEG	NEG	B
	22 Feb 99	NEG	NEG	NEG	B
	26 Feb 99	NEG	NEG	Not tested	F
	16 March 99	NEG	NEG	NEG	B
Second episode of hepatitis	12 Nov 99	NEG	POS ≥ 1/1000	Not tested	F
	4 Dec 99	NEG	POS: 1/100	NEG	B
	Feb 00	NEG	POS: 1/50	NEG	B
	19 July 00	NEG	POS: 1/50	NEG	B
	19 July 00	NEG	NEG	Not tested	F

NEG = negative ; POS = positive

Telithromycin cannot be excluded as a possible cause for the first episode of hepatitis. However, a determination of causality is difficult due to the following confounding factors: an increases in transaminases at baseline which suggests the possibility of a pre-existing undiagnosed liver disease, concomitant administration of paracetamol, and the presence of mildly positive auto-antibodies. In contrast, due to the long period (9 months) from discontinuation of therapy to the onset of the second episode, a role for telithromycin in the occurrence of this second episode would be unlikely. Further, the occurrence of the second episode lessens the likelihood that the first was also due to telithromycin.

Subject 0259/005: A 19-year-old white man in Study 3008 demonstrated increased AST (SGOT), ALT (SGPT) and lactate dehydrogenase (LDH) on 10 April 1999 after treatment with telithromycin for tonsillitis. This event was assessed as medically important. The subject had no associated signs or symptoms, but stated that he had ingested an excessive amount of alcohol during the previous evening. He received telithromycin from 29 Mar 1999 to 7 April 1999. Study medication was completed as planned on 7 April 1999, 3 days prior to the laboratory draw, which showed elevated SGOT, SGPT and LDH. There was no counteractive treatment given. By 18 April 1999, the SGOT, SGPT, and LDH had decreased to near baseline values and by 28 April 1999 had returned to baseline values. Relevant laboratory values are presented in the following table.

Laboratory test results for subject 0259/005

Laboratory analyte	29 Mar 99 Pretherapy /entry	1 Apr 99 On-therapy	10 Apr 99 End of therapy	18 Apr 99 TOC	28 Apr 99 LPT
AST/SGOT (NR = 11-36 U/L)	23	ND	273	29	19
ALT/SGPT (NR = 6-43 U/L)	27	ND	124	44	28
SGGT(NR = 10-61 U/L)	31	ND	37	39	35
LDH (NR = 53-234 U/L)	192	ND	592	133	108
Bilirubin (NR = 3-21 µmol/L)	21	ND	14	22	15

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

The investigator assessed the clinical outcome for this subject as cure at posttherapy/TOC and late posttherapy and suspected the excessive alcohol intake as the most probable cause of the acute liver injury. The sponsor commented that the history of excessive alcohol intake, and the AST/ALT ratio of 2:1 was compatible with an alcohol-related etiology. It is not known if the subject has early alcoholic liver disease or a history of chronic alcohol abuse.