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BRIEFING DOCUMENT AVAILABLE FOR PUBLIC DISCLOSURE

KETEK® (telithromycin)

December 14-15, 2006, Anti-infective Drugs Advisory Committee/Drug Safety and Risk Management Advisory Committee Meeting

NDA 21-144

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LIST OF ABBREVIATIONS

ABS	Acute bacterial sinusitis
ADR	Adverse drug reaction
AE	Adverse event
AECB	Acute exacerbation of chronic bronchitis
AERS	FDA Adverse Event Reporting System
AESI	Adverse event of special interest
AIDAC	Anti-Infective Drugs Advisory Committee
ALF	Acute liver failure
AMC	Amoxicillin-clavulanic acid
AMX	Amoxicillin
AOM	Acute otitis media
ASLI	Acute severe liver injury
ALT	Alanine aminotransferase (previously SGPT)
AST	Aspartate aminotransferase (previously SGOT)
ATC	Anatomic and therapeutic classification
AZI	Azithromycin
bmITT	Modified intent-to-treat analysis of bacteriologic outcome
CAP	Community-acquired pneumonia
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control
CEC	Clinical Events Committee
CEF	Cefuroxime
CHMP	Committee on Medicinal Products for Human Use
CI	Confidence interval
CLA	Clarithromycin
CNALV	Clinically noteworthy abnormal laboratory value
COPD	Chronic obstructive pulmonary disease
CRF	Case record form
CSP	Clinical study protocol
CSR	Clinical study report
DAIOP	Division of Anti-Infective and Ophthalmologic Products (formerly the Division of Anti-Infective Drug Products)

DSaRM	Drug Safety and Risk Management Advisory Committee
EBGM	Empirical Bayesian geometric mean
EC	European Commission
EMEA	European Medicines Agency
ERG	Electroretinography
ERSP	Erythromycin-resistant *Streptococcus pneumoniae*
ERY	Erythromycin
ERY-R	Erythromycin-resistant
FDA	Food and Drug Administration (US)
FEV_1/FVC	Forced expiratory volume in 1 second/forced vital capacity
FOI	Freedom of Information
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GIDB	Global Integrated Database
GSO	Global safety officer
HLGT	High-level group term
HLT	High-level term
HR-QOL	Health-related quality of life
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy
IC_{50}	Concentration inhibiting 50% of the response
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMS	Intercontinental Medical Statistics
IND	Investigational New Drug
ITT	Intent to treat
LEV	Levofloxacin
LOC	Loss of consciousness
MDRSP	Multidrug-resistant *Streptococcus pneumoniae* (includes isolates known as PRSP [penicillin-resistant Streptococcus pneumoniae] and are isolates resistant to 2 or more of the following antimicrobials: penicillins, 2nd generation cephalosporins [eg, cefuroxime], macrolides, tetracyclines, and trimethoprim/sulfamethoxazole)
MedDRA	Medical Dictionary of Regulatory Activities
MEF	Middle ear fluid
MGPS	Multi-item gamma Poisson shrinkage
MIC	Minimum inhibitory concentration
mITT	Modified intent-to-treat

MLS_B	Macrolide-lincosamide-$streptogramin_B$
NOAEL	No observed adverse effect level
NOS	Not otherwise specified
OB	Office of Biostatistics
OSE	Office of Surveillance and Epidemiology
OTC	Over the counter
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEN	Penicillin
PEN-I	Intermediate resistance to penicillin
PEN-R	Penicillin resistant
PIL	Patient Information Leaflet (in EU)
PK	Pharmacokinetic
PORT	Pneumonia Patient Outcomes Research Team
PPb	Per-protocol population for analysis of bacteriologic outcome
PPc	Per-protocol population for analysis of clinical outcome
PPI	Patient Package Insert (in US)
PRSP	Penicillin-resistant *Streptococcus pneumoniae*
PROTEKT	Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
PSUR	Periodic Safety Update Report
PT	Preferred Term
QTc	QT interval on electrocardiogram corrected for heart rate
QTcB	QT corrected using the Bazett formula
QTcF	QT corrected using the Fridericia formula
QTcN	QT corrected for population under investigation
rRNA	Ribosomal RNA
RTI	Respiratory tract infection
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SPC	Summary of Product Characteristics (EU labeling)
TEAE	Treatment-emergent adverse event
TEL	Telithromycin
TELICAST	Telithromycin and Chlamydia in Asthma study (Study A3503)
TOC	Test of cure

T/P	Tonsillitis/pharyngitis
TPD	Therapeutic Products Directorate
TVA	Trovafloxacin
ULN	Upper limit of normal range
US	United States
USPI	US Prescribing Information (US labeling)
VEP	Visual evoked potential
XDRSP	Extended drug-resistant *Streptococcus pneumoniae* (isolates that are resistant to 5 or 6 antibacterials)

EXECUTIVE SUMMARY

INTRODUCTION

On October 5, 2006, sanofi-aventis was notified that a joint meeting of Anti-infective Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee had been scheduled for December 14 and 15, 2006.

This document includes the following:

- Clinical trial data and information supporting the role of telithromycin, a summary of the efficacy and safety data available at the time of initial approval in the US (including ex-US postmarketing safety data following an estimated 6 million patient exposures);
- Efficacy and safety data obtained in the postapproval period (including current worldwide postmarketing safety data following an estimated 28 million patient exposures);
- Evolving labeling agreed upon with the FDA based on ongoing and regular review of emerging safety data; and
- Finally, a comprehensive assessment of benefit/risk, provided in an effort to put this information into perspective.

Telithromycin was first approved in the European Union where it received marketing authorization by centralized procedure for the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinusitis in patients ≥18 years of age and tonsillitis/pharyngitis in patients ≥12 years of age in 2001. It was subsequently approved in Canada and Japan in 2003, before receiving approval from the US Food and Drug Administration in 2004 for the treatment of respiratory tract infections. In the US, telithromycin is indicated for the treatment of mild to moderate community-acquired pneumonia, including infections due to multidrug-resistant *S. pneumoniae*, acute exacerbation of chronic bronchitis, and acute bacterial sinusitis in patients 18 years of age or older (*APPENDIX D: FDA APPROVAL LETTER* and *APPENDIX G: LABELING*). As of August 31, 2006, the estimated worldwide market exposure to telithromycin is 28 million courses of treatment.

MEDICAL NEED

Community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute bacterial sinusitis are among the most frequent infectious diseases encountered in the ambulatory care setting and are associated with significant morbidity. In the US these infectious diseases are usually treated empirically with the following antibiotics: β-lactams (eg, amoxicillin, amoxicillin-clavulanic acid, oral cephalosporins), macrolides (eg, clarithromycin, azithromycin, and erythromycin), ketolides (telithromycin) and quinolones (eg, levofloxacin, moxifloxacins). There is an ongoing medical need for therapeutic options to address the following limitations in existing antibiotic therapies: (1) decreased antibacterial susceptibility as a result of resistance (particularly *S. pneumoniae*) and (2) a collateral effect on nonrespiratory pathogens resulting in the selection of resistance in nonrespiratory pathogens or overgrowth of other bacteria (such as enteric Gram-negative pathogens). In patients with acute bacterial infections in the ambulatory setting the clinical relevance of antibacterial resistance is not always demonstrable. However, recent studies provide evidence that macrolide resistance is associated with a higher rate of treatment failure with bacteremia and a risk of suppurative complications in patients treated with these antibiotics.

Telithromycin is a ketolide, derived from the macrolide family of antibiotics and developed for the treatment of community-acquired RTIs. Overall, telithromycin differs from macrolides by its more efficient activity against *Streptococcus pneumoniae*, its activity against multidrug-resistant respiratory tract infection pathogens. Because of its novel mechanism of action, telithromycin is active against bacteria that harbor a macrolide-lincosamide-streptogramin$_B$ (MLS_B)-inducible type of resistance (*erm*) and does not induce MLS_B resistance in vitro. It is active in vitro against Gram-positive cocci (*S. pneumoniae*) resistant to the macrolides via an efflux mechanism and is 2 to 4 times more active than clarithromycin, and 4 to 8 times more active than azithromycin against Gram-positive cocci susceptible to macrolides.

Occurrence of *S. pneumoniae* resistance to telithromycin is rare, and, in particular, telithromycin remains active in vitro against strains of *S. pneumoniae* with multiple mechanisms of resistance to macrolides, ie, *erm*(B) + *mef*(A); these strains are associated with high-level macrolide resistance and even β-lactam resistance, and have been recently on the rise in the US.

Overall, the antibacterial spectrum of telithromycin is targeted against respiratory tract infection pathogens: *S. pneumoniae* (including multidrug-resistant strains), *H. influenzae* (including β-lactamase-positive strains), *M. catarrhalis* (including β-lactamase-positive strains), *S. pyogenes* (susceptible to macrolides or resistant to macrolides by the presence of *mef* or *erm*TR genes), *S. aureus* (susceptible to macrolides or resistant to macrolides by an inducible mechanism), and atypical and intracellular pathogens *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. Telithromycin's weak in vitro activity against enteric Gram-negative rods makes it less likely than fluoroquinolones or β-lactams to contribute to the development of clinically significant antibiotic resistance among enteric pathogens of concern.

SUMMARY OF EFFICACY AND SAFETY DATA AVAILABLE PRIOR TO FDA APPROVAL

The clinical efficacy of telithromycin was evaluated in 14 Phase III pivotal efficacy and safety studies in 3 indications, community-acquired pneumonia (4 randomized, controlled studies and 4 open label studies), acute exacerbation of chronic bronchitis (2 randomized controlled studies) and acute bacterial sinusitis (2 randomized comparator-controlled studies and 1 randomized, double-blind comparison of two treatment durations with documentation of infection). All comparative studies were designed as noninferiority trials, consistent with guidance from health authorities. The treatment regimen was 800 mg once daily for 5 days in acute exacerbation of chronic bronchitis and acute bacterial sinusitis and 7 to 10 days in community-acquired pneumonia. Efficacy was also observed in subjects at higher risk of treatment failure, such as elderly patients, patients with community-acquired pneumonia and pneumococcal bacteremia, patients with acute exacerbation of chronic bronchitis and bronchial obstruction, and patients with acute bacterial sinusitis rated as "severe" by the Investigator.

Summary of preapproval efficacy data for community-acquired pneumonia

In Phase III community-acquired pneumonia studies, in a large number of patients, telithromycin showed clinical efficacy against the key bacterial organisms responsible for pneumonia in the ambulatory setting, including both common and atypical/intracellular pathogens: *S. pneumoniae* (93.7% clinical cure [312/333]), *H. influenzae* (89.3% [222/253]), *M. catarrhalis* (85.5% [47/55]), *M. pneumoniae* (97.1% [33/34]), and *C. pneumoniae* (94.3% [33/35]).

Telithromycin also showed clinical efficacy in treating subjects infected with antibiotic-resistant strains of *S. pneumoniae,* including macrolide- (erythromycin A-) resistant *S. pneumoniae* isolated, and penicillin G-resistant *S. pneumoniae* isolated as a single or mixed pathogen infection. The clinical cure rate was 91.9% (34/37) in subjects with community-acquired pneumonia due to multidrug-resistant *S. pneumoniae*; it was 84.6% (11/13) in subjects with multidrug-resistant *S. pneumoniae* bacteremia.

Summary of preapproval efficacy data for acute exacerbation of chronic bronchitis

In Phase III acute exacerbation of chronic bronchitis studies, telithromycin was shown to be noninferior in clinical efficacy to widely used treatments (cefuroxime axetil, clarithromycin, or amoxicillin-clavulanic acid, administered 2 to 3 times daily). The clinical cure rate for telithromycin was 86.0% (413/480). The efficacy of telithromycin was consistent across all subgroups of subjects, including those with increased risk for morbidity, eg, patients ≥65 years of age, at 85.3% (157/184); and subjects with severe bronchial obstruction, defined by a ratio of forced expiratory volume at 1 second to forced vital capacity <60%, at 78.5% (117/149).

Summary of preapproval efficacy data for acute bacterial sinusitis

The clinical efficacy of telithromycin 800 mg once daily for 5 days was shown to be noninferior to accepted treatments (cefuroxime axetil or amoxicillin-clavulanic acid, administered 2 to 3 times daily) given for 10 days in 2 Phase III double-blind randomized controlled acute bacterial sinusitis studies. The clinical cure rate for telithromycin is 80.9% (271/335).

Clinical cure rates with telithromycin were similar to those of comparators in subjects at increased risk of treatment failure (eg, subjects with Investigator-rated "severe" infections, total sinus opacification, or sinus muscosal thickening).

SAFETY EVALUATION

During the course of clinical development, several safety topics were identified as potential adverse events of special interest based upon consideration of known effects of the related macrolide class of drugs and review of preclinical, clinical pharmacology and/or clinical data. The combination of recognized macrolide class drug effects and preclinical findings led to close monitoring of hepatic and cardiac adverse events during clinical trials and the execution of specific clinical pharmacology investigations. Visual effects were identified during the comparative clinical trials, leading to the subsequent performance of targeted preclinical and clinical pharmacology investigations.

PREAPPROVAL SAFETY DATA

The clinical safety database includes 14 Phase III studies, which form the basis for the FDA-approved indications, and data from the 2 Phase III T/P studies. Therefore, the Phase III safety database contains data from 6919 safety-evaluable subjects in 16 integrated Phase III pivotal efficacy and safety studies, including 12 randomized controlled studies. Of the 6919 safety-evaluable subjects, 4780 subjects received telithromycin and 2139 subjects received comparator drugs. Safety data available preapproval also included postmarketing safety data following an estimated ex-US marketed exposure of 6 million patients.

Additional safety data were generated in a large simple safety study (Study A3014). A total of 24,137 adult outpatients were enrolled and were safety evaluable (12,159 subjects in the telithromycin treatment group and 11,978 in the amoxicillin-clavulanic acid treatment group). The FDA raised concerns about Good Clinical Practice violations at several clinical study sites and did not rely on Study A3014 as a basis for approval. Information on this study is not referenced in the US labeling and is not included in the Phase III safety database information provided in this document.

Summary of safety data prior to FDA approval

- In clinical trials, the incidence and nature of the most frequently reported treatment-emergent adverse events were, in general, similar between telithromycin and comparators. Treatment-emergent adverse events of the Gastrointestinal disorders system organ class (eg, diarrhea not otherwise specified, nausea and vomiting) were most frequently reported and were generally mild or moderate in intensity.
- The overall incidence of death was the same (0.4%) in both telithromycin and comparator groups in clinical trials. None of the deaths were assessed by the Investigator as being possibly related to study medication.
- The incidence of serious adverse events (SAEs) in clinical trials was similar in both telithromycin and comparator treatment groups.
- Adverse events requiring discontinuation of study medications were uncommon and balanced between treatment groups: telithromycin (119/2702, 4.4%) and comparators (92/2139, 4.3%). The most frequently reported treatment-emergent adverse events leading to discontinuation in both telithromycin- and comparator-treated subjects were diarrhea not otherwise specified (0.9% vs. 0.7%, respectively), vomiting not otherwise specified (0.8% vs. 0.5%, respectively) and nausea (0.7% vs. 0.5%, respectively).
- The frequency and pattern of treatment-emergent adverse events did not differ significantly between the randomized controlled and open label studies.

Summary of adverse events of special interest:

Hepatic adverse events

- The incidence of hepatic adverse events was similar between treatment groups in all Phase III studies and hepatic laboratory values (such as combined total bilirubin and alanine aminotransferase increases and clinically noteworthy abnormal laboratory values for alanine aminotransferase and aspartate aminotransferase, which were defined consistently across studies) were balanced between telithromycin- and comparator-treated groups.
- Postmarketing data available preapproval in the US revealed predominantly moderate and reversible reports of hepatic injury, with an infrequent reporting of Acute Severe Liver Injury. No cases of drug-related hepatic failure or death, or hepatic injury resulting in transplantation, had been reported after an estimated 6 million exposures outside the US.
- The initial US labeling included information on hepatic adverse events in the PRECAUTIONS section.

Cardiac adverse events

- At therapeutic dose, telithromycin was associated with a 1.5-ms mean increase in QTc interval. QTc outlier values were uncommon and similar in frequency to those seen with clarithromycin and non-macrolide antibiotics. No excess in risk for significant QTc interval prolongation was noted, even in at-risk populations.
- Ex-US postmarketing spontaneous reports prior to FDA approval included isolated reports of torsades de pointes and ventricular fibrillation. These reports lacked information to establish the diagnosis, were confounded by the coadministration of other medications known to affect cardiac repolarization, or occurred in patients with significant underlying cardiac disease or concurrent illness, which may otherwise explain the event onset.
- The initial US labeling includes information regarding QTc prolongation from clinical trials with telithromycin and characterization of the potential for cardiovascular events with QTc prolongation in the Warnings section.

Visual adverse events

- The incidence of visual treatment emergent adverse events was higher in the telithromycin group than in the comparator group (1.1% vs. 0.4%). Most were mild or moderate in severity. The most common visual event, blurred vision, generally mild, transient, and fully reversible, was rarely reported (0.5%) in Phase III clinical studies. Subsequent Phase I investigations indicated that the mechanism of blurred vision is consistent with a transient delay in accommodation.
- In ex-US postmarketing spontaneous reports prior to FDA approval, the most frequently reported visual AEs were visual disorders (vision blurred, “visual disturbances,” accommodation disorder, and diplopia). For the most part, these events were consistent with mild and transient visual blurring described in the clinical studies.
- The initial US labeling includes visual disorders in the PRECAUTIONS section.

Exacerbation of myasthenia gravis

- There were no reported cases of myasthenia gravis or worsening of pre-existing myasthenia gravis identified in the Phase III development program.
- Exacerbation of myasthenia gravis was identified from ex-US postmarketing spontaneous reports prior to FDA approval.
- The initial US labeling includes myasthenia gravis in the WARNINGS section.

POSTAPPROVAL MICROBIOLOGY DATA

The Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) studies – PROTEKT Global, an international study initiated in 1999, and PROTEKT US, initiated in 2000 – are longitudinal microbiological surveillance studies designed to evaluate the activity of telithromycin against *S. pneumoniae* and other common respiratory tract infection pathogens and to compare its activity with that of other antibacterial agents. The PROTEKT Global and PROTEKT US study results show that telithromycin retains high activity against *S. pneumoniae*. In particular, telithromycin displays potent in vitro activity against *S. pneumoniae* including strains resistant to antibiotics by a variety of mechanisms (eg, multidrug-resistant *S. pneumoniae*). There is a low prevalence of telithromycin-resistant *S. pneumoniae*, with no signal of increased resistance or clonal spread of resistance.

Telithromycin-resistant *S. pneumoniae* isolates, first described prior to launch of the product in October 2001, remain rare. Very few cases of emerging resistance in clinical setting have been described. Several alterations (among *erm*[B], ribosomal RNA, or proteins) seem to be necessary to obtain strains with high level of resistance to telithromycin. Given its targeted spectrum activity on respiratory tract infection pathogens, telithromycin microbiological activity supports its use in the treatment of community-acquired respiratory tract infection pathogens.

POSTAPPROVAL CLINICAL STUDIES

A total of 10 Phase IV randomized controlled studies of telithromycin have been conducted by sanofi-aventis to expand the clinical efficacy information for telithromycin in approved indications in the US and have been completed (database locked): 3 in community-acquired pneumonia, 4 in acute exacerbation of chronic bronchitis, and 3 in acute bacterial sinusitis. Safety data are also available from 2 comparative studies to assess the impact of telithromycin on the bacterial flora of healthy subjects. A total of 3,136 patients were treated with telithromycin vs. 3,846 patients with comparators. Results of these Phase IV studies confirm that overall telithromycin is effective in the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute bacterial sinusitis. Data show potential benefits in 3 areas: a trend toward superior efficacy compared to local customary treatment was observed in the treatment of community-acquired pneumonia in countries with high prevalence of antibiotic-resistant *S. pneumoniae*. In subjects with acute exacerbation of chronic bronchitis, focusing on the population of subjects with *S. pneumoniae* at baseline, there was a significant decrease in carriage of penicillin- or macrolide-resistant *S. pneumoniae* compared to azithromycin. In subjects with ABS, evaluation of time to symptom resolution showed that telithromycin was comparable to moxifloxacin and potentially better than treatment with amoxicillin-clavulanic acid, both recognized as highly effective treatments in this indication. In addition, 1 proof of concept study was conducted in patients with acute exacerbations of asthma.

Overall, Phase IV safety data did not reveal any new safety signals compared to Phase III studies.

POSTMARKETING DATA

Sanofi-aventis rigorously monitors and evaluates all reports of adverse events obtained through postmarketing safety surveillance and clinical trials. These data are provided regularly to the FDA and other health authorities as required by regulations. Sanofi-aventis has routinely reviewed and analyzed postmarketing safety data as they beome available. As is usual in the evolution of product labeling, sanofi-aventis and the FDA have interacted and exchanged information to update the labeling in order to provide healthcare professionals with important additional information regarding use of telithromycin.

In the period from July 2001 through September 15, 2006, a total of 5579 postmarketing spontaneous reports of adverse events have been received worldwide by sanofi-aventis Global Pharmacovigilance, giving an overall reporting rate for spontaneous adverse events of approximately 199 reports per million exposures.

Reporting rates in the first 29 months since approval in the US (269 reports per million exposures) were generally similar to those seen worldwide, ex-US, in the 29-month period prior to FDA approval (207 reports per million exposures). The decrease seen when compared to the current worldwide reporting rate likely reflects the decrease in overall reporting expected with the Weber effect. (The term "Weber effect" refers to the fact that for any drug, postmarketing spontaneous event reporting rates are generally higher during the first 2 years that a drug is on the market with subsequent decreases in report rates seen thereafter.) The adverse event profile was generally comparable for all analyses.

As postmarketing safety data have led to an improved understanding of the frequency, severity, or risk of adverse events and adverse events of special interest for all patients or special populations, additional information has been added to the US labeling, including:

- Information regarding dosage reduction in patients with severe renal impairment and multiple impairments (submitted as a Prior Approval Supplement in April 2004);
- Clinical safety information on a potential drug-drug interaction with oral anticoagulants (submitted in as a Changes Being Effected Supplement in August 2004);
- Clinical safety information on postmarketing reports of pancreatitis, palpitations, and syncope (submitted as a Changes Being Effected Supplement in November 2004); and
- Clinical safety information on postmarketing reports of severe hepatic adverse events and exacerbation of myasthenia gravis with fatal outcome (submitted as a Changes Being Effected Supplement June 2006).

In addition to postapproval labeling modifications, sanofi-aventis's risk management plan includes communications with healthcare professionals, educational programming, and additional epidemiologic investigations (eg, to assess postmarketing safety data and antibiotic resistant patterns). Communications to healthcare professionals have included, for example, a "Dear Healthcare Professional" Letter, issued in connection with a recent labeling change related to severe hepatic adverse events and exacerbation of myasthenia gravis with fatal outcome.

EPIDEMIOLOGY

To further elucidate the safety profile of telithromycin, analyses from the FDA Freedom of Information database were performed for telithromycin as well as for other oral antibiotics typically used to treat community-acquired respiratory tract infections (β-lactams, macrolides, and fluoroquinolones). These analyses identify signals of hepatic adverse events, visual adverse events, and exacerbation of myasthenia gravis for telithromycin. Since characteristic safety profiles of drugs are unique, other marketed antibiotics show different signals (eg, pseudomembranous colitis, anaphylactic reactions, tendon rupture) that are not signals for telithromycin.

The results from these signal generation methods should be interpreted with caution because the spontaneous reports of adverse events are subject to multiple biases, including stimulated reporting, incomplete unverified data, secular trends in reporting, and the Weber effect.

A more rigorous method for evaluation of potential safety signals, an epidemiologic study using PHARMetrics database, was conducted by sanofi-aventis. Results indicate that, compared to other antibiotics, there is no evidence of an increased risk of severe hepatic injury in telithromycin compared to antibiotics with similar indications. In addition, the preliminary medical review data from the Ingenix epidemiologic study and information from the United Network for Organ Sharing indicate that acute liver failure is a rare event following telithromycin use.

CONCLUSIONS OF BENEFIT/RISK ASSESSMENT

Telithromycin is active against *S. pneumoniae*, including strains with various mechanisms of antibiotic resistance (eg, multidrug-resistant *S. pneumoniae*) and an antibacterial spectrum specifically targeted to respiratory tract infection pathogens. Both features are of particular importance in the context of bacterial resistance. Several US regions have reached significant levels of *S. pneumoniae* resistance, with a growing number of strains that are highly resistant to numerous antibiotics. In addition, resistance of non-respiratory pathogens has been favored by the use of antibiotics with a broader spectrum of activity and maybe associated with difficult-to-treat infections of high morbidity and mortality.

Clinical trials in community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute bacterial sinusitis have consistently demonstrated the clinical efficacy of telithromycin. A short treatment duration of 5 days is effective for the treatment of patients with acute exacerbation of chronic bronchitis and acute bacterial sinusitis. A 7 to 10-day treatment period is effective for the treatment of community-acquired pneumonia. The short treatment duration of 5 days may enhance compliance and further reduce the development of antibiotic resistance.

Overall, the risks associated with telithromycin appear to be comparable to those of other marketed antibiotics prescribed for the treatment of community-acquired respiratory-tract infections, including β-lactams, macrolides, and fluoroquinolones. Each antibiotic has a different benefit/risk profile. By understanding the attendant benefits and the risks, healthcare professionals are better able to choose the appropriate treatment based on the infection, local resistance pattern, patient history, and concomitant medications. Therefore, telithromycin is an important therapeutic option for its approved indications in the treatment of community-acquired respiratory tract infections.

1 INTRODUCTION

On October 5, 2006, sanofi-aventis was notified that a joint meeting of Anti-infective Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee had been scheduled for December 14 and 15, 2006. Sanofi-aventis is pleased to provide a comprehensive review of data and information on telithromycin (KETEK®). In 2001, telithromycin received marketing authorization from the European Union (EU) by centralized procedure for the treatment of community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), acute sinusitis in patients ≥18 years of age and tonsillitis/pharyngitis (T/P) in patients ≥12 years of age. It was subsequently approved in Canada and Japan in 2003, before receiving FDA approval in 2004 for the treatment of respiratory tract infections (RTIs). In the US, telithromycin is indicated for the treatment of mild to moderate CAP, including infections due to multidrug-resistant *Streptococcus pneumoniae* (MDRSP), AECB, and acute bacterial sinusitis (ABS) in patients 18 years of age or older. As of September 15, 2006, the estimated worldwide market exposure to telithromycin is 28 million courses of treatment.

This Briefing Document includes:

- A brief description of telithromycin;
- A review of the medical need for safe and effective oral antibiotics to treat community-acquired respiratory tract infections (RTIs), including those infections due to antibiotic-resistant *Streptococcus pneumoniae*;
- A summary of the preapproval microbiology (in vitro, clinical pharmacology), clinical efficacy (Phase III), and safety (preclinical, Phase I, Phase III, intensified monitoring, and ex-US postmarketing) data to support the FDA approval of telithromycin on April 1, 2004;
- A summary of the available postapproval microbiology (epidemiology survey), efficacy (Phase IV) and safety (Phase IV and global postmarketing as well as preclinical investigations to evaluate AESIs) data as of September 15, 2006; and
- An assessment of the comparative benefit/risk profile of telithromycin.

As discussed throughout this Briefing Document as well as in the conclusions and overall summary, based on the available data, sanofi-aventis considers that telithromycin is an important therapeutic option in the treatment of its labeled indications.

Table 1 – Key dates in approval process for telithromycin

Event	Date
IND Application submitted by "sanofi-aventis"[a] to FDA	February 19, 1998
NDA Application submitted by sanofi-aventis to FDA	February 28, 2000
First FDA Advisory Committee Meeting	April 26, 2001
First FDA Approvable Letter from FDA for CAP, AECB, ABS[b]	June 1, 2001
Marketing authorization from EU (Centralized procedure)	July 9, 2001
Sanofi-aventis submits response to first FDA Approvable Letter[c]	July 24, 2002
Second FDA Advisory Committee Meeting	January 8, 2003
Second FDA Approvable Letter	January 24, 2003
Health authority in Canada approves telithromycin	May 28, 2003
Healthy authority in Japan approves telithromycin	October 16, 2003
Sanofi-aventis submits response to second FDA Approvable Letter	October 17, 2003
Sanofi-aventis submits 5-month Bridging Safety Update Report	February 27, 2004
Sanofi-aventis submitted revised Risk Management Plan to FDA	March 1, 2004
FDA approves Ketek NDA 21-144	April 1, 2004
Sanofi-aventis EMEA application for first 5-year renewal of marketing authorization	January 9, 2006
EU decision to renew marketing authorization	September 7, 2006

[a] "Sponsor will be referred to as "sanofi-aventis" throughout this document. See explanation in Footnote 3 of this document.
[b] "Approvable" = pending review of additional efficacy and safety data; "not approvable" for tonsillitis/pharyngitis indication.
[c] Including proposal for a Risk Management Plan.

2 DESCRIPTION OF TELITHROMYCIN

Telithromycin is the first in a new class of antimicrobial agents, the ketolides. These compounds were originally designed to overcome erythromycin resistance in *S. pneumoniae* isolates. Ketolides are characterized by the lack of the α-L-cladinose sugar at position 3 of the erythronolide a moiety, which is replaced by a keto group. The chemical name for telithromycin is 11,12 dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-6-0-methyl-3-oxo-12,11-[oxycarbonyl[[(4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-erythromycin, and its structural formula is $C_{43}H_{65}N_5O_{10}$.

When telithromycin received marketing authorization from the EU via a Centralized Procedure on July 9, 2001, it became the first member of this new class to be approved for the following indications: CAP, including infections due to erythromycin-resistant *S. pneumoniae*, AECB, and acute sinusitis in patients ≥18 years of age as well as T/P in patients ≥12 years of age. Since then, telithromycin has been approved by health authorities in more than 90 countries worldwide, including Canada (May 28, 2003), Japan (October 16, 2003), and the United States (US; April 1, 2004). There have been postapproval labeling changes based on updated safety information in each country where telithromycin is approved for marketed use. The EU health authority recently approved sanofi-aventis's application (required by EU regulations) for a 5-year renewal of the marketing authorization for telithromycin for the approved 4 indications based on a review of postmarketing safety and efficacy data. As of August 31, 2006, the estimated marketed exposure to telithromycin worldwide is 28 million courses of treatment.

3 PUBLIC HEALTH NEED

3.1 BURDEN OF DISEASE

Community-acquired RTIs are among the most frequent infectious diseases encountered in outpatients and are associated with significant morbidity.

Approximately 5.6 million cases of CAP are diagnosed in the US annually, with approximately 1.1 million requiring hospitalization [American Thoracic Society, 2001]. The mortality rate in patients with CAP varies with the severity of disease. In the US, the mortality rate in patients with CAP is <1% in outpatients, reaching 10% in the most severe cases requiring hospitalization [Fine et al., 1997; Marie, 2004; Kollef et al., 2006].

Studies which evaluated the impact of CAP on patient quality of life (QOL) have shown that the recovery time may be prolonged even in patients with mild illness treated in the outpatient setting. In a meta-analysis by Fine and colleagues [Fine et al., 1996], the authors reported the time to return to usual activities as 6 weeks for 45% of a cohort of hospitalized elderly patients and 8 weeks for 81.2% of a cohort of ambulatory and hospitalized adult patients.

In 2004, it was estimated that 9 million Americans reported a physician diagnosis of chronic bronchitis [American Lung Association, 2006]. Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the US and its incidence is on the rise, but less is known, however; about the mortality associated with acute exacerbation of chronic bronchitis (AECB) in outpatients. For exacerbations of COPD leading to hospitalization (not necessarily due to a bacterial infection, and representing the most severe cases), the short-term death rates are estimated to be about 8 to 11% [Connors et al., 1996; Groenewengen et al., 2003]. It is estimated that 470,000 patients are hospitalized each year with a primary diagnosis of obstructive chronic bronchitis with acute exacerbation [Kozak et al., 2004].

Doll and Miravitllas [Doll et al., 2005] performed a literature review of health-related quality of life (HR-QOL) in AECB and COPD. Poor HR-QOL scores were reported by all patients during acute exacerbations with the effect noted in general and disease-specific measures, and in physical and emotional domains.

The number of episodes of ABS in the community is estimated to be approximately 20 to 30 millions cases per year in the US [Kozak et al., 2005]. Complications of acute sinusitis are considered to be rare, but their exact frequency is unknown [Gwaltney et al., 2004]. These complications can be serious (eg, brain abscess, meningitis) and are associated with a high degree of morbidity when they occur [Jones et al., 2002].

The key bacterial organisms associated with these infections include common pathogens such as *S. pneumoniae* (including penicillin- and/or macrolide-resistant and/or multidrug-resistant strains, or MDRSP[1]), *Haemophilus influenzae* and *Moraxella catarrhalis* (including β-lactamase-producing strains), *Staphylococcus aureus*, and *Streptococcus pyogenes*. In addition, atypical and intracellular pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and to a lesser extent *Legionella pneumophila* [File, 2003], represent important causes of CAP in outpatients with infections that are often clinically refractory to the β-lactam antibiotics.

Clinical investigations have shown that *S. pneumoniae* and atypical organisms are the pathogens most frequently diagnosed as causative in CAP, whereas *H. influenzae* and *S. pneumoniae* are those most frequently thought to be causative in AECB and ABS. In fact, the exact distribution of the pathogens encountered in RTIs from the community is difficult to assess. In addition, it is difficult to accurately assess the causes of CAP due to the variations in detection methods and effects of the sensitivity and specificity of those tests. Organisms without a means of rapid testing may be under-reported. In AECB and ABS, bacteriological documentation is not obtained in usual practice, and treatment of RTIs is essentially empirical.

Certain patients may be at higher risk of infections due to antibiotic-resistant *S. pneumoniae*. Factors that increase the risk of developing antibiotic resistance include age >65 years, β-lactam therapy within the past 3 months, alcoholism, immunosuppression, multiple medical comorbidities, or exposure to a child in a daycare center [Mandell, 2004]; and for invasive pneumococcal infections, previous use of an antibiotic of the same class (penicillin, trimethoprim-sulfamoxazole, macrolide, fluoroquinolone) [Vanderkooi et al., 2005].

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[1] *Streptococcus pneumoniae* (MDRSP) includes isolates previously known as PRSP (penicillin-resistant *S. pneumoniae*) and are strains resistant to 2 or more of the following antibiotics: penicillin (MIC ≥2 μg/mL), 2nd generation cephalosporins (eg, cefuroxime) macrolides, tetracyclines, and trimethoprim-sulfamethoxazole.

Viruses may have a significant causative role in one-third to one-half of AECB and acute sinusitis cases encountered in the community. The curative role of antibiotics in these indications has been a matter of some scientific debate. A Cochrane review of antibiotics for acute exacerbation of COPD concludes to a reduction of the short-term mortality of 77%, and a decrease of treatment failure by 53%. However, the authors mentioned that the results of the analysis should be interpreted with caution, given the lack of homogeneity of the material reviewed principally [Ram, 2006]. Two recent reviews were also performed to evaluate the effects of antibiotics vs. placebo in ABS, both showing some trends of better efficacy in antibiotic-treated patients, but also concluding that other studies were needed, given the insufficient documentation of the diagnosis used to enroll patients [Gwaltney et al., 2004; Williams, 2003.].

The appropriate outcome measure used to assess antibacterial treatment effect for AECB and ABS (clinical success as assessed by the physician, patient-related outcome, or complications) is under review by the scientific community.

3.2 CURRENT ANTIBIOTIC TREATMENT OF RESPIRATORY TRACT INFECTIONS AND THEIR LIMITATIONS

Treatment of RTIs is generally empirical, and antibiotics used to treat these infections should be active in vitro against the most common pathogens involved in these infections. Antibiotic use varies across countries according to local clinical practice guidelines and the level of antibiotic susceptibility. In the US, these infectious diseases are usually treated with the following antibiotics: β-lactams (eg, amoxicillin, amoxicillin-clavulanic acid, oral cephalosporins), macrolides (eg, clarithromycin, azithromycin, erythromycin), ketolides (eg, telithromycin) and quinolones (eg, levofloxacin, moxifloxacin). To a lesser extent, tetracyclines, trimethoprim-sulfamethoxazole, and clindamycin are also used in the treatment of RTIs.

Among the antibiotics mentioned above, only new fluoroquinolones (eg, levofloxacin, moxifloxacin) and telithromycin are labeled for the treatment of MDRSP in CAP.

There is an ongoing medical need for therapeutic options to address the following key limitations in existing antibiotic therapies:

- A decrease of in vitro activity against key RTI pathogens, which exposes the patient to a risk of complication of their infection by lack of efficacy (macrolides, β-lactams);
- A collateral effect on nonrespiratory tract pathogens from the normal antimicrobial flora when their antibiotic spectrum is not specifically targeted to respiratory pathogens (quinolones, some β-lactams); this may result in the selection of resistance in nonrespiratory pathogens (eg, enteric Gram-negative bacteria) or favor the overgrowth of other bacteria such as *Clostridium difficile*.

3.2.1 Antibiotic resistance of respiratory tract infection pathogens

Resistance of community-acquired RTI pathogens to commonly used antibiotics has developed over recent decades.

3.2.1.1 Streptococcus pneumoniae resistance

Overall rate and trend of Streptococcus pneumoniae resistance in the US

- The prevalence of penicillin-resistant, macrolide-resistant, or multidrug-resistant strains of *S. pneumoniae* within the US has been evaluated for 5 years in a large epidemiology study [PROTEKT US], showing that the rate of penicillin-resistant strains has slightly decreased to around 15%, and that the rate of macrolide-resistant or multidrug-resistant strains has remained stable around 25 to 30% in *S. pneumoniae* isolated from patients with RTIs.
- These trends of *S. pneumoniae* resistance are consistent with data obtained from invasive infections through the Centers for Disease Control (CDC) Active Bacterial Core Surveillance network (http://www.cdc.gov/ncidod/dbmd/abcs/survreports.htm) showing that the rate of penicillin-resistance has also slightly decreased from 15% in 2001 to 9% in 2005, and the rate of macrolide-resistant strains appears also stable around 19% (2001 and 2005) in this study. The rate of resistance of the subgroup of *S. pneumoniae* blood isolate strains from PROTEKT is also consistent with the rates of resistance reported by the CDC for invasive infections in 2005: 11% vs. 9.5% for penicillin-resistant *S. pneumoniae*; and 23.2% vs. 19.4 for erythromycin-resistant *S. pneumoniae,* respectively.

Distribution of Streptococcus pneumoniae resistance across US regions

- The decrease of antibacterial susceptibility to β-lactams and macrolides varies across different regions in the US, as indicated in the table below.

Table 2 - PROTEKT US: Prevalence of penicillin and macrolide resistance in different regions of US, Year 5 (data on file, study report ongoing)

Region	Number of strains	PEN-I (%)	PEN-R (%)	ERY-R (%)
Total US	9487	20.1	17.5	30.9
North Central	1821	20	20.7	36.7
North East	3128	17.7	14.9	27.3
North West	525	14.7	14.3	20.8
South Central	1905	23.8	19.7	36.1
South East	1258	21.6	21	34.5
South West	850	21.7	11.9	20.7

PEN-I=intermediate resistance to penicillin; PEN-R=penicillin-resistant; ERY-R=erythromycin-resistant.

Impact of 7-valent conjugate vaccine

- Following the introduction of the conjugate vaccine in the US, a decrease in the rate of invasive pneumococcal disease caused by penicillin nonsusceptible strains of *S. pneumoniae* has been observed in children and elderly adults (from 70.3 to 13.1 cases/100,000 in children <2 years of age, and from 16.4 to 8.4 cases/100,000 in patients >65 years of age), between 1999 and 2004 [Kyaw et al., 2006].
- However, an increase in infections caused by serotypes not included in the vaccine is noted, particularly due to the 19A serotype, which has increased by 238% (313% in children, 72% in elderly adults) [Kyaw et al., 2006]. This serotype is particularly resistant to antibiotics as reported by Jacobs et al. (2006): 87% resistant to penicillin, 88% to amoxicillin, 98% to erythromycin. Results from PROTEKT US also show high resistance rates at the whole US territory level, but slightly lower than those reported by Jacobs et al: 42.3, 63.5, and 30% resistant to penicillin, azithromycin, and amoxicillin, respectively.

Increase in strains with a higher level resistance to macrolides in the US

- The mechanism of resistance to macrolides has evolved in recent years in the US, with a higher proportion of *erm*(B) + *mef*(A)[2], and a higher level of resistance level to amoxicillin-clavulanic acid. The proportion of *erm*(B) + *mef*(A) among erythromycin-resistant strains has increased from 9.7 to 20.1% between 2000 and 2004. This increase has been observed in all age groups (10.7 to 34.9% in children <2 years of age, 8.9 to 14.1% in adults 14 to 64 years of age, 8 to 14% in adults ≥65 years of age).
- In parallel, resistance to amoxicillin-clavulanic acid among *erm*(B) + *mef*(A) macrolide-resistant strains has increased and is thought to be due to a clonal diffusion. More than 95% of *erm*(B)+*mef*(A) strains isolated in 2004 to 2005 belong to the international Taiwan19F-14 clonal complex 271 (CC271) [Jenkins, 2006] as already described in previous years [Farrell et al., 2005a]. Isolates belonging to this clone are mainly of 19F and 19A serotypes.

[2] The most common mutation in the US is associated with bacterium membrane-associated pumps that remove antibiotics from inside the cell to its outside [*mef*(A) mutation-associated efflux], thus protecting the bacterium. The second most common mutation is associated with the addition of methyl (CH_3-) groups to ribosomes [*erm*(B)] interfering with the ability of macrolides to kill bacteria.

Clinical impact of antibiotic resistance

Evaluation of the relevance of penicillin-resistance has been essentially evaluated in CAP patients. Convincing evidence that resistance has an adverse effect on clinical outcomes, particularly mortality, is lacking. A recent review by Tleyjeh [Tleyjeh, 2006] suggests, however, that resistance may need to be reconsidered as an independent predictor of poor clinical response, but interpretation of the studies is difficult due to confounding factors such as comorbidities, severity of illness, and age. The impact of resistance in the ambulatory care setting has not been studied in depth. Only a limited number of studies investigate discordant therapy, and most of the studies have been conducted in hospitalized patients for whom adequate serum and tissue levels could be achieved with appropriate doses of parenteral β-lactams to effectively treat the great majority of pneumococcal strains, which are considered "nonsusceptible" to penicillin on the basis of the present microbiologic criteria [File, 2006]. Consequently, except for an association of clinical failure with cefuroxime-resistant infections in the study by Yu et al. [Yu et al., 2003], discordant therapy has not been shown to affect mortality.

An increase of the dose of available β-lactams has therefore been proposed to treat infections suspected to be due to *S. pneumoniae*, in most countries where resistance rates were considered significant, or in case of risk factors of *S. pneumoniae* resistance.

On the other hand, some mechanisms of resistance such as macrolide resistance among *S. pneumoniae*, far above plasma or extracellular tissue levels of available antibiotics, are expected to result in a loss of antibacterial efficacy. In patients with acute bacterial infections in the ambulatory setting the clinical relevance of antibacterial resistance is not always demonstrable as it is, for example, in patients with tuberculosis infections due to resistant strains. A recent study using a large claims database found no statistically significant association between *S. pneumoniae* susceptibility and RTI treatment outcomes in AECB and ABS, conditions that are not associated with bacteremia [Furuno, 2006].

However, treatment failure, defined as the isolation of erythromycin-resistant *S. pneumoniae* from normally sterile body fluids (mostly blood) in patients taking macrolide antibiotics, initially appeared in case reports [Kelley et al., 2000; Fogarty et al., 2000]. Four recent studies focusing on patients with pneumococcal bacteremia provide evidence that macrolide-resistant *S. pneumoniae* contributes to an increased risk of treatment failure with macrolides [Lonks et al, 2002; Van Kerkhoven et al, 2003; Danneman et al, 2006; Grant et al., 2006].

3.2.1.2 Haemophilus influenzae *resistance*

The level of β-lactamase-producing strains, resistant to amoxicillin is at 27.3% in PROTEKT US 2004 to 2005.

Recently, an additional mechanism of resistance, found in β-lactamase-negative ampicillin-resistant strains, which are resistant to amoxicillin-clavulanic acid, has emerged among *H. influenzae*, mostly in Japan, but is still observed at a low rate in the US (0.26% in 2000, 0.3% in 2005 in PROTEKT US). The clinical impact of *H. influenzae* resistance to β-lactams through β-lactamase-producing strains has not been evaluated. Because this type of resistance is generally associated with high MICs, it is expected to impact the clinical efficacy of the antibiotic not active in vitro.

3.2.2 Effects on nonrespiratory pathogens

3.2.2.1 Effects on Gram-negative flora

The proportion of *Escherichia coli* strains resistant to amoxicillin-clavulanic acid and to fluoroquinolones and amoxicillin-clavulanic acid is now >20% in North America in a recent study [Hoban et al., 2005]. Carbapenemase-producing *Klebsiella pneumoniae* resistant to quinolones and often associated with multidrug resistance to available antibiotics [Bratu et al., 2005] is being reported in some areas of the US. This decreases the use of these antibiotics in infections due to this pathogen, and leads to an increase in the use of broader-spectrum antibiotics, normally reserved for more severe infections.

Infection due to *Clostridium difficile*

Recent reports of infection due to *C. difficile* hyperproducers of virulent toxins and resistant to quinolones in hospitalized patients, which have been associated with a higher morbidity and mortality [Muto et al., 2005; McDonald et al., 2005] have raised a public health concern. Some classes of antibiotics (mainly quinolone, clindamycin, cephalosporins) have been identified as risk factors for *C. difficile* infections [Bartlet and Perl, 2005]. However, the risk of *C. difficile* infection exists with all antibiotics and work is still in progress to better understand the risk associated with specific antibiotics. Recent data suggest that *C. difficile* may be spreading in the community setting [Chernak et al., 2005].

3.2.3 Summary of bacteriologic limitations of antibiotics other than telithromycin marketed for the treatment of respiratory tract infections

A summary of decrease of susceptibility and effects on non-respiratory pathogens observed with antibiotics used in the treatment of CAP, AECB, and ABS (other than telithromycin) is provided in the table below. Telithromycin has a spectrum of antibacterial activity specifically targeted to RTI pathogens including antibiotic-resistant strains of *S. pneumoniae*. It thus addresses these main bacteriologic limitations.

Table 3 - Summary of bacteriologic limitations of currently marketed antibiotics for the treatment of respiratory tract infections (other than telithromycin)

	Decrease of susceptibility observed	Effect on non-respiratory pathogens
β-Lactams	*Streptococcus pneumoniae* (amoxicillin, cephalosporins)	β-Lactam resistance of enteric Gram-negative bacteria
	Haemophilus influenzae β-lactamase-positive (amoxicillin)	
	Moraxella catarrhalis β-lactamase-positive (amoxicillin)	
Macrolides	*S. pneumoniae*	
Quinolones	*S. pneumoniae* (currently at low level)	Quinolone-resistance of enteric Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*)
Tetracyclines, trimethoprim-sulfamethoxazole	*S. pneumoniae*	

4 US – SUMMARY OF PREAPPROVAL DATA

4.1 INVESTIGATIONAL NEW DRUG APPLICATION

An Investigational New Drug (IND) Application for telithromycin drug substance, formulated as a tablet, was submitted to the US Food and Drug Administration (FDA) on February 19, 1998, and assigned IND number 55,283. The Sponsor ("sanofi-aventis"[3]) drug code for telithromycin in the adult development program is HMR3647A.

The purpose of IND 55,283 was to investigate the efficacy and safety of telithromycin tablets in adults with CAP, AECB, ABS, or T/P, with a 7 to 10 day treatment regimen for CAP (800 mg once a day) and a 5-day treatment indication for the other indications.

4.2 PREAPPROVAL: MICROBIOLOGY DATA

4.2.1 Structure-activity relationship and mode of action

Telithromycin is the first of the new ketolide class of antibacterial agents, derived from the macrolide family of antibiotics. Overall, telithromycin differs from macrolides by more efficient activity against *S. pneumoniae*, activity against multidrug-resistant RTI pathogens, and a lower propensity to select for antibiotic-resistant isolates of *S. pneumoniae* in vitro compared to the macrolides (which select for macrolide-resistant *S. pneumoniae*).

Telithromycin differs from erythromycin A by the replacement of the neutral sugar, α-L-cladinose, at position 3 of the erythronolide ring with a keto group. Because of the lack of a 3-α-L-cladinose moiety, telithromycin retains activity against Gram-positive bacteria expressing the inducible MLS_B mechanism of resistance and does not induce MLS_B resistance. A C11-C12 carbamate residue in addition to the erythronolide A ring is responsible for telithromycin's strong anti Gram-positive in vitro activity. The imidazole-pyridinium ring extension to the carbamate side chain further enhances its in vitro activity, its pharmacokinetics and pharmacodynamics, its intracellular concentration, and its retention of in vitro activity against strains of Gram-positive bacteria with an efflux mechanism of resistance to the macrolides. As with the macrolides,

[3] At the time Ketek® (telithromycin) was approved in the United States in April 2004, Hoechst Marion Roussel (HMR) the entity that originally developed telithroymcyin, had become part of the Aventis Group. Susequently, on August 20, 2004, Sanofi-Synthelabo S.A.acquired Aventis S.A. and became sanofi-aventis. sanofi-aventis currently operates in the United States primarily through 2 affiliated entities, sanofi-aventis US LLC (holder of the NDA) and sanofi-aventis US Inc. (holder of the IND). In the remainder of this document, entities that are currently part of the sanofi-aventis Group will be referred to as "sanofi-aventis".

telithromycin prevents bacterial protein synthesis by binding to specific sites on the bacterial ribosome and interfering with elongation of nascent polypeptide chains. 14- and 15-membered-ring macrolides and telithromycin interact with domain V of the 23S rRNA. In addition, unlike macrolides, telithromycin binds strongly to domain II of 23S rRNA. As a result, telithromycin binds approximately 10-20- fold more tightly than erythromycin A to MLS_B -susceptible ribosomes and may retain activity when domain V is neutralized, leading to resistance to macrolides.

4.2.2 In vitro studies

In vitro microbiology studies demonstrated that telithromycin has a spectrum of antimicrobial activity that is targeted against RTI pathogens:

- Strong activity against *S. pneumoniae*: higher intrinsic activity against macrolide-susceptible strains than macrolides (erythromycin, clarithromycin, azithromycin), activity against macrolide-resistant strains, irrespective of the mechanism of resistance (*erm*, *mef*);
- Activity against *H. influenzae*, with minimum inhibitory concentrations (MICs) similar or slightly higher to those of azithromycin;
- Activity against *M. catarrhalis*;
- Activity against *S. pyogenes* susceptible to macrolides or resistant to macrolides by the presence of *mef* or *erm*TR genes;
- Activity against *S. aureus* susceptible to macrolides or resistant to macrolides by an inducible mechanism;
- Activity against respiratory atypical and intracellular pathogens: *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*.

These studies also demonstrated that telithromycin is inactive against methicillin-resistant *S. aureus* (most of which were resistant to macrolides by a constitutive mechanism), Enterobacteriaceae, and nonfermentative Gram-negative bacilli (eg, Pseudomonas, Acinetobacter).

A summary of MICs performed in the preregistration period is shown in the following tables.

Table 4 – MIC values for telithromycin against pathogens associated with community-acquired RTIs[a]

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

[a] PROTEKT international respiratory tract pathogen surveillance program; includes organisms collected from 1999 to 2001 worldwide, except for *M. pneumoniae* and *C. pneumoniae*.

Table 5 – MIC values for telithromycin against pathogens associated with community-acquired RTIs[a]

Pathogen	N	MIC µg/mL		
		MIC_{50}	MIC_{90}	Range
Erythromycin susceptible/intermediate	11384	0.015	0.015	≤0.002 - 1
Erythromycin A resistant	5288	0.12	1.0	0.008 - 8
Genotype *erm*(B)[b]	657	0.06	0.5	0.008 - 8
Genotype *mef*(A)[b]	436	0.12	0.5	0.008 - 1
Genotype *mef*(A) and *erm*(B)[b]	71	0.5	0.5	0.06 - 1
Penicillin G resistant[c]	4027	0.12	1	0.004 - 8
Levofloxacin resistant	154	0.03	0.5	0.004 - 1
Multidrug resistant[d]	1500	0.12	1.0	0.008 - 8

[a] PROTEKT international respiratory tract pathogen surveillance program; includes organisms collected from 1999 to 2001 worldwide.
[b] Only a subset of erythromycin-resistant strains was genotyped for their mechanism of resistance.
[c] Includes macrolide-resistant strains.
[d] Includes strains concomitantly resistant to penicillin G, the macrolides, trimethoprim-sulfamethoxazole, and tetracycline.

In vitro, telithromycin was shown to be bactericidal against *S. pneumoniae* and *C. pneumoniae*.

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

4.3 PREAPPROVAL: CLINICAL PHARMACOLOGY DATA

After oral administration, absorption of telithromycin is almost complete (90%), and the absolute bioavailability is 57% in subjects of all ages. The rate and extent of absorption are not influenced by food. Mean maximum concentration (Cmax) 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 (Cmax 2.89 µg/mL). Telithromycin has a terminal half-life of 9.8 hours. It is distributed extensively in human tissues; the Cmax in pulmonary epithelial lining fluid of patients with RTIs was 14.9 µg/mL, and Cmax in white blood cells of healthy subjects was 83 µg/mL, with a substantial concentration (20.9 µg/mL) at 24 hours after dosing. Telithromycin is 60 to 70% bound to serum proteins.

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

Telithromycin has multiple pathways by which it is eliminated as unchanged drug, and several metabolites that are mediated by CYP3A4 and non-CYP3A4 pathways. Non-CYP450 pathways are not known to be involved in drug interactions. Due to these multiple pathways of elimination, the increase in telithromycin exposure due to impairment of these pathways is minimal. This has been observed in several studies in subjects with renal or hepatic impairment, and in subjects whose metabolic pathway was impaired by administration of a potent CYP3A4 inhibitor (exposure did not exceed 2-fold in any of these populations). In agreement with the Biopharmaceutics Division of the FDA, a study was carried out to further characterize telithromycin exposure in subjects where more than 1 pathway was impaired. This study was performed in subjects >60 years of age who had mild to moderate renal impairment and, in addition, who were administered ketoconazole to block their CYP3A4 metabolic capacity. The increase in telithromycin exposure under these conditions of multiple impairment was modestly more than that observed when the CYP3A4 pathway alone was blocked (healthy subjects [n=11] treated with telithromycin: Cmax ss [SD]=2.02 mg/L [0.77] mg/L and AUC (0-24) ss [SD]=14.4 mg·h/L [5.6]; healthy subjects treated with telithromycin plus ketoconazole Cmax ss [SD]=3.13 mg/L [1.12] mg/L and AUC (0-24) ss [SD]=28.6 mg·h/L [8.9]; elderly subjects with renal impairment [n=10] treated with telithromycin plus ketoconazole: Cmax ss [SD]=3.6 mg/L [0.8] mg/L and AUC (0-24) ss [SD]=33.4 mg·h/L [10.2]).

Like clarithromycin, telithromycin is a strong inhibitor of the cytochrome P450 3A4 system. Coadministration of telithromycin tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentration of the drug coadministered with telithromycin that could increase or prolong both the therapeutic and adverse effects. Therefore, appropriate dosage adjustments may be necessary for the drug coadministered with telithromycin. Simvastatin, lovastatin, or atorvastatin should be avoided in patients receiving telithromycin. If telithromycin is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be stopped during the course of treatment. Further details about potential drug-drug interactions with telithromycin are provided in the labeling for telithromycin *(APPENDIX G: LABELING)*. Telithromycin is a mild inhibitor of CYP2D6.

4.4 PREAPPROVAL: EFFICACY DATA

The adult Phase III studies to support the approval of telithromycin were discussed with the DAIOP in early 1998, at which time the FDA was developing guidances to update recommendations from *Points To Consider Clinical Development and Labeling of Anti-Infective Drug Products* (October 26, 1992). In July 1998, 18 draft guidances were published by the Agency (Docket Number 98D-0548) dealing with development of anti-infective products (Federal Register Notice dated July 29, 1998 http://www.fda.gov/ohrms/dockets/98fr/072998d.pdf). The clinical development program for telithromycin was based on "sanofi-aventis"'s interactions with the FDA and were in general agreement with the recommendations provided in these draft guidances.

Fourteen Phase III studies were conducted in the US, the EU, South America, Australia, and South Africa to support the claim for the 3 targeted indications: 10 double-blind comparative trials and 4 open label noncomparative trials.

- A total of 7 Phase III CAP, AECB, and ABS studies were included in the initial NDA (NDA 21-144): 3 randomized controlled CAP Studies (A3001, A3006, A3009); 2 randomized controlled AECB Studies (A3003 and A3007); 1 randomized controlled ABS Study (A3005) and 1 randomized double blind comparison of treatment duration and documentation of bacterial infection by sinus puncture (A3002).
- An additional 7 Phase III studies were conducted to support the FDA approval of telithromycin: 1 randomized controlled CAP Study (A4003) and 4 open label CAP studies to increase the number of antibiotic-resistant *S. pneumoniae* isolates (A3000, A3009OL, A3010, and A3012); 1 randomized controlled AECB Study (A3013); and 1 randomized controlled ABS Study (A3011).

Two Phase III randomized controlled studies in patients with T/P studies were included in the initial NDA (NDA 21-391), Studies A3004 and A3008. As the T/P indication was subsequently not approved by the FDA, these studies are not further discussed in this section, but the safety data are presented in the Preapproval: Safety data section.

The pivotal active-comparator, noninferiority study designs were developed in consultation with the DAIOP. Particular attention was paid to rigorous case definition. Noninferiority analyses were performed on both the per protocol (PPc) and modified intent-to-treat (mITT) populations. For all comparative studies the primary efficacy analysis was based on clinical outcome (cure) at the posttherapy/test of cure visit (TOC, Visit 3) in the PPc population

In the dossier used for approval, a total of 6127 subjects were randomized (or assigned, as in open label studies) to telithromycin (4388 subjects) or comparator drugs (1739 subjects) in the Phase III clinical program: 4378 were treated with telithromycin and 1735 with a comparator antibiotic. In all Phase III studies, telithromycin was administered as an oral dose of 800 mg once daily. Key features related to study design, treatment regimen, and enrollment in the 14 Phase III studies used for approval are summarized in the table below. Subject numbers are given for the mITT population.

Table 6 - Phase III studies in NDA 21-144, by approved treatment indications

Study No.	Study design	Days of treatment	Study drug	No. of mITT subjects	Treatment regimen
			Community-acquired pneumonia		
A3001	Double blind	10 d	TEL	199	800 mg qd
		10 d	AMX	205	1000 mg tid
A3006	Double blind	10 d	TEL	204	800 mg qd
		10 d	CLA	212	500 mg bid
A3009 [a]	Double blind	7 to 10 d	TEL	100	800 mg qd
		7 to 10 d	TVA	104	200 mg qd
A4003	Double blind	5 d	TEL	187	800 mg qd
		7 d	TEL	191	800 mg qd
		10 d	CLA	181	500 mg bid
A3000	Open label	7 to 10 d	TEL	240	800 mg qd
A3009OL	Open label	7 to 10 d	TEL	212	800 mg qd
A3010	Open label	7 d	TEL	418	800 mg qd
A3012	Open label	7 d	TEL	831	800 mg qd
		Total CAP	TEL	2582	
			Comparators	702	
			Acute exacerbation of chronic bronchitis		
A3003	Double blind	5 d	TEL	160	800 mg qd
		10 d	AMC	160	500 mg/125 mg tid
A3007	Double blind	5 d	TEL	182	800 mg qd
		10 d	CEF	191	500 mg bid
A3013	Double blind	5 d	TEL	270	800 mg qd
		10 d	CLA	282	500 mg bid
		Total AECB	TEL	612	
			Comparators	633	
			Acute bacterial sinusitis		
A3002	Double blind	5 d	TEL	167	800 mg qd
		10 d	TEL	168	800 mg qd
A3005	Double blind	5 d	TEL	201	800 mg qd
		10 d	TEL	204	800 mg qd
		10 d	AMC	202	500 mg/125 mg tid
A3011	Double blind	5 d	TEL	240	800 mg qd
		10 d	CEF	116	250 mg bid
		Total ABS	TEL	980	
			Comparators	318	

[a] Study terminated early. TEL=telithromycin; AMX=amoxicillin; CLA=clarithromycin; TVA=trovafloxacin; LEV=levofloxacin; AMC=amoxicillin-clavulanic acid (Augmentin®); CEF=cefuroxime axetil.

4.4.1 Populations for analysis and statistical approaches

For inclusion in the efficacy analysis a confirmed clinical diagnosis of the disease of interest at baseline was required (mITT population; see table below). The PPc population was used as the primary efficacy population and the mITT population as the secondary (supportive) efficacy population. Efficacy analyses used the assessment of cure at the posttherapy/TOC visit (Visit 3), in the Day 17-24 window. The persistence of bacteria was assessed by bacteriologic eradication evaluated in the PPb population at posttherapy/TOC visit. Bacteriologic eradication was determined by the presence or absence of causative pathogens at TOC. If the subject was clinically cured and a postbaseline culture was not obtainable, the subject was considered presumed eradicated. If a postbaseline culture was obtained, the assessment of bacteriologic eradication was based on the culture results.

Table 7 - Analysis populations

Population	Definition
mITT	All randomized subjects, 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.
bmITT	All mITT subjects with a pathogen at pretherapy/entry considered by the Investigator to be responsible for the infection.
PPb	All PPc subjects with isolation of a causative pathogen from an adequate culture at pretherapy/entry.

Population definitions: mITT=modified intent-to-treat; PPc=clinically evaluable per protocol; bmITT=bacteriologically evaluable modified intent-to-treat; PPb=bacteriologically evaluable per protocol. Subjects with a pathogen of interest at baseline are included in the PPb population.

The prespecified noninferiority margin was 15% in the comparative studies for CAP, AECB, and ABS. This noninferiority margin was used for sample size determination and for the active comparator noninferiority tests. For all comparative studies the primary efficacy analysis was based on clinical outcome (cure) at the posttherapy/TOC (Visit 3) in the PPc population. In studies with 3 treatment groups (Studies A3005 and A4003), a closed sequential comparison test was performed, comparing 10 days (7 days for Study A4003) of telithromycin treatment with 10 days of comparator treatment, and 5 days of telithromycin treatment with 10 days of comparator treatment if noninferiority was demonstrated in the first comparison.

Further details on the statistical methods of analysis are provided in *APPENDIX A: BIOSTATISTICAL METHODS* .

4.4.2 Community-acquired pneumonia

4.4.2.1 Study population

Of subjects with CAP in the mITT population, males comprised 56.4% (females 43.6%) of telithromycin-treated subjects and 50.9% (females 49.1%) of comparator-treated subjects.

Mean age was 45.3 years in subjects treated with telithromycin and 45.6 years in subjects treated with comparators. Subjects 18 years or younger comprised 2.4% vs. 3.0% of CAP subjects in telithromycin and comparator populations, respectively. Subjects 65 years of age or older made up 15.4% of the population of telithromycin-treated subjects, and 17.7% of comparator-treated subjects. Percentages of smokers in the CAP population were 36.4% vs. 40.1% for telithromycin vs. comparator subjects, respectively.

The clinical and bacteriologic effectiveness of 800 mg of telithromycin administered once daily for 7-10 days in the treatment of CAP was evaluated in 4 Phase III double blind and 4 Phase III open label clinical studies. Baseline characteristics of the overall CAP population studied (2582 telithromycin, 702 comparators) were balanced between treatment groups. Although the studies targeted ambulatory subjects with CAP, they included subjects with risk factors: ≥65 years of age (398 subjects), with Pneumonia Patient Outcomes Research Team [PORT] score ≥III (408 subjects), or with bilateral pneumonia (485 subjects) [Fine et al., 1997].

4.4.2.2 Clinical outcome

Clinical cure rates with 7 to 10 days of telithromycin treatment were not inferior in any of the 3 completed double blind studies, relative to amoxicillin or clarithromycin.

In Study A3009 that used trovafloxacin as comparator, both treatments gave cure rates exceeding 90%. Enrollment in this study was stopped before reaching target enrollment because the FDA restricted the use of trovafloxacin.

Table 8 - CAP: Clinical cure rates by study for telithromycin and comparator(s) at posttherapy/TOC

	Telithromycin			Comparator(s)			Difference	95% CI[a]
	N	n	(%)	N	n	(%)		
PPc population								
Study A3001	149	141	(94.6)	152	137	(90.1)	4.50%	[-2.1; 11.1]
Study A3006	162	143	(88.3)	156	138	(88.5)	-0.19%	[-7.8; 7. 5]
A3009 *	80	72	(90.0)	86	81	(94.2)	-4.19%	[-13.9; 5.2]
Study A4003 TEL 7 d								
Study A4003 TEL 5 d [b]	159	142	(89.3)	146	134	(91.8)	-2.47%	[-9.7; 4.7]
TEL 7 d	161	143	(88.8)	146	134	(91.8)	-2.96%	[-10.18; 4.26]
Comparative CAP pooled [c]	*552*	*499*	*(90.4)*	*394*	*356*	*(90.4*	*-0.04%*	[-4.0; 4.1] [c]
Study A3000	197	183	(92.9)					
Study A3009OL	187	175	(93.6)					
Study A3010	357	332	(93.0)					
Study A3012	723	646	(89.3)					
All CAP studies TEL 7 to 10 d [c]	*2016*	*1835*	*(91.0)*					
mITT population								
Study A3001	199	171	(85.9)	205	161	(78.5)	7.39%	[-0.48; 15.26]
Study A3006	204	161	(78.9)	212	171	(80.7)	-1.74%	[-9.90; 6.42]
A3009 [d]	100	82	(82.0)	104	89	(85.6)	-3.58%	[-14.62; 7.47]
Study A4003 TEL 5 d [b]	187	154	(82.4)	181	147	(81.2)	1.14%	[-7.25; 9.53]
TEL 7 d	191	157	(82.2)	181	147	(81.2)	0.98%	[-7.38; 9.34]
Comparative CAP pooled [c]	694	571	(82.3)	521	421	(80.8)	1.47%	[-3.1; 6.0]
Study A3000	240	191	(79.6)					
Study A3009OL	212	182	(85.8)					
Study A3010	418	357	(85.4)					
Study A3012	831	688	(82.8)					
All CAP studies TEL 7 to 10 d [c]	*2395*	*1989*	*(83.0)*					

Population definitions: mITT=modified intent-to-treat; PPc=clinically evaluable per protocol; bmITT=bacteriologically evaluable modified intent-to-treat; PPb=bacteriologically evaluable per protocol; N=number of subjects; n=number clinically cured.

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

[b] The 5-day treatment group is not included in US Product Information.

[c] Excluding the 5-day treatment group, which is not included in US Prescribing Information.

[d] Study terminated early.

Comparators: A3001 amoxicillin, A3002 5- vs. 10-days duration of telithromycin, A3003 amoxicillin-clavulanic acid, A3005 amoxicillin-clavulanic acid, A3006 clarithromycin, A3007 cefuroxime, A3009 trovafloxacin, A3011 cefuroxime axetil, A3013 clarithromycin, A4003 clarithromycin.

4.4.2.3 Clinical cure rates by pathogen, including antibiotic resistant pathogens

The clinical cure rates at posttherapy/TOC for subjects with a causative pathogen (the PPb population) are presented below. The cure rate for the telithromycin-treated subjects was 93.7% for *S. pneumoniae*, 89.3% for *H. influenzae*, and 85.5% for *M. catarrhalis*.

Table 9 - CAP: Clinical cure rates by pathogen – PPb population

Causative pathogen	Clinical cure					
	TEL			Comparator		
	N	n	(%)	N	n	(%)
S. pneumoniae	333	312	(93.7)	70	63	(90.0)
H. influenzae	253	226	(89.3)	44	42	(95.5)
M. catarrhalis	55	47	(85.5)	9	7	(77.8)
Total	641	585	(91.3)	123	112	(91.0)

PPb=bacteriologically evaluable per protocol; N=subjects in PPb population with causative pathogen (single + multiple pathogens) isolated at pretherapy/entry; n=subjects in the PPb population whose causative pathogen was eradicated or who were assessed as clinical cure. The comparators used were AMX=amoxicillin; CLA=clarithromycin; TVA=trovafloxacin; LEV=levofloxacin.

Antibiotic-resistant Streptococcus pneumoniae

Clinical cure rates in subjects infected with antibiotic-resistant *S. pneumoniae* are presented in the table below. *S. pneumoniae* is the most common virulent bacterium associated with CAP in the ambulatory care setting. When *S. pneumoniae* develops a decreased susceptibility to one antibiotic, decreased susceptibility to other antibiotics may be also observed. Therefore, clinical cure rates to MDRSP that includes penicillin-resistant *S. pneumoniae*, and isolates resistant to 2 or more of the following antibiotics – penicillin, 2nd generation cephalosporins, eg, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole – is also characterized.

The cure rates for resistant *S. pneumoniae* are consistent with rates observed for the overall *S. pneumoniae* population.

Table 10 - CAP (All Studies): Clinical cure rates at posttherapy/TOC for *Streptococcus pneumoniae*-resistant isolates[a] – PPb population

Causative pathogen	CAP Studies					
	Telithromycin			Comparators		
	N	n	%	N	n	%
Single and mixed pathogen infections						
All *S. pneumoniae*	333	312	(93.7)	70	63	90
PEN-R	23	20	(87.0)	1	1	*b*
ERY-R	33	29	(87.9)	5	4	*b*
PEN-R and/or ERY-R	41	37	(90.2)	6	5	*b*
MDRSP	37	34	(91.9)	6	5	*b*

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

[a] Excluding the 5-day treatment group, which is not included in US Prescribing Information.

[b] The numbers of isolates are too small for percentages to be meaningful.

Macrolide-resistant Streptococcus pneumoniae – *clinical cure rates according to genotype*

Streptococcus pneumoniae develops resistance to macrolides by several types of genetic mutations. The genetic mutations may result in a different degree of reduction in susceptibility.

The most common mutation in the US is associated with bacterium membrane-associated pumps that remove antibiotics from inside the cell to its outside [*mef*(A) mutation-associated efflux], thus protecting the bacterium. The second most common mutation is associated with the addition of methyl (CH_3-) groups to ribosomes [*erm*(B)] interfering with the ability of macrolides to kill bacteria. Both the *mef*(A) and *erm*(B) mutations may also be present at the same time. Telithromycin treatment is associated with clinical cure rates for resistant *S. pneumoniae* similar to rates observed for *S. pneumoniae* overall (see table below).

Cure rates for *S. pneumoniae* resistant to erythromycin by either the *erm* or *mef* gene mutations were comparable to the overall *S. pneumoniae* infected population in the table below.

Table 11 - CAP: Clinical cure rates by genotype among subjects with *Streptococcus pneumoniae* isolates resistant to erythromycin A from single and mixed pathogen infections – PPb population

Genotype	Clinical cure		
	N	n	(%)
erm(B)	15	13	(86.7)
mef(A)	15	13	(86.7)
erm(B)/*mef*(A)	3	3	*a*
Negative for *erm*(B) and *mef*(A)	1	1	*a*

PPb=bacteriologically evaluable per protocol.

[a] The numbers of isolates are too small for percentages to be meaningful.

Clinical cure according to level of resistance to macrolides and penicillin

The level of susceptibility to an antibiotic is variable. Therefore, to characterize the potency of telithromycin, the relationship between the level of susceptibility and the clinical cure and eradication rates at posttherapy/TOC in the PPb population in all CAP studies is displayed in the table below according to MIC values for *S. pneumoniae*-resistant to macrolides and penicillin in telithromycin-treated subjects

Efficacy was observed in penicillin G- and macrolide-resistant *S. pneumoniae* up to an MIC of 1 µg/mL (the highest MIC observed in the subjects treated with telithromycin).

Table 12 - CAP: Bacteriologic eradication and clinical cure rates at posttherapy/TOC for resistant isolates of *Streptococcus pneumoniae* according to MIC in telithromycin-treated subjects – PPb population

	Bacteriologic eradication			Clinical cure		
MIC (µg/mL)	N	n	%	N	n	%
Penicillin G-resistant *S. pneumoniae*						
0.008	3	3	(100)	3	3	(100)
0.016 [a]	3	3	(100)	3	3	(100)
0.03	6	4	(66.7)	6	4	(66.7)
0.06	3	3	(100)	3	3	(100)
0.12	2	1	(50.0)	2	1	(50.0)
0.25	1	1	(100)	1	1	(100)
0.5	4	4	(100)	4	4	(100)
1	1	1	(100)	1	1	(100)
Total	23	20	(87.0)	23	20	(87.0)
Macrolide- (erythromycin A-) resistant *S. pneumoniae*						
0.016 [a]	2	2	(100)	2	2	(100)
0.03	10	8	(80.0)	10	8	(80.0)
0.06	7	7	(100)	7	7	(100)
0.12	6	4	(66.7)	6	4	(66.7)
0.25	1	1	(100)	1	1	(100)
0.5	5	5	(100)	5	5	(100)
1	5	5	(100)	5	5	(100)
Total	36	32	(88.9)	36	32	(88.9)

PPb=bacteriologically evaluable per protocol; N=subjects; n=number of subjects bacteriologically or clinically cured; PEN-R=penicillin G-resistant (MIC≥1.0 µg/mL).

[a] Data for MIC values of 0.15 and 0.16 µg/mL have been pooled. Data from all studies are pooled.

Streptococcus pneumoniae bacteremia including antibiotic-resistant strains

Infections associated with bacteria in the bloodstream increase the risk of complications. The following table presents data on *S. pneumoniae*, including macrolide- and/or penicillin-resistant strains isolated from blood cultures. The clinical cure rates with bacteremia for antibiotic-resistant strains of *S. pneumoniae* are similar to those of the overall population with bacteremia.

Table 13 - CAP: Clinical cure in subjects with pneumococcal bacteremia in telithromycin-treated subjects at posttherapy/TOC – PPb population

Causative pathogen	All CAP	
Blood culture positive	**N**	**n**
All *S. pneumoniae*	76	67 (88.1%)
PEN-R	7	5 [a]
ERY-R	10	8 (80%)
PEN-R and/or ERY-R	13	11 (84.6 %)
MDRSP	13	11 (84.6 %)

PPb=bacteriologically evaluable per protocol; N=number of subjects; n=number clinically cured; PEN-R=penicillin G-resistant (MIC ≥2.0 μg/mL); ERY-R=erythromycin A- (macrolide-) resistant (MIC ≥1.0 μg/mL).

[a] The numbers of isolates are too small for percentages to be meaningful.

MDRSP includes penicillin-resistant *S. pneumoniae*, and isolates resistant to 2 or more of the following antibiotics - penicillin, 2nd generation cephalosporins, eg, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

For comparator-treated subjects with bacteremia, the clinical cure rates are not assessable because sample sizes are too small (≤1).

Haemophilus influenzae

Haemophilus influenzae is the second most frequent bacterium in CAP. Bacteriologic eradication and clinical cure rates at posttherapy/TOC according to MIC values for *H. influenzae* in telithromycin-treated subjects are displayed below for the PPb population from all CAP studies. Efficacy was observed at an MIC of 8, with 11 of 11 subjects clinically cured and bacteriologic eradication in 10 of 11 subjects with CAP caused by *H. influenzae*.

Table 14 - CAP: Bacteriologic eradication and clinical cure rates at posttherapy/TOC for *Haemophilus influenzae* according to MIC in telithromycin-treated subjects – PPb population

MIC (µg/mL)	Bacteriologic eradication			Clinical cure		
	N	n	(%)	N	n	(%)
H. influenzae						
0.002	1	1	(100)	1	1	(100)
0.12	1	1	(100)	1	1	(100)
0.25	3	3	(100)	3	3	(100)
0.5	6	3	(50.0)	6	4	(66.7)
1	50	44	(88.0)	50	43	(86.0)
2	123	110	(89.4)	123	112	(91.1)
4	51	43	(84.3)	51	44	(86.3)
8	11	10	(90.9)	11	11	(100)
N/A	32	30	(93.8)	32	29	(90.6)
Total	278	245	(88.1)	278	248	(89.2)

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

Moraxella catarrhalis is the third most common bacterium in CAP. Most strains of this species recovered from patients in the US are β-lactamase positive and resistant to amoxicillin and other penicillins. Clinical cure among subjects infected with *M. catarrhalis* in controlled studies is 85.7% (12/14), in open label studies is 88.6% (31/35), and when data from all CAP studies are pooled the cure rate is 87.8% (43/49).

Atypical and intracellular pathogens

Chlamydophila pneumoniae and M. *pneumoniae* are frequently responsible for CAP and may be refractory to β-lactams. Telithromycin has demonstrated potent in vitro activity against the atypical and intracellular group of pathogens. The clinical cure rates with telithromycin for these 2 pathogens in subjects that meet stringent diagnostic criteria recommended by the FDA are shown in the table below. In controlled clinical trials, the clinical cure rate for subjects infected with *M. pneumoniae* is 95.7% (22/23) and for *C. pneumoniae* is 92.0% (23/25).

Table 15 - CAP: Clinical cure at posttherapy/test of cure in atypical and intracellular pathogen isolates using specific criteria – PPc

Pathogen	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
Mycoplasma pneumoniae	34	33	(97.1)	22	20	(90.9)
Chlamydophila pneumoniae	35	33	(94.3)	19	18	(94.7)

N= number of subjects; n=number clinically cured.
Data on telithromycin from both Phase III randomized controlled and open label clinical trials.

Diagnostic criteria for these atypical bacteria required a negative culture for "typical bacteria." For the diagnosis of *M. pneumoniae* one of the following had to be present: positive culture, or fourfold increase in paired IgG titers, or a single IgM titer ≥1:16 with a positive PCR. For the diagnosis of *C. pneumoniae* one of the following had to be present: positive culture, or a fourfold increase in paired IgG/IgM titers, or a single IgM titer ≥1:32 with a positive PCR.

4.4.2.4 Efficacy in subgroups of special interest

Population subsets were stratified by factors that may increase risk of treatment failure. Clinical cure in telithromycin-treated subjects with more severe disease was similar to that of comparators. The rates of clinical cure in telithromycin treated subjects with risk factors such as PORT score ≥III, age >65, and multilobar pneumonia is similar to the overall population with CAP.

Table 16 - CAP: Clinical cure rates for subsets of special interest in telithromycin-treated subjects at posttherapy/TOC – PPc population

Subgroup	Clinical Cure					
	Telithromycin			Comparators		
	N	n	(%)	N	n	(%)
Per protocol (overall)	2175	1977	(90.9)	540	490	(90.7)
Age (years)						
<65	1840	1682	(91.4)	444	407	(91.7)
≥65	335	295	(88.1)	96	83	(86.5)
X-ray findings						
Bilateral	419	380	(90.7)	40	37	(92.5)
Multiple lobes	309	274	(88.7)	46	38	(82.6)
PORT score						
Class I	1059	969	(91.5)	252	239	(94.8)
Class II	774	702	(90.7)	178	158	(88.8)
Class ≥III	342	306	(89.5)	110	93	(84.5)

N=number of subjects, n=number clinically cured
PORT- Pneumonia Patient Outcomes Research Team [Fine et al., 1997

4.4.2.5 Summary of community-acquired pneumonia

- Telithromycin 800 mg/d for 7 to 10 days was shown to be noninferior in clinical efficacy to widely used treatments (amoxicillin or clarithromycin, administered 2 to 3 times daily) given for 10 days. Telithromycin in 3 double blind controlled studies was effective 499/552 (90.4%) vs. comparators 356/394 (90.4%). Activity was demonstrated in subjects at risk for morbidity and mortality: ≥65 years of age (88.1%, 295/335), documented pneumococcal bacteremia (88.2%, 67/76), and PORT score ≥III (89.5%, 306/342).
- Cure rates with telithromycin against the key pathogens responsible for pneumonia, including both common and atypical/intracellular pathogens were:
  - *Streptococcus pneumoniae* 93.7% clinical cure (312/333);
  - *Haemophilus influenzae* 89.3% (226/253);
  - *Moraxella catarrhalis* 87.8% (43/49);
  - *Mycoplasma pneumoniae* 97.1% (33/34); and
  - *Chlamydophila pneumoniae* 94.3% (33/35).

- Cure rates with telithromycin in subjects with pneumonia or bacteremia with antibiotic-resistant strains of *S. pneumoniae* were:
  - macrolide- (erythromycin A-) resistant strains 87.9% (29/33);
  - penicillin G-resistant strains 87.0% (20/23);
  - MDRSP 91.9% (34/37);
  - ERSP bacteremia 8/10;
  - PRSP bacteremia 5/7; and
  - MDRSP bacteremia 11/13.

4.4.3 Acute exacerbation of chronic bronchitis

4.4.3.1 Study population

The clinical effectiveness of 800 mg of telithromycin administered once daily for 5 days in the treatment of AECB was evaluated in 3 Phase III clinical studies. In the mITT population, males comprised 52.6% (females 47.4%) of telithromycin-treated subjects and 55.8% (females 44.2%) of comparator-treated subjects.

Mean age was 57.7 years in subjects treated with telithromycin and 59.0 years in subjects treated with comparators. Only 0.2% of subjects treated with either telithromycin or comparators were 18 years of age or younger. Subjects 65 years of age or older made up 36.4% of the population of telithromycin-treated subjects, and 41.7% of comparator-treated subjects. Subjects with a history of COPD comprised 71.4% in both treatment groups.

4.4.3.2 Clinical outcome

Clinical cure rates with 5 days of telithromycin treatment was not inferior in all 3 double-blind controlled studies, relative to amoxicillin-clavulanic acid, cefuroxime or clarithromycin.

Table 17 - AECB: Clinical cure rates by study for telithromycin and comparator(s) at posttherapy/TOC, PPc population

	Telithromycin			Comparators			95% CI[a]
	N	n	(%)	N	n	(%)	
PPc population							
Study A3003	115	99	(86.1)	112	92	(82.1)	[-6.4; 14.3]
Study A3007	140	121	(86.4)	142	118	(83.1)	[-5.8; 12.4]
Study A3013	225	193	(85.8)	231	206	(89.2)	[-9.9; 3.1]
All AECB	480	413	(86.0)	485	416	(85.8)	[-4.3; 4.9]
mITT population							
Study A3003	160	130	(81.3)	160	125	(78.1)	[-6.3; 12.6]
Study A3007	182	142	(78.0)	191	138	(72.3)	[-3.5; 15.1]
Study A3013	270	224	(83.0)	282	236	(83.7)	[-7.3; 5.9]
All AECB	612	496	(81.0)	633	499	(78.8)	[-2.4; 6.8]

N=number of subjects; n=number clinically cured

[a]95% confidence interval of the difference in cure rates between the treatment groups.
Comparators: A3003 amoxicillin-clavulanic acid, A3007 cefuroxime, A3013 clarithromycin

4.4.3.3 Clinical cure rates by pathogen

The causative bacteria for AECB are similar to those of CAP. The clinical cure rates at posttherapy/TOC for the PPb population are summarized in the table below for the 3 targeted causative pathogens.

Table 18 - AECB: Clinical cure rates by pathogen – PPb population

Causative pathogen	Clinical cure					
	Telithromycin			Comparators		
	N	n	(%)	N	N	(%)
Streptococcus pneumoniae	27	22	(81.5)	19	15	(78.9)
Haemophilus influenzae	60	44	(73.3)	53	45	(84.9)
Moraxella catarrhalis	29	27	(93.1)	34	29	(85.3)
Total	116	93	(80.1)	106	89	(84.0)

N=subjects in PPb population with causative pathogen isolated at pretherapy/entry; n=number clinically cured.

4.4.3.4 Efficacy in subgroups of special interest

Population subsets were stratified by factors that may increase risk of treatment failure. Clinical cure in telithromycin-treated subjects with more severe disease is similar to that of comparators. Clinical cure rates are similar to comparators for subjects ≥65 years of age, <65 years of age, and with 1 or ≥2 risk factors for morbidity. As expected, subjects with a history of documented bronchial obstruction (FEV1/FVC <60%) had lower cure rates but the cure rates were similar to that of comparators (telithromycin 78.5% [117/149] vs. comparators 82.2%, [129/157]).

Table 19 - AECB: Clinical cure rates at posttherapy/TOC by risk subgroup – PPc population

Subgroup	Clinical outcome: Cure					
	Telithromycin			Comparators		
	N	n	(%)	N	N	(%)
	480	413	(86.0)	485	416	(85.8)
Age (yrs)						
<65	296	256	(86.5)	270	237	(87.8)
≥65	184	157	(85.3)	215	179	(83.3)
Risk factors for morbidity[a]						
At least 1	338	290	(85.8)	332	284	(85.5)
At least 2	171	142	(83.0)	181	152	(84.0)
FEV1/FVC <60%	149	117	(78.5)	157	129	(82.2)

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

[a]Respiratory insufficiency, congestive heart failure, diabetes mellitus, alcoholism, renal disease, sickle-cell disease, liver disease, coronary artery disease, cancer (other than pulmonary), cerebrovascular disease (Studies A3003 and A3007); COPD, allergy to antibiotics, intravenous drug use, inhaled corticosteroid use (past 30 days) (Study A3007).

4.4.3.5 Summary of acute exacerbation of chronic bronchitis

- Telithromycin 800 mg once daily for 5 days was noninferior in clinical efficacy to well accepted treatments (cefuroxime axetil. clarithromycin, or amoxicillin-clavulanic acid, administered 2 to 3 times daily) given for 10 days. Telithromycin 800 mg/d for 5 days in 3 double blind controlled studies was effective 413/480 (86.0%) vs. 416/485 (85.8%). The efficacy of telithromycin was consistent across all subgroups of subjects, including those with increased risk: ≥65 years of age (85.3%), with at least 2 concomitant medical conditions (83%), and bronchial obstruction defined by FEV1/FVC <60%, (78.5%).

- The clinical cure rates by pathogen was numerically comparable to comparators for pathogens of interest:
  - *Streptococcus pneumoniae* 81.5% (22/27);
  - *Haemophilus influenzae* 73.3% (44/60); and
  - *Moraxella catarrhalis* 93.1% (27/29).

4.4.4 Acute bacterial sinusitis

4.4.4.1 Study population

The clinical and bacteriologic effectiveness of 800 mg oral telithromycin administered once daily for 5 or 10 days in the treatment of acute bacterial sinusitis was evaluated in 3 comparative studies (Studies A3002, A3005, and A3011). A total of 608 subjects were treated with a 5-day regimen of telithromycin, 372 subjects with a 10-day regimen of telithromycin, and 318 subjects with a 10-day regimen of a comparator.

In the mITT population, males comprised 45.2% (females 54.8%) of telithromycin-treated subjects in the 5-day regimen; 44.9% (females 55.1%) of telithromycin-treated subjects in the 10-day regimen; and 37.1% (62.9% females) in the comparator-treated subjects. The mean age was 39.2 years in subjects treated with telithromycin for 5 days, 40.3 years for subjects treated with telithromycin for 10 days, and 40.1 years for subjects treated with comparators. Subjects 18 years of age or younger comprised 2.1% of subjects treated with 5 days of telithromycin; 1.1% of those treated with 10 days of telithromycin; and 1.9% of subjects treated with comparators. Subjects 65 years of age or older made up <6% of subjects in any treatment regimen.

Cultures for causative were attempted at entry by sinus puncture in Study A3002 and attempted by sinus puncture at the US sites and by sinus endoscopy at all non-US sites in Study A3011.

4.4.4.2 Clinical outcome

The clinical cure rates in 2 double-blind studies with 5 days of telithromycin were not inferior to 10 days of therapy with either cefuroxime axetil or amoxicillin-clavulanic acid.

Table 20 - ABS: Clinical cure rates by study at posttherapy/TOC, PPc population

	Telithromycin						Comparators			Difference	95% CI[a]
	5-day			10-day			5-day				
	N	n	(%)				N	n	(%)		
PPc population											
Study A3005	146	110	(75.3)	140	102	(72.9)	137	102	(74.5)	0.89%	[-9.9; 11.7][a]
Study A3011	189	161	(85.2)	NA			89	73	(82.0)	3.16%	[-7.1; 13.4]
All ABS randomized controlled studies	335	271	(80.9)				226	175	(77.4)	3.46%	[-3.8; 10.7]
Study A3002	123	112	(91.1)	133	121	(91.0)	NA				
mITT population											
Study A3005	201	140	(69.7)	204	140	(68.6)	202	138	(68.3)	1.33%	[-8.2; 10.9][a]
Study A3011	240	193	(80.4)	NA			116	84	(72.4)	7.59%	[-2.2; 18.2][a]
All ABS randomized controlled studies	441	332	(75.3)				318	222	(69.8)	5.47%	[1.4; 13.9][a]
Study A3002	167	138	(82.6)	168	147	(87.5)					

Comparators= 5- vs. 10-days duration of telithromycin (A3002), amoxicillin-clavulanic acid (Study A3005), and cefuroxime axetil (Study A3011). NA=not applicable; ABS=acute sinusitis; N=number of subjects; n=number of clinically cured.

[a] Pairwise comparison between 5-day telithromycin regimen and 10-day comparator regimen.

4.4.4.3 Clinical cure rates by pathogen

The causative bacteria for ABS are similar to those of CAP and AECB. The clinical cure rates at posttherapy/TOC for the PPb population are summarized in the table below for the 4 causative pathogens of interest. The cure rates for pathogens evaluated with 5 days treatment with telithromycin is similar to comparators administered for 10 days.

Table 21 - ABS: Clinical cure rates by pathogen – PPb population

	Clinical cure											
	Telithromycin[a]									Comparators		
	5-day randomized controlled [b]			5-day all studies [c]			5- and 10-day all studies [c]			10-day		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
S. pneumoniae	31	27	(87.1)	61	55	(90.2)	91	82	(90.1)	16	14	(87.5)
H. influenzae	34	28	(82.4)	48	42	(87.5)	64	57	(89.1)	15	13	(86.7)
M. catarrhalis	7	7	(100)	14	13	(92.9)	18	16	(88.9)	7	7	(100)
S. aureus	8	8	(100)	19	18	(94.7)	23	22	(95.6)	3	2	(66.7)
Total	80	70	(87.5)	142	128	(90.1)	196	177	(90.3)	41	36	(87.8)

N=subjects in PPb population with causative pathogen isolated at pretherapy/entry; n=number clinically cured;

[a] Telithromycin has more isolates because Study A3002 only had telithromycin treatments (duration 5 vs. 10 days).

[b] Studies A3005 and A3011.

[c] Studies A3005, A3011, and A3002.

Antibiotic-resistant Streptococcus pneumoniae

Data in the table below show that subjects with *S. pneumoniae* resistant to penicillin G, erythromycin A, a combination of penicillin G and/or erythromycin A, as well as MDRSP treated for 5 days have clinical cure rates consistent with the overall population infected with *S. pneumoniae* as well with comparators administered for 10 days.

Table 22 - ABS: Clinical efficacy for antibiotic-resistant *Streptococcus pneumoniae* isolates from single and mixed pathogen infections in telithromycin-treated subjects at posttherapy/TOC – PPb population

Causative pathogen	All ABS studies					
	Telithromycin 5 days			Comparator 10 days		
	N	n	(%)	N	N	(%)
All *S. pneumoniae*	31	27	(87.1)	6	6	*a*
PEN-R	9	7	b	3	3	*a*
ERY-R	12	10	(83.3)	5	5	*a*
PEN-R and/or ERY-R	14	12	(85.7)	6	6	*a*
MDRSP	11	9	(81.8)	4	4	*a*

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

[a] The number of isolates is too small for percentages to be meaningful.

MDRSP includes penicillin-resistant *S. pneumoniae,* and isolates resistant to 2 or more of the following antibiotics - penicillin, 2nd generation cephalosporins, eg, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Data from controlled studies A3005 (5days) and A3011 used in US labeling. N=number of subjects, n=number clinically cured.

For a more complete description of microbiologic activity of telithromycin in the ABS indication, data from all 3 studies including the 5- and 10-day treatment groups in Study A3002 are pooled. The clinical cure rates with pooled data are 90.1% (82/91) for *S. pneumoniae*; 84.6% (11/13) for PEN-R *S. pneumoniae*; 85.7% (18/21) for ERY-R *S. pneumoniae*; 87.0% (20/23) for PEN-R and/or ERY-R *S. pneumoniae*, and 88.9% (16/18) for MDRSP.

4.4.4.4 Efficacy in subgroups of special interest

Population subsets were stratified by factors that increase the risk of treatment failure. The clinical cure rates in subjects treated with 5 days of telithromycin were similar to those in subjects treated with 10 days of the comparator antibiotic. Clinical cure rates were similar between the telithromycin- and comparator-treated subpopulations with ABS rated as “severe” by the Investigators, total sinus opacification, or sinus muscosal thickening. The clinical cure rates for subjects with a history of allergic rhinitis in the last 30 days were 81.3% (61/75) in the telithromycin-treated group and 62.8% (27/43) in the comparator-treated group.

Table 23 - ABS: Clinical cure rates at posttherapy/test of cure by selected pretherapy/entry characteristics and prognostic factors – PPc population

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

[a]Level of mucosal thickening in Study A3005 was ≥6 mm. The level in Study A3011 was ≥10 mm. Only total opacity or air fluid level was to be present in Study A3002. Telithromycin 5- and 10-day treatment groups are included.
N=number of subjects; n=number clinically cured.

4.4.4.5 Summary of acute bacterial sinusitis

Telithromycin 800 mg once daily for 5 days was shown to be noninferior in clinical efficacy to accepted treatments (cefuroxime axetil or amoxicillin-clavulanic acid, administered 2 to 3 times daily) given for 10 days. Telithromycin 800 mg/d for 5 days in 2 double blind controlled studies was effective 271/335 (80.9%) vs. comparators administered for 10 days was 175/226 (77.4%).

Clinical cure rates were similar to comparators in subjects with risk factors such as Investigator-rated severe infection, total sinus opacification or sinus muscosal thickening. The cure rates for subjects with a history of allergic rhinitis in the last 30 days with 5 days treatment of telithromycin was 81.3% (61/75) and for comparators administered for 10 days was 62.8% (27/43).

- The clinical cure rates for pooled 5 and 10 days treatment or 5 day treatment alone according to pathogen of interest in subjects treated with telithromycin were:
  - *Streptococcus pneumoniae* 90.1% (82/91) in all studies (5 to 10 days), and 87.1% (27/31) in 5 days;
  - *Haemophilus influenzae* 89.1% (57/64] in all studies (5 to 10 days, and 82.4% (28/34) in 5 days;
  - *Moraxella catarrhalis* 88.9% (16/18) in all studies (5 to 10 days) and 7/7 in 5 days; and
  - *Staphylococcus aureus* 95.6% (22/23) in all studies (5 to 10 days) and 8/8 in 5 days.

- The clinical cure rates for antibacterial-resistant *S. pneumoniae* isolates in the 5 or 10-day treatment groups were:
  - Penicillin G-resistant *S. pneumoniae*, 80.0% (8/10) for 5 days, and 3/3 for 10 days,
  - Macrolide- (erythromycin A-) resistant *S. pneumoniae* 85.7% (12/14) for 5 days and 6/7 for 10 days
  - MDRSP 83.3% (10/12) for 5 days, 6/6 for 10 days

4.4.5 Summary of Phase III clinical efficacy data

The efficacy of telithromycin is demonstrated for the treatment of RTIs in 14 Phase III studies in 3 indications, CAP, AECB and ABS. Telithromycin has been shown to be as effective as accepted comparators in the indications studied:

- CAP treated for 7 to 10 days relative to amoxicillin and clarithromycin given for 10 days
- AECB treated for 5 days relative to amoxicillin, cefuroxime, or clarithromycin for 10 days
- ABS treated for 5 days relative to amoxicillin or cefuroxime for 10 days

Efficacy is also observed in subpopulations at risk, such as elderly adults, patients with pneumococcal bacteremia in CAP, patients with comorbid conditions in AECB, and patients with ABS rated as severe by the Investigator.

Efficacy is also observed in subjects with penicillin- or macrolide-resistant *S. pneumoniae* or MDRSP (ie, resistant to ≥2 or more classes of antibacterials).

The spectrum of activity of telithromycin is focused on bacteria associated with RTIs. Telithromycin demonstrates clinical efficacy among patients in the ambulatory care setting infected with *S. pneumoniae* (including antibiotic-resistant strains), *H. influenzae*, and *M. catarrhalis* (irrespective of β-lactamase production), as well as *S. aureus*. Telithromycin also demonstrates efficacy against the atypical and intracellular pathogens *M. pneumoniae* and *C. pneumoniae*.

4.5 PREAPPROVAL: SAFETY DATA

During the course of clinical development, several safety topics were identified as potential AESIs based upon consideration of known effects of the related macrolide class of drugs and review of preclinical, clinical pharmacology and/or clinical data. The combination of recognized macrolide class drug effects and preclinical findings led to close monitoring of hepatic and cardiac events during clinical trials and the execution of specific clinical pharmacology investigations. Visual effects were identified during the comparative clinical trials, leading to the subsequent performance of targeted preclinical and clinical pharmacology investigations. Other events, such as exacerbation of myasthenia gravis exacerbation and syncope, were events identified from postmarketing spontaneous reports. Work-up of these events led to a review of preclinical and clinical trial data to further elucidate the nature of these suspected adverse drug reactions (ADRs).

The following section describes the preapproval clinical safety profile of telithromycin in 2 parts. The first part describes the general safety data, based on clinical trial, intensified monitoring, and postmarketing surveillance data as of December 2003 from countries where telithromycin was marketed and approved prior to the FDA approval. The second part summarizes these data by AESI, which will be defined in their respective subsections. The combination of recognized macrolide class drug effects and preclinical findings led to close monitoring of hepatic and cardiac events during clinical trials and the execution of specific clinical pharmacology investigations. This section represents a summary of safety data available at the time of FDA approval (April 1, 2004).

4.5.1 Phase I studies

The Phase I program included 55 studies with 1319 subjects. Relevant data from these studies will be discussed in the context of AESIs.

4.5.2 General safety: Phase III studies

The Phase III safety database contains data from 6919 safety-evaluable subjects in 16 integrated Phase III studies, including 12 controlled studies. The 16 studies included 2 T/P Studies (A3004 and A3008) in addition to the list of 14 Phase III studies noted in

Table 6 of the PREAPPROVAL: EFFICACY section. The Phase III safety-evaluable population included all subjects who received at least 1 dose of study treatment and had at least 1 safety assessment following randomization. The randomized controlled studies will be discussed first, followed by the open label studies.

Of the 6919 safety-evaluable subjects, 4780 subjects received telithromycin and 2139 subjects received comparator drugs. Comparators used in these randomized controlled studies included amoxicillin, amoxicillin-clavulanic acid, cefuroxime, clarithromycin, levofloxacin, and trovafloxacin. Completed safety data for these Phase III studies were available at the time of FDA approval (April 1, 2004) and are summarized below.

Table 24 - Safety-evaluable population in telithromycin Phase III clinical program

All Phase III studies[a, b]		Randomized controlled [b]		Open label	
TEL	COMP	TEL	COMP	TEL	TEL
4780	2139	2702	2139	2078	4780

[a] Includes a total of 16 Phase III studies in CAP, AECB, ABS, and T/P.
[b] These numbers do not include data from Study A3014.
TEL=telithromycin; COMP=pooled active comparators

4.5.2.1 Phase III randomized controlled studies

A total of 2702 telithromycin-treated and 2139 comparator-treated subjects were enrolled in the 12 Phase III randomized controlled studies. These exposure data, as well as AE data in this section do not include those from Study A3014.

Treatment-emergent adverse events in Phase III randomized controlled studies

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

The on-treatment period encompassed the period from the first day of study medication to 7 days after the last dose was taken.

Of the 2702 subjects treated with telithromycin in the 12 Phase III randomized controlled studies, 1348 subjects (49.9%) reported at least 1 TEAE as compared to 1035 of 2139 subjects (48.4%) treated with a comparator drug. Treatment-emergent adverse events that were considered possibly

related by the Investigator were reported in 861 subjects (31.9%) treated with telithromycin compared with 606 subjects (28.3%) treated with a comparator drug.

Common events will be discussed first by MedDRA system organ class (SOC), followed by the individual most frequently reported adverse event (AE) Preferred Terms (PT). The following table shows the MedDRA SOCs for which the most commonly reported TEAEs (all TEAEs and those that were considered possibly related by the Investigator) in the Phase III randomized controlled studies. Treatment-emergent adverse events of the SOCs Gastrointestinal and Nervous system disorders were the most common events reported.

Table 25 - Treatment-emergent adverse events (all and possibly related) most commonly reported in Phase III randomized controlled studies, by system organ class

	Number (%) of subjects	
MedDRA system organ class	**Telithromycin N=2702**	**Comparator N=2139**
All TEAEs [a]		
Subjects with TEAEs	1348 (49.9)	1035 (48.4)
Gastrointestinal disorders	712 (26.4)	459 (21.5)
Nervous system disorders	318 (11.8)	262 (12.2)
Infections and infestations	260 (9.6)	227 (10.6)
Respiratory, thoracic and mediastinal disorders	212 (7.8)	176 (8.2)
Investigations [b]	115 (4.3)	101 (4.7)
Possibly related TEAEs [a]		
Subjects with possibly related TEAEs	861 (31.9)	606 (28.3)
Gastrointestinal disorders	620 (22.9)	369 (17.3)
Nervous system disorders	178 (6.6)	168 (7.9)
Infections and infestations	63 (2.3)	70 (3.3)
Investigations [b]	61(2.3)	54 (2.5)
Skin and subcutaneous tissue disorders	39 (1.4)	35 (1.6)

TEAE=treatment-emergent adverse event.

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

[b] The Investigations SOC includes asymptomatic laboratory abnormalities (including liver enzymes such as AST, ALT, total bilirubin).

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

Table 26 - Treatment-emergent adverse events (all and possibly related) in Phase III randomized controlled studies, by decreasing frequency

	Number (%) of subjects	
Preferred Term	**Telithromycin N=2702**	**Comparator N=2139**
All TEAEs [a]		
Subjects with TEAEs	1348 (49.9)	1035 (48.4)
Diarrhea NOS	292 (10.8)	185 (8.6)
Nausea	213 (7.9)	99 (4.6)
Headache NOS	148 (5.5)	126 (5.9)
Dizziness (excl. vertigo)	99 (3.7)	57 (2.7)
Vomiting NOS	79 (2.9)	48 (2.2)
Loose stools	63 (2.3)	33 (1.5)
Dysgeusia	43 (1.6)	77 (3.6)
Possibly related TEAEs [a]		
Subjects with possibly related TEAEs	861 (31.9)	606 (28.3)
Diarrhea NOS	270 (10.0)	172 (8.0)
Nausea	190 (7.0)	87 (4.1)
Headache NOS	54 (2.0)	54 (2.5)
Dizziness (excl. vertigo)	75 (2.8)	33 (1.5)
Vomiting NOS	64 (2.4)	30 (1.4)
Loose stools	58 (2.1)	30 (1.4)
Dyspepsia	38 (1.4)	22 (1.0)
Dysgeusia	40 (1.5)	76 (3.6)

[a] Based on a frequency of all TEAEs of ≥2.0% and possibly related TEAEs of ≥1.0% in telithromycin or comparator treatment groups.
TEAE=treatment-emergent adverse event; NOS=not otherwise specified.

Diarrhea NOS was the most common individual TEAE in the telithromycin and comparator treatment groups in the Phase III randomized controlled studies. None of the individual AEs that were pooled according to the AESI definitions occurred with an incidence ≥2%. These will be presented in their respective AESI sections.

Deaths, serious adverse events, and discontinuations due to treatment-emergent adverse events in Phase III randomized controlled studies

A total of 18 subjects died in the 12 Phase III randomized controlled studies (telithromycin: 9/2702, 0.3%; comparators 9/2139, 0.4%). None of the deaths were considered related to study medication by the study Investigator or the reviewing Sponsor physician. As expected, most of

the deaths occurred in CAP studies where subjects tend to have underlying conditions or illnesses associated with increased mortality.

The number (%) of deaths occurring on-treatment or posttreatment in the Phase III randomized controlled studies is presented in the following table. On-treatment AEs were defined as those occurring within 7 days of last dose *or* at any time after treatment if they were considered treatment-related by the Investigator. Posttreatment events were defined as those occurring more than 7 days after the last dose of study medication.

Table 27 - Deaths (on-treatment and posttreatment) in Phase III randomized controlled studies

	n/N (%) subjects	
Indication	**Telithromycin**	**Comparator**
CAP	5/916 (0.5)	5/723 (0.7)
AECB	4/609 (0.7)	3/626 (0.5)
ABS	0/750 (0.0)	0/366 (0.0)
T/P	0/427 (0.0)	1/424 (0.2)
Total	9/2702 (0.3)	9/2139 (0.4)

n=number of subjects who died; N=number of subjects in population; NA=not applicable; CAP=community-acquired pneumonia; AECB=acute exacerbation of chronic bronchitis; ABS=acute bacterial sinusitis; T/P=tonsillitis/pharyngitis.

A listing and brief narrative for each of the subjects who had a TEAE with an outcome of death is presented in *APPENDIX B: PHASE III SAFETY DATA , in Phase III studies*.

In the 12 Phase III randomized controlled studies, the frequency of serious TEAEs was comparable between treatment groups (telithromycin: 59/2702, 2.2%; comparators: 61/2139, 2.9%). The incidence of possibly related serious TEAEs was low in each treatment group (telithromycin: 9/2702, 0.3%; comparators: 6/2139, 0.3%).

The following table shows the SOCs for serious TEAEs (all and those considered possibly related by the Investigator) that were most commonly reported in the Phase III randomized controlled studies.

Table 28 - System organ classes for serious treatment-emergent adverse events (all and possibly related) most commonly reported in Phase III randomized controlled studies

	Number (%) of subjects	
MedDRA system organ class	**Telithromycin (N=2702)**	**Comparator (N=2139)**
Subjects with serious TEAEs [a]	**59 (2.2)**	**61 (2.9)**
Infections and infestations	14 (0.5)	23 (1.1)
Respiratory, thoracic, and mediastinal disorders	16 (0.6)	11 (0.5)
Vascular disorders	3 (0.1)	1 (0.0)
Renal and urinary disorders	4 (0.1)	3 (0.1)
Immune system disorders	4 (0.1)	1 (0.0)
Cardiac disorders	3 (0.1)	8 (0.4)
Gastrointestinal disorders	3 (0.1)	4 (0.2)
Psychiatric disorders	2 (0.1)	4 (0.2)
Subjects with possibly related serious TEAEs [b]	**9 (0.3)**	**6 (0.3)**
Infections and infestations	2 (0.1)	1 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.0)	1 (0.0)
Gastrointestinal disorders	1 (0.0)	1 (0.0)
Hepatobiliary disorders	2 (0.1)	0 (0.0)
Immune system disorders	2 (0.1)	1 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.0)
Psychiatric disorders	0 (0.0)	1 (0.0)
Skin and subcutaneous tissue disorders	1 (0.0)	0 (0.0)

[a] Based on the 5 most frequently affected SOCs in each treatment group (ie, maximum of 10).

[b] All SOCs for which possibly related serious TEAEs were reported in Phase III randomized controlled studies are shown.
SOC=system organ class; TEAE=treatment-emergent adverse event.

In the Phase III randomized controlled studies, serious TEAEs irrespective of causality were reported most frequently for the Infections and infestations SOC, in both telithromycin and comparator treatment groups. Most serious TEAEs were respiratory in nature, likely representative of the underlying indications for treatment. Pneumonia was the most common individual serious TEAE in the comparator-treated group (15/2139, 0.7%) and was reported more frequently than in the telithromycin-treated group (2/2702, 0.1%). Acute exacerbation of chronic bronchitis NOS and pleural effusion were the most common serious TEAEs in the telithromycin-treated group (both 3/2702, 0.1%) and were reported at similar rates in the comparator-treated group (3/2139, 0.1% and 1/2139, <0.1%, respectively). The most frequently reported seriousness criteria in both treatment groups were those requiring hospitalization (telithromycin: 42/2702, 1.6%; comparators: 49/2139, 2.3%) and those deemed medically important by the Investigator (telithromycin: 23/2702, 0.9%; comparators: 22/2139, 1.0%).

The following table shows that the frequency of all TEAEs leading to discontinuation was similar between treatment groups in the Phase III randomized controlled studies (telithromycin: 119/2702, 4.4%; comparators: 92/2139, 4.3%). Diarrhea was the most common event leading to discontinuation both groups.

The frequency of possibly related TEAEs (Investigator assessed) leading to discontinuation was 3.2% in the telithromycin-treated group vs. 2.8% in the comparator-treated group.

Table 29 – Treatment-emergent adverse events (all and possibly related)[a] resulting in discontinuation of study medication in Phase III randomized controlled studies

	Number (%) of subjects	
Preferred Term	**Telithromycin (N=2702)**	**Comparator (N=2139)**
Subjects with TEAEs resulting in discontinuation of study medication	119 (4.4)	92 (4.3)
Diarrhea NOS	23 (0.9)	14 (0.7)
Vomiting NOS	21 (0.8)	10 (0.5)
Nausea	19 (0.7)	10 (0.5)
Liver function tests NOS abnormal	5 (0.2)	5 (0.2)
Abdominal pain NOS	5 (0.2)	2 (0.1)
Dizziness (excl. vertigo)	5 (0.2)	1 (0.0)
Headache NOS	2 (0.1)	7 (0.3)
Rash NOS	2 (0.1)	5 (0.2)
Subjects with possibly related TEAEs resulting in discontinuation of study medication	**86 (3.2)**	**60 (2.8)**
Diarrhea NOS	22 (0.8)	14 (0.7)
Vomiting NOS	21 (0.8)	7 (0.3)
Nausea	19 (0.7)	9 (0.4)
Liver function tests NOS abnormal	3 (0.1)	3 (0.1)
Abdominal pain NOS	5 (0.2)	2 (0.1)
Dizziness (excl. vertigo)	5 (0.2)	1 (0.0)
Headache NOS	2 (0.1)	5 (0.2)
Rash NOS	2 (0.1)	5 (0.2)

[a] Based on a frequency of all TEAEs resulting in discontinuation of ≥0.2% in telithromycin or comparator treatment groups in Phase III randomized controlled studies.
Note: The numbers in each column are not additive because a subject may have had more than 1 adverse event that resulted in discontinuation of study medication.
NOS=not otherwise specified.

Frequency of clinically noteworthy laboratory values in Phase III randomized controlled studies

The frequencies of CNALVs for each analyte are presented for all 12 Phase III randomized controlled studies, as well as by CAP and non-CAP indication. The treatment groups compared for the Phase III randomized controlled studies are telithromycin (5 to 10 days) vs. comparator (7 to 10 days) for CAP and telithromycin (5 or 10 days) vs. comparator (10 days) for non-CAP indications. The criteria for CNALVs are outlined in *APPENDIX B: PHASE III SAFETY DATA*
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Table 30 - Clinically noteworthy laboratory analytes in Phase III randomized controlled studies

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

n/N=number of subjects with CNALV for specific analyte/number of subjects with measurement of analyte
Key: ↑ is an increased value in the analyte; ↓ is a decreased value in the analyte. PT=prothrombin time; INR=international normalized ratio; ULN=upper limit of normal range; Neutrophils (Abs)=absolute neutrophil count; Eosinophils (Abs)=absolute eosinophil count; Alk phos=alkaline phosphatase; CrCL=creatinine clearance; TEL=telithromycin; COMP=comparators.

There were no meaningful differences in CNALVs between the telithromycin- and comparator-treated groups. In addition to CNALVs, no concomitant elevations in transaminases and total bilirubin in the absence of cholestasis were identified.

4.5.2.2 Phase III open label studies

A total of 2078 telithromycin-treated subjects were enrolled in the 4 Phase III open label studies.

Treatment-emergent adverse events in Phase III open label studies

A total of 738 (35.5%) of the 2078 telithromycin-treated subjects in the Phase III open label studies reported at least 1 TEAE; 426 (20.6%) of these TEAEs were reported as possibly related by the Investigator. The table below shows the most frequently reported TEAEs and possibly related TEAEs by MedDRA SOC in the Phase III open label studies, which were similar to those reported in Phase III randomized controlled studies.

Table 31 - All and possibly related treatment-emergent adverse events most commonly reported in Phase III open label studies, by system organ class

	Number (%) of subjects
MedDRA system organ class	**Telithromycin (N= 2078)**
All TEAEs [a]	
Subjects with TEAEs	738 (35.5)
Gastrointestinal disorders	328 (15.8)
Infections and infestations	147 (7.1)
Nervous system disorders	103 (5.0)
Respiratory, thoracic and mediastinal disorders	101 (4.9)
Investigations [b]	76 (3.7)
Possibly related TEAEs [a]	
Subjects with possibly related TEAEs	426 (20.6)
Gastrointestinal disorders	259 (12.5)
Investigations [b]	55 (2.6)
Nervous system disorders	53 (2.6)
Infections and infestations	38 (1.8)
Skin and subcutaneous tissue disorders	19 (0.9)

SOC=system organ class; TEAE=treatment-emergent adverse event.

[a] Based on the 5 most frequently affected SOCs.

[b] The Investigations SOC includes asymptomatic laboratory abnormalities (including liver enzymes such as AST, ALT, total bilirubin, etc)

Treatment-emergent adverse events occurring in ≥2% of subjects and possibly related TEAEs occurring in ≥1% of subjects in Phase III open label studies are shown by decreasing frequency in the table below. Diarrhea NOS was the most common individual TEAE in both the Phase III open label and Phase III randomized controlled studies.

Table 32 - All and possibly related TEAEs by decreasing frequency in Phase III open label studies

	Number (%) of subjects
Preferred Term	**Telithromycin N= 2078**
All TEAEs [a]	
Subjects with TEAEs	738 (35.5)
Diarrhea NOS	129 (6.2)
Nausea	92 (4.4)
Headache NOS	55 (2.6)
Vomiting NOS	41 (2.0)
Possibly related TEAEs [a]	
Subjects with possibly related TEAEs	428 (20.6)
Diarrhea NOS	117 (5.6)
Nausea	72 (3.5)
Vomiting NOS	29 (1.4)
Liver function tests abnormal	22 (1.1)

[a] Based on a frequency of all TEAEs of ≥2.0% and possibly related TEAEs (by Investigator) of ≥1.0% in all subjects.
SOC=system organ class; TEAE=treatment-emergent adverse event.

Deaths, serious adverse events, and discontinuations due to treatment-emergent adverse events in Phase III open label studies

There were a total of 10 deaths (on treatment and posttreatment) in Phase III open label studies (0.5% of subjects). All of the 10 deaths occurred in subjects with CAP. None of the deaths were considered related to study medication by the study Investigator or the reviewing Sponsor physician.

A listing and brief narrative for each of the subjects who had a TEAE with an outcome of death is presented in *APPENDIX B: PHASE III SAFETY DATA* .

The following table shows the SOCs for which all and possibly related serious TEAEs were most commonly reported in the Phase III open label studies. Serious TEAEs, irrespective of causality, were reported most frequently for the Infections and infestations SOC and Respiratory, thoracic and mediastinal disorders SOC. As reported for the Phase III randomized controlled studies, most of the serious TEAEs were respiratory in nature, with pneumonia as the most common individual serious TEAE (14/2078, 0.7%). All other serious TEAEs occurred in no more than 0.2% of all subjects in the Phase III open label studies.

Table 33 - All and possibly related serious treatment-emergent adverse events most commonly reported in Phase III open label studies, by system organ class

	Number (%) of subjects
MedDRA system organ class	**Telithromycin (N=2078)**
Subjects with serious TEAEs [a]	69 (3.3)
Infections and infestations	26 (1.3)
Respiratory, thoracic and mediastinal disorders	18 (0.9)
Neoplasms benign, malignant and unspecified	7 (0.3)
Cardiac disorders	6 (0.3)
General disorders and admin site conditions	4 (0.2)
Subjects with possibly related serious TEAEs [b]	
Infections and infestations	1
Respiratory, thoracic and mediastinal disorders	1
Hepatobiliary disorders	1
Immune system disorders	1
Skin and subcutaneous tissue disorders	1
Blood and lymphatic system disorder	1
Investigations	1

SOC=system organ class; TEAE=treatment-emergent adverse event.

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

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

Discontinuations were infrequently reported in Phase III open label studies. The table below highlights those SOCs wherein the discontinuations occurred in of ≥0.2% of all subjects per each SOC. In over 95% of the discontinuations, the occurrence of each event was reported by <0.2% of all subjects.

Table 34 - All and possibly related treatment-emergent adverse events[a] resulting in discontinuation of study medication in Phase III open label studies

	Number (%) of subjects
Preferred Term	**Telithromycin (N=2078)**
Subjects with TEAE resulting in discontinuation of study medication	**48 (2.3)**
Vomiting NOS	5 (0.2)
Diarrhea	4 (0.2)
Subjects with possibly related TEAE resulting in discontinuation of study medication	
Vomiting NOS	5 (0.2)
Diarrhea	4 (0.2)

[a] Based on a frequency of all TEAEs by SOCs resulting in discontinuation of ≥0.2% per Preferred Term in all Phase III open label studies
NOS= not otherwise specified.

In summary:

- The incidence and nature of the most frequently reported TEAEs were, in general, similar between the telithromycin- and comparator-treated groups. Treatment-emergent adverse events of the Gastrointestinal disorders SOC (eg, diarrhea NOS, nausea, and vomiting) were most frequently reported and were generally mild or moderate in intensity.
- The overall incidence of death was the same (0.4%) in both the telithromycin- and comparator-treated groups. None of the deaths were assessed by the Investigator as being possibly related to study medication.
- The incidence of SAEs was similar in both the telithromycin- and comparator-treated groups.
- Adverse events requiring discontinuation of study medications were uncommon and balanced between treatment groups: telithromycin (119/2702, 4.4%) and comparators (92/2139, 4.3%). The most frequently reported TEAEs leading to discontinuation in both telithromycin- and comparator-treated subjects were diarrhea NOS (0.9% vs. 0.7%, respectively), vomiting NOS (0.8% vs. 0.5%, respectively), and nausea (0.7% vs. 0.5%, respectively).
- The frequency and pattern of TEAEs in the Phase III open label studies did not differ significantly from those in the Phase III randomized controlled studies.

4.5.3 General safety: Large simple safety study (Study A3014)

4.5.3.1 Study A3014 (Large simple safety study)

Study A3014 was a large simple safety study conducted in response to FDA's request in the June 1, 2001, Approvable Letter for an additional assessment of telithromycin, including a broader population of patients 50 years of age or older and subjects with multiple underlying diseases. A total of 24,137 adult outpatients were enrolled and safety evaluable at 1824 primary care sites across the US. The study compared telithromycin to amoxicillin-clavulanic acid, and was designed to characterize and assess 4 categories of AESIs – hepatic, cardiac, visual, and vasculitic – in a usual care setting and a diverse population. It was the first large simple safety study conducted preapproval in the anti-infective area.

Patient enrollment began in October 2001 and the study was completed in May 2002. Monitoring was performed by an experienced independent contract research organization, and included weekly scripted telephone calls to each site and selective on-site monitoring; a limited number of clinical quality assurance audits were performed by sanofi-aventis. Among other measures, special forms were developed to ensure protocol compliance, including separate forms designed to elicit reports regarding AESIs. The CSR was submitted to the FDA in July 2002.

Good clinical practice (GCP) violations were noted by sanofi-aventis during the course of the study at a number of sites, and follow-up and corrective actions were instituted. Data from 2 sites that could not be brought into compliance with requirements were excluded from the CSR submitted in July 2002. In December 2002, the FDA expressed concern over the integrity of Study A3014 data based upon FDA's then recent Investigator site inspections. Subsequent actual investigator fraud by 1 of the site Investigators was identified following an FDA criminal investigation initiated in late 2002, which resulted in the indictment of that Investigator in August 2003 for mail fraud and false statements. The Investigator pled guilty in October 2003 to 1 count of mail fraud that involved creating records for a non-existent patient. Data from this site had been included in the data submitted to the FDA in July 2002 and presented at the advisory committee meeting in January 2003. The safety data from the study was subsequently reanalyzed and data from this site as well as data from another site where the Investigator was disqualified from participating in clinical studies based upon conduct in a separate trial with another sponsor were excluded, and revised results were submitted to the FDA. The results of sensitivity analysis with and without data from these 2 sites did not alter the overall conclusion.

The FDA ultimately approved telithromycin based upon pivotal Phase III trials, ex-US postmarketing experience and additional analyses provided by sanofi-aventis. Study A3014 data were not used as a basis for approval of telithromycin. The data from Study A3014 are not referenced in the USPI.

Despite GCP violation concerns raised with the study, sanofi-aventis considers that the data from Study A3014 provided useful information regarding AESIs that complements the overall safety profile of telithromycin as reflected in other Phase III studies and postmarketing experience.

4.5.4 General safety: Intensified monitoring survey (German postmarketing observational survey)

As required by German regulations, a postmarketing observational survey was conducted. Data were collected from 34,929 patients presenting to medical practices in the community between October 2001 and December 2003 as part of a noninterventional telithromycin trial.

A total of 34,929 patients were enrolled in this intensified monitoring survey. An interim report following enrollment of 29,439 subjects was submitted in response to the second FDA Approvable Letter (October 17, 2003). Overall, telithromycin was well tolerated. The most frequently reported possibly related AEs (per Investigator) were typical, anticipated antimicrobial-associated AEs such as nausea and diarrhea. There were no clinically relevant telithromycin-related cases of hepatotoxicity or cardiotoxicity.

The survey targeted patients with CAP (n=5640; 16.15%), AECB (n= 9957; 28.51%), ABS (n=12,860; 36.82%) and T/P (n=8337; 23.87%). In 80 patients treatment was given because of other infections. Overall, the incidence of AEs was low. The incidence of all AEs was 2.08% while ADRs, which were events where a causal relationship with telithromycin could not be excluded), occurred in 1.85% of patients. The most common AEs occurred in the Gastrointestinal SOC (1.26%) and Nervous system disorders SOC (0.34%). The most common AEs by MedDRA PT were diarrhea (0.6%), nausea (0.48%) and vomiting (0.23%). There were a total of 141 SAEs occurring in 32 patients. There were no deaths in the survey (see *APPENDIX I: POSTMARKETING SURVEY*).

4.5.5 General safety: Ex-US postmarketing safety data prior to FDA approval

Telithromycin was approved for marketed use in the treatment of RTIs (CAP, AECB, ABS, and T/P) by the EU health authority on July 9, 2001.

Sanofi-aventis has in place a detailed process for the collection, follow-up, and review of postmarketing spontaneous reports for marketed products, including telithromycin. This process is outlined in *APPENDIX C: POSTMARKETING SAFETY METHODS* .

Beyond these routine pharmacovigilance activities, the surveillance of spontaneous reports for telithromycin have been augmented through the use of regular and ad hoc aggregate reviews of general safety data.

4.5.5.1 Aggregate reviews of general safety data

Based on information gained pre-approval, hepatic, cardiac and visual AEs plus exacerbation of myasthenia gravis had been defined as adverse events of special interest (AESIs). These are described in more detail below.

Beyond routine pharmacovigilance activities, the surveillance of spontaneous reports for telithromycin have been augmented through the use of the following:

- Adverse event of special interest forms;
- Regular aggregate reviews of AESIs; and
- Augmented expedited reporting of hepatic AEs.

Adverse event of special interest forms

As discussed previously, potential hepatic, cardiac, and visual effects were identified during the development program for telithromycin. For these events, augmented pharmacovigilance activities implemented since May 2003 included the use of questionnaires designed to collect consistent specific detailed information. These forms, or the questions contained therein, are sent to reporters at time of case receipt. Queries incorporated in the AESI forms include details regarding relevant medical history, diagnostic work-up and laboratory testing, and possible confounding factors in the event etiology. Copies of these AESI forms are included in *APPENDIX C: POSTMARKETING SAFETY METHODS* .

Aggregate reviews of special interest

For telithromycin, aggregate postmarketing safety analyses of all safety data have been performed at frequent intervals, with particular focus included for the designated events of interest. In addition to the required IND expedited reports and periodic reports, cumulative analyses of hepatic, cardiac (including syncope), and visual AEs were performed at 6-month intervals in Periodic Safety Update Reports (PSURs), covering the period from January 2002 through September 2006. These PSURs, which are submitted to the EU health authority as part of the International Conference on Harmonization (ICH) guidance for safety reporting, have are also submitted to the FDA.

In the FDA Approvable Letter dated January 24, 2003, sanofi-aventis was asked to provide a cumulative review of postmarketing data through January 31, 2003, and additional monthly postmarketing reviews of individual AE cases obtained during the period leading up to the response (October 17, 2003).

Thereafter, prior to the US approval, sanofi-aventis continued to submit monthly safety update reports – safety reviews of both monthly interval and cumulative aggregate safety analyses – with the final report containing postmarketing data through December 31, 2003. These December 2003 data reflected the most current postmarketing safety data available prior to the FDA approval of telithromycin on April 1, 2004.

Augmented expedited reporting of hepatic adverse events

As part of the ongoing close surveillance of hepatic reports, sanofi-aventis began submitting all hepatic SAE reports received from outside of the US to the FDA in August 2003, although the reporting of these events (as "foreign" expected/listed events) are not required by regulations and have not, to our knowledge, been routinely submitted for other antibiotics with hepatitis included in their labeling.

4.5.5.2 Postmarking exposure prior to US approval

As of December 31, 2003, telithromycin had been marketed in 42 countries, with estimated postmarketing exposure of 6.0 million courses of treatment. Countries with the greatest exposure were France (2.2 million), Germany (0.9 million), Italy (0.7 million), and Spain (0.4 million).

4.5.5.3 Postmarketing spontaneous reports of adverse events prior to FDA approval

From initial EU approval through December 31, 2003, a total of 1231 postmarketing spontaneous AE reports had been received worldwide by "sanofi-aventis" (reporting rate 207 cases/million exposures). However, it should be noted that reporting rates do not reflect the incidence of ADRs, due to the underreporting of events inherent in a voluntary reporting system.

The most common spontaneously reported individual AEs for this period are presented by MedDRA PT below.

Table 35 - Most commonly reported adverse events, postmarketing spontaneous reports received by December 31, 2003

MedDRA PT	MedDRA SOC	No. of AE reports	Reporting rate (per 10^6 exposures)
Total		1231	207
Vision blurred	Eye disorders	268	45.0
Nausea	Gastrointestinal disorders	140	23.5
Dizziness	Nervous system disorders	121	20.3
Diarrhoea NOS	Gastrointestinal disorders	84	14.1
Headache	Nervous system disorders	83	13.9
Visual disturbance NOS	Eye disorders	76	12.8
Vomiting NOS	Gastrointestinal disorders	65	10.9
Abdominal pain NOS	Gastrointestinal disorders	51	8.6
Pruritus	Skin and subcutaneous tissue disorders	51	8.6
Malaise	General disorders and administration site conditions	43	7.2
Vertigo	Ear and labyrinth disorders	40	6.7
Accommodation disorder	Eye disorders	39	6.5
Paraesthesia	Nervous system disorders	38	6.4
Diplopia	Eye disorders	37	6.2
Urticaria	Skin and subcutaneous tissue disorders	37	6.2

Estimates worldwide exposure (through December 2003): 6.0 million courses of treatment.
MedDRA version 6.0.
SOC=System Organ Class; PT=Preferred Term; AE=adverse event; NOS=not otherwise specified.

The postmarketing safety profile for telithromycin prior to FDA approval was generally consistent with that observed in clinical trials, with events most frequently reported from the Eye, Nervous system, and Gastrointestinal disorders SOCs.

Of note, the proportional reporting rate for visual AEs was increased as compared to clinical trials, with blurred vision, visual disturbance and accommodation disorder among the most frequently reported AEs with marketed use. This reporting shift may reflect the general "unexpectedness" of this event for an oral antibiotic, as compared to more "usual" antibiotic-related events (eg, nausea, diarrhea, or rash), which may be less likely to be spontaneously reported by healthcare practitioners.

4.5.6 Adverse events of special interest

During the course of clinical development, several safety topics were identified as potential AESIs based upon consideration of known effects of the related macrolide class of drugs and review of preclinical, clinical pharmacology, and/or clinical data. The combination of recognized macrolide class drug effects and preclinical findings led to close monitoring of hepatic and cardiac events during clinical trials and the execution of specific clinical pharmacology investigations. Visual effects were identified during the comparative clinical trials, leading to the subsequent performance of targeted preclinical and clinical pharmacology investigations. Other events, such as exacerbation of myasthenia gravis exacerbation and syncope, were events identified from postmarketing spontaneous reports. Work-up of these events led to a review of preclinical and clinical trial data to further elucidate the nature of these suspected ADRs.

Sanofi-aventis rigorously followed up and investigated potential safety signals that started to emerge preapproval; using intensive case review and expert consultation, as well as additional studies in animals and healthy human subjects to elucidate the mechanism of action. To facilitate review of safety data on AESIs, relevant preclinical and Phase I safety data have been integrated into the presentation.

The following sections outline the data collected and reviewed by sanofi-aventis to assess the hepatic, cardiac, and visual events as well as exacerbation of myasthenia gravis prior to US approval.

4.5.7 Adverse events of special interest: Hepatic adverse events

Hepatic AEs were identified early in the development program as a potential AESI for telithromycin, based upon recognized macrolide effects and the preclinical findings. As a result, hepatic effects were closely monitored during the clinical studies, with a detailed review of clinical AEs and hepatic laboratory analytes.

Additionally, following the approval of telithromycin in the EU in July 2001, these events have been regularly assessed from postmarketing spontaneous reports. Beginning in May 2003, the Study A3014 hepatic AESI form has been applied to the spontaneous report follow-up.

4.5.7.1 Preclinical studies related to hepatic adverse events

The preclinical safety of telithromycin was evaluated in the adult rat, dog, and monkey after repeated daily oral administrations of up to 6 months, 9 months, and 1 month, respectively. Most of these studies included toxicokinetic evaluation, and the reversibility of the changes was assessed after 1- and 6-month dosing in rats and after 3-month dosing in dogs.

In the toxicity studies in rats, liver effects were noted at 150 mg/kg/d and above and were characterized by elevations of liver enzymes (AST, ALT, and alkaline phosphatase), increases in liver weights and microscopic findings consisting mainly of multifocal hepatic necrosis, hepatocellular hypertrophy, hepatocellular anisokaryosis, and multinucleated hepatocytes, in addition to phospholipidosis-related changes (vacuolation of bile duct epithelium, enlarged sinusoidal and peribiliary/perivascular macrophages). Liver findings were dose related and partially reversible after a 4-week recovery period. The no-observed adverse effect level (NOAEL) for the liver in rat studies was 50 mg/kg/d for administration of 1 month or longer. Relative to exposure levels in man at the therapeutic dose, these NOAELs gave ratios of approximately 1, based on free fractions of drugs.

In the toxicity studies in dogs, liver effects were noted at 150 mg/kg/d and above and were characterized by increases in liver enzymes (AST, ALT and alkaline phosphatase), increases in liver weights and microscopic findings consistent with phospholipidosis (enlarged peribiliary and sinusoidal macrophages). In addition, enlarged macrophages were observed in the lamina propria of the gallbladder at 50 and 150 mg/kg/d. Liver findings were dose related and reversible after a 12-week recovery period. The NOAEL for the liver in dog studies was 50 mg/kg/d for administration of 1 month or longer. Relative to exposure levels in man at the therapeutic dose; these NOAELs gave ratios of 8.4 to 9.8, based on free fractions of drugs.

The 1-month oral toxicity study in the monkey also identified the liver as a target organ with mild increases in transaminases and liver weights at the high dose of 120 mg/kg/d, but without histological correlates. The NOAEL of 60 mg/kg/d for the liver in the monkey corresponded to an exposure, based on levels of free drug, 2.3 times that in man at the therapeutic dose [Abbott Laboratories, 1993, 1988; Chu et al. 1993; Davey 1991; Kohno et al. 1989].

In addition, in order to investigate the pathogenesis of telithromycin-associated hepatotoxicity, potential formation of reactive metabolites and inhibition of mitochondrial β-oxidation were evaluated for telithromycin in comparison with other marketed macrolides, ie, clarithromycin and azithromycin. The in vitro study with human liver microsomes showed telithromycin to undergo slightly less covalent binding to microsomal proteins than clarithromycin or azithromycin. A significant inhibition of mitochondrial β-oxidation was noted after a single intraperitoneal administration of telithromycin at 150 mg/kg to fasted rats, which was quantitatively similar to that noted after administration of clarithromycin or azithromycin at the same dose.

4.5.7.2 Phase I studies related to hepatic adverse events

In the Phase I program, 1319 subjects were enrolled in a total of 55 studies. Fourteen subjects Phase I subjects reported hepatic-related AEs. The details of these TEAEs are shown in the table below. These TEAEs represent reversible enzyme elevations, and none were reported as SAEs.

Table 36 - Hepatic-related adverse events, Phase I studies

Study no.	Subject ID (age/sex)	Treatment-emergent adverse event coding	Treatment dose
A1001	49 (26/M)	Elevated AST	TEL 800 mg
A1005	55 (20/M)	Increase of CK >2xULN Increase of AST >2xULN	TEL 800 mg TEL 800 mg
A1016	2012 (55/F with mild renal impairment)	Liver function test abnormal	TEL 800 mg
A1017	14 (19/M)	Elevated alkaline phosphatase	TEL 800 mg
A1018	26 (33/M)	Liver function test abnormal	TEL 5 µg/mL – 10 mL
A1030	5 (39/F)	ALT (SGPT) increased AST (SGOT) increased	TEL 2000 mg
	10 (72/F)	Liver damage[a]	TEL 2000 mg
	12 (62/M)	Liver damage[a]	Placebo
	16 (69/M)	Liver damage[a]	TEL 2000 mg
A1032	2 (22/M)	Increase in AST >2XULN	TEL 800 mg
1046	56 (35/F)	ALT (SGPT) increased	TEL 3200 mg
1047	6 (26/M)	Liver function test abnormal	TEL 800 mg
1056	2 (23/M)	SGPT/SGOT/CPK increased	TEL 800 mg
1068	24 (33/F)	ALT increased	TEL 800 mg

ULN=upper limit of normal.

[a] These 3 cases of asymptomatic transient transaminase elevations greater than 4-6 times the ULN, reported as "liver injury, were coded as "liver damage" and were associated with changes in antibody titers against CMV and/or EBV.

An additional 2 Phase I studies were conducted in subjects with hepatic impairment: Study A1015 at single dose and Study A1060 with repeated administration and in comparison with matched healthy subjects. A third study (Study A1063) was conducted to investigate the effect of ketoconazole on PK and safety of telithromycin in elderly subjects with diminished renal function.

Overall, the results of Studies A1015 and A1060 showed that single or multiple doses of 800 mg of telithromycin were well tolerated in subjects with hepatic impairment. Laboratory abnormalities that occurred in those subjects were related to the underlying liver disease or considered not clinically relevant by the Investigator. In Study A1063, the at-risk population with multiple impairments demonstrated mean plasma concentrations consistent with the highest concentrations seen in Phase III studies with no reported hepatic AEs.

4.5.7.3 Phase III safety data related to hepatic adverse events

For all Phase III studies hepatic TEAEs included any on-treatment AE that was not present before treatment or was present before treatment and became more intense (increased in severity) or more frequent during the treatment period, as determined by the Investigators.

Hepatic AEs were defined as using primary SOC (MedDRA version 6.0) Hepatobiliary disorders plus the following terms from other SOCs which may reflect primary hepatic events: high-level group term (HLGT) Hepatobiliary investigations, high level term (HLT) Hepatic therapeutic procedures and PTs Blood alkaline phosphatase increased; and Blood lactate dehydrogenase increased.

The incidence of hepatic TEAEs in Phase III randomized controlled studies was similar between treatment groups (2.7% in telithromycin vs. 2.8% in comparator group). Possibly related hepatic TEAEs were reported in 54 subjects (2.0%) compared to 41 subjects (1.9%) treated with comparator drug. In Phase III open label studies the incidence of hepatic AEs was 3.1%. The table below shows the MedDRA PTs for which hepatic TEAEs were reported. The data in this section do not include those from Study A3014.

Table 37 - Hepatic treatment-emergent adverse events in Phase III studies

Preferred Term	TEL (n=2702)	COMP (n=2139)	TEL open label (n=2078)
	No. subjects (%)	No. subjects (%)	No. subjects (%)
Subjects with hepatic TEAEs	72 (2.7)	58 (2.8)	64 (3.1)
LFT abnormal NOS	28 (1.0)	26 (1.2)	24 (1.2)
ALT increased	21 (0.8)	17 (0.8)	8 (0.4)
Transaminases increased NOS	6 (0.2)	3 (0.1)	10 (0.5)
AST increased	10 (0.4)	6 (0.1)	4 (0.2)
Blood AP increased NOS	6 (0.2)	3 (0.1)	4 (0.2)
Blood bilirubin increased	1 (0.0)	1 (0.0)	0 (0.0)
GGT increased	5 (0.2)	4 (0.2)	0 (0.0)
Blood lactate dehydrogenase increased	5 (0.2)	3 (0.1)	0 (0.0)
Hepatocellular damage	2 (0.1)	0 (0.0)	1 (0.0)
Hepatic function abnormal NOS	1 (0.0)	1 (0.0)	6 (0.3)
Hepatic pain	1 (0.0)	O (0.0)	0 (0.0)
Hepatomegaly	0 (0.0)	1 (0.0)	1 (0.0)
Jaundice NOS	0 (0.0)	1 (0.0)	0 (0.0)
Hepatitis NOS	2 (0.1)	1 (0.0)	2 (0.1)
Cholestasis	2 (0.1)	0 (0.0)	1 (0.0)
Cholecystitis NOS	0 (0.0)	1 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	1 (0.0)	3 (0.1)
Hepatic cyst	0 (0.0)	1 (0.0)	1 (0.0)
Hepatotoxicity NOS	0 (0.0)	0 (0.0)	1 (0.0)

A total of 6 subjects experienced serious hepatic TEAEs in Phase III studies, 5 in the telithromycin-treated group. Three of events occurred in subjects in Phase III randomized controlled trials (Studies A3006 and A3008). All of the cases are outlined in the table below.

Table 38 – Subjects with serious hepatic treatment-emergent adverse events, Phase III studies

Subject ID	Age/sex/race	AE Preferred Term/ Reported term	Possibly related to treatment	Adverse event severity	Outcome	Serious criteria
3006/0060/039	76 /F/W	Hepatocellular damage/ Liver injury	Yes	Severe	Recovered	Hospitalization
3008/0259/005	19/M/W	Hepatocellular damage/ Liver injury	Yes	Mild	Recovered	Medically Important
3010/0473/001	54/M/W	Bile duct obstruction/ Biliary tract occlusion, gallstone	No	Moderate	Recovered	Hospitalization
3012/1027/006	19/M	Transaminase increased/ Worsening of transaminases	Yes	Moderate	Recovered	Hospitalization
3000/0502/069	54/M	Hepatitis/Hepatitis	Yes	Severe	Recovered	Hospitalization
3006/0425/011[a]	61/M/W	Jaundice NOS/ Icteric syndrome	No	Moderate	Not resolved	Medically Important

[a]Please note that the subject received the comparator study drug (clarithromycin). Jaundice was considered related to disseminated neoplasm.

Two of these subjects reported hepatic AEs that were considered severe. One case (Subject 3000/0502/069) involved a 54 year-old male who developed hepatitis 3 days after discontinuing telithromycin. Liver biopsy revealed granulomatous hepatitis with eosinophilic infiltration that resolved, but had an asymptomatic recurrence 9 months later without telithromycin re-exposure suggesting a pre-existing and undiagnosed autoimmune disorder as a cause. The subject's transaminases subsequently resolved. The second case (Subject 3006/0060/039) involved a 76 year-old female who developed hepatocellular injury with elevated transaminases on day 4 of telithromycin therapy. She was discontinued from medication and transaminases normalized 7 days later. Of note, the subject was concomitantly taking PRAVACHOL®, which is also known to increase transaminases, provides a possible alternative explanation. Narratives for all 6 subjects are presented in *APPENDIX B: PHASE III SAFETY DATA* .

In summary:

- The incidence of hepatic TEAEs was similar between treatment groups in all Phase III studies.
- Hepatic laboratory values (such as combined total bilirubin and ALT increases and CNALVs for ALT and AST) were balanced between the telithromycin-treated and comparator-treated groups.
- As outlined in Table 30 abnormal liver function tests were balanced between telithromycin and comparators.

4.5.7.4 Ex-US postmarketing safety data related to hepatic adverse events prior to FDA approval

The liver was recognized during the development program for telithromycin as a potential end organ, and these events were monitored closely during the development. This enhanced monitoring included (1) the voluntary expedited reporting of all serious hepatic AE reports to the FDA, regardless of inclusion in the US Prescribing Information (USPI) (ie, listedness) or country of origin – a practice in excess of reporting requirements as dictated by §CFR 314.80; (2) regular periodic reviews (plus additional ad hoc reviews, as mandated by spontaneous reporting patterns) of interval and cumulative data; (3) the use of specialized data collection forms for spontaneous report follow-up (AESI forms, as noted below); and (4) periodic comparative epidemiologic investigations utilizing a variety of data sources and methods.

Since 2003, following the development of a special data collection form for hepatic events, for use in the large simple safety study, sanofi-aventis has monitored hepatic AE reports using a specific AESI form to collect case information. This hepatic AESI form, intended to standardize and maximize data collection on hepatic AEs, includes a request for laboratory values, medical history and concomitant medication use, alcohol use diagnostic work-up of the hepatic event (ie, viral hepatitis serology, ultrasound, CT scan, and liver biopsy findings).

A total of 58 case reports, describing a total of individual 124 hepatic AEs, have been received by sanofi-aventis as of December 31, 2003, at which time the cumulative worldwide postmarketing exposure was estimated at 6.0 million prescriptions. A summary of hepatic AE reporting as assessed by several parameters is presented below.

These hepatic AEs are presented below by MedDRA PT.

Table 39 – Postmarketing spontaneous reports of hepatic AEs, received by December 31, 2003

MedDRA PT	No. of hepatic AE cases	Hepatic AE reporting rate (per 10^6 exposures)
Total hepatic AE cases	**58**	**9.7**
Transaminases increased	17	2.9
Hepatocellular damage	15	2.5
Liver function test abnormal	14	2.3
Jaundice NOS	13	2.2
Hepatitis NOS	10	1.7
Gamma-glutamyl transferase increased	9	1.5
Alanine aminotransferase increased	8	1.3
Blood alkaline phosphatase increased	6	1.0
Aspartate aminotransferase increased	5	0.8
Blood bilirubin increased	5	0.8
Cytolytic hepatitis	3	0.5
Cholestasis	2	0.3
Hepatitis cholestatic	2	0.3
Hepatitis toxic	2	0.3

Includes both serious and nonserious hepatic AEs.
Reports not additive, as a single patient may have reported multiple hepatic events (diagnoses or symptoms).
Table includes hepatic events reported in 2 or more patients.
Events reported in single patients include hepatic cirrhosis, ascites, hepatitis fulminant, hepatic disorder NOS, hepatitis acute, hepatic steatosis, and hepatomegaly.
MedDRA version 6.0.
NOS=not otherwise specified; PT=Preferred Term; AE=adverse event; ASLI=acute severe liver injury; ALF=acute liver failure.

The majority of these hepatic AE cases represented either asymptomatic laboratory elevations or moderate and reversible hepatic injury (with or without associated jaundice). In May 2006, as a part of labeling changes made with the FDA regarding severe hepatic AEs, sanofi-aventis created definitions of acute severe liver injury (ASLI) and acute liver failure (ALF) in cooperation with several internal and external hepatic experts. These definitions, consistent with universally recognized definitions for severe liver injury and hepatic failure, are presented below:

- Acute severe liver injury: Hepatic SAE reports of hepatocellular jaundice (ALT >3x ULN and direct bilirubin >3 mg/dL in the absence of significant alkaline phosphatase increase) ***OR*** any hepatic event resulting in the hospitalization of the patient.
- Acute liver failure: Reports of ASLI associated with encephalopathy and/or coagulopathy in the absence of underlying hepatic disease.

These definitions were re-applied to the hepatic cases as reported in the period prior to approval in the US, as presented in the table below.

Table 40 - Postmarketing reports of acute severe liver injury and acute liver failure, received by December 31, 2003

MedDRA PT	No. of hepatic AE cases	Hepatic AE reporting rate (per 10^6 exposures)
Total hepatic AE cases	58	9.7
ASLI cases	16	2.7
ALF cases	1	0.2

AE=adverse event; ASLI=acute severe liver injury; ALF=acute liver failure.

Of note, a single spontaneous report met the definition of ALF. This report, received from France, involved fatal, fulminant hepatitis with multisystem organ failure (including the liver) occurring in an elderly gentleman with Q fever and acute hepatitis A infection. In this latter case, reviewed by multiple hepatic experts and presented at the January 2003 meeting of the AIDAC, the association to telithromycin appeared doubtful, as the underlying infections provide the most plausible explanation for the observed events.

In summary, the worldwide postmarketing data available preapproval in the US revealed predominantly moderate and reversible reports of hepatic injury, with an infrequent reporting of ASLI. No cases of drug-related hepatic failure or death, or hepatic injury resulting in transplantation, had been reported after an estimated 6 million exposures outside the US.

4.5.8 Adverse events of special interest: Cardiac adverse events

Erythromycin and other macrolides have been shown to have an effect on cardiac repolarization resulting in an increase of the electrocardiographic QT interval. Given its structural similarity to the macrolide class, telithromycin was thoroughly assessed for potential effects on cardiac repolarization during the development program. This assessment included multiple preclinical in vitro and in vivo studies, extensive clinical pharmacodynamic investigations in Phase I and Phase III studies, and analyses of QT interval data and cardiac AEs from Phase III studies. Finally, a review of the available postmarketing reports from outside of the US was performed.

4.5.8.1 Assessment of the effect of telithromycin on cardiac repolarization

Preclinical studies were performed to assess the effect of telithromycin on the repolarization current in the myocardium. These studies identified a weak inhibitory effect on the Ikr (human ether a-go-go [hERG]) channel, which was comparable to, or slightly lower than, that seen with the macrolide antibiotics. Little or no evidence of early after-depolarizations was seen.

4.5.8.2 Preclinical studies

Telithromycin, clarithromycin, and erythromycin inhibited cloned hERG channels with IC50 values in the range 40 to 55 µM (corresponding to >30 µg/mL for telithromycin). In vitro studies on isolated Purkinje fibers showed that telithromycin increased action potential duration at concentrations above 8 µg/mL, and this was also seen with structurally related drugs clarithromycin, erythromycin, and to a lesser extent roxithromycin. Drug interaction studies showed that telithromycin, like clarithromycin, has additive or synergistic effects with quinidine and sotalol on Purkinje fibers.

In rats, the single oral administration of 300 mg/kg telithromycin to conscious rats slightly increased blood pressure (+10 mmHg) but did not affect heart rate, whereas there were no effects at 100 mg/kg.

Cardiovascular effects in dogs were evaluated in specific safety pharmacology studies and also as part of the repeated-dose toxicity studies in this species. Administration of telithromycin to dogs, whether conscious or anesthetized, intravenously or orally, as a single or repeated dose had little or no effect on blood pressure. The effects of telithromycin, erythromycin, and clarithromycin were compared in conscious dogs after a bolus of 15 mg/kg intravenously of each compound. All 3 compounds increased heart rate and QTc, with telithromycin causing a maximum + 29 msec in QTc (corrected according to Bazett's formula) as compared to +17 msec for clarithromycin and +10 msec for erythromycin. Mean plasma levels immediately after injection were 23 µg/mL for telithromycin, 125 µg/mL for erythromycin and 8.53 µg/mL for clarithromycin. Across the range of studies carried out in the dog, the effects of telithromycin on QTc were seen at doses which gave circulating total plasma levels above 10 µg/mL, corresponding to approximately 6 µg/mL of unbound drug (40% protein binding in the dog), which should be compared to approximately 0.8 µg/mL as Cmax of circulating unbound drug after oral administration of 800 mg to man. Increased heart rate was also seen after oral administration to dogs, whether in the safety pharmacology studies after single administration or in repeated-dose toxicology studies. This effect was seen at doses of 150 mg/kg and above, doses that also increased QTc and gave total plasma concentrations above 10 µg/mL.

4.5.8.3 Phase I studies

Extensive ECG testing was performed in Phase I studies. All studies included analysis of QTc using Bazett and Fridericia's formulas. In some late studies a population corrected QT formula was also used as proposed by Malik [Malik et al., 2001]. Some studies were more dedicated to the investigation of QT interval (Studies A1031 and A1032), where the QT interval of telithromycin-treated subjects was compared to that of placebo-treated subjects at fixed heart rate from 60 to 150 bpm in an exercise tolerance test; Study A1049 was performed in subjects with underlying cardiovascular disease; and Study A1060 in subjects with hepatic impairment included a serial comparison of QT interval at the same heart rate at baseline and post dose on long-term ECG recordings.

QTc effects were also investigated in interaction studies with CYP3A4 inhibitors (ketoconazole in Study A1045 in healthy subjects as well as in Study A1063 in elderly subjects with diminished renal function; itraconazole in Study A1037), drugs metabolized by CYP3A4 (cisapride, an agent with the potential to also increase QT interval, in Study A1041), and with sotalol in Study A1057. In Study A1045, values for telithromycin in healthy subjects in absence or presence of ketoconazole were as follows:

Table 41 – Healthy

Population	Cmax ss (SD) mg/L	AUC (0-24) ss (SD) mg*h/L
Healthy Subjects n=11 (Study A1045)		
TEL	2.02 (0.77)	14.4 (5.6)
TEL + Ketoconazole	3.13 (1.12)	28.6 (8.9)
Elderly w/renal impairment n=10 (Study A1063)		
TEL + Ketoconazole	3.6 (0.8)	33.4 (10.2)

Note: No subjects in Study A1063 received telithromycin as a single agent.

The inhibition of CYP3A4 in elderly with renal impairment (creatinine clearance is between 30 and 80 mL/min) leads to increase of telithromycin exposure that is comparable to the increase observed in healthy subjects.

Population PK studies were performed and showed that a shallow relationship of telithromycin to corrected QT interval was established across a wide range of concentrations in populations of healthy cubjects.

4.5.8.4 Phase III safety data related to cardiac adverse events

Twelve-lead ECGs were routinely obtained in 12 of the 16 Phase III studies. Electrocardiograms were recorded in all subjects enrolled in these studies pretherapy, during therapy with the active drug/comparator, and posttherapy. The time windows were defined as follows.

- Pretherapy: Last ECG done within 72 hours prior to starting drug therapy. This includes ECGs performed at baseline
- On-therapy[4]: 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

All ECGs were over-read by a central reader, blinded to treatment, ECG sequence, demographics and medical history. All 12 leads were manually reviewed with the longest and shortest QT interval reported. Any changes made to the ECG reading by the central reader were added to the telithromycin study database. For each ECG, QTc interval was derived by calculating the mean value of the longest and shortest QT intervals.

A summary of the integrated ECG data obtained for telithromycin-treated subjects from these 12 Phase III studies is provided in the following table. The table excludes information from Studies A3010, A3011, A3012, and A4003, as ECGs were not performed systematically in all subjects at entry in those studies, but only in a selected population of at-risk subjects for monitoring purposes. Data on outlier values observed in those studies are detailed in the table below. The data in this section do not include those from Study A3014.

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

Table 42 - QT interval data for telithromycin-treated subjects in Phase III studies

Variable	Pretherapy (N=3098)	On-therapy (N=2411) [b]	Posttherapy (N=1867) [c]
QTc (ms)	408.0 ± 23.6	409.7 ± 23.4	405.7 ± 22.8
ΔQTc (ms)	-	1.5 ± 22.3 [d]	-2.0 ± 23.3 [e]
QTc increase (n/N (%) subjects)			
≥30 and <60 ms	-	212/2411 (8.8)	124/1867 (6.6)
≥60 ms	-	22/2411 (0.9)	9/1867 (0.5)
QTc outlier (n/N (%) subjects)			
≥500 ms (men or women)	8/3098 (0.3)	4/2451 (0.2)	2/1867 (0.1)
QT dispersion (ms)	24.2 ± 16.9	23.3 ± 15.6	22.9 ± 11.9

Data are mean ± SD; QTc was calculated following Bazett.

[a] Excludes Studies A3010, A3011, A3012, and A4003 where ECGs were performed only in selected subjects

[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 represents 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 1.5 ms. The frequency of telithromycin-treated subjects with QTc increase ≥60 ms was 0.9%. Only 4/2451 (0.2%) of subjects had a QTc interval ≥500 ms.

Three comparative Phase III Studies (A3006, A3008, and A3013) compared QT interval data of telithromycin vs. clarithromycin. QTc interval changes were comparable between the 2 treatment groups. The frequency of subjects with QTc increase of ≥60 ms on-therapy was low and similar between the treatment groups, as was the frequency of subjects with QTc outliers. No subject in either treatment group had an on-therapy and posttherapy QTc value ≥500 ms. The QTc data for these studies are provided in Table 1 found in *APPENDIX B: PHASE III SAFETY DATA* .

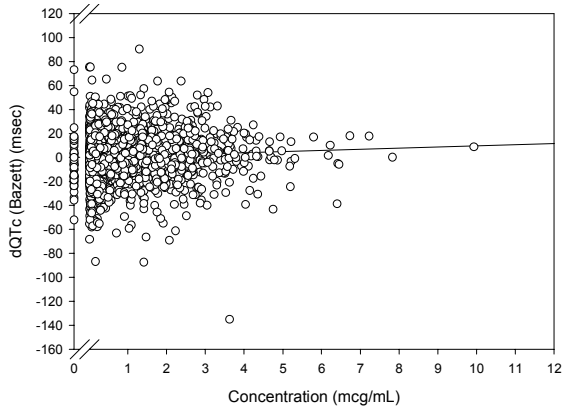
QTc interval data for telithromycin compared with other comparators not known to impact cardiac repolarization (penicillin, amoxicillin, amoxicillin-clavulanic acid, cefuroxime, trovafloxacin) are summarized in Table 2 found in *APPENDIX B: PHASE III SAFETY DATA* . There was a small change in QTc of ~1 ms observed in telithromycin-treated subjects, which is consistent with what was seen in the other Phase III studies. Although a small difference was noted in comparison to the non-macrolide comparators, this would appear to be of minimal clinical significance in light of the observed variability. There was no difference in the frequency of subjects with changes in QTc ≥30 ms or ≥60 ms, nor in the frequency of outliers, between the 2 treatment groups.

The relationship between plasma concentration and QT interval was determined in 8 of the Phase III Studies (A3000, A3001, A3002, A3003, A3005, A3006, A3007, and A3008). A plasma level was to be obtained from all subjects enrolled in 1 of these 8 Phase III studies that received telithromycin and had an ECG recording. These plasma levels were used to determine the relationship of plasma level to corrected QT interval (described below).

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

A total of 1611 observations obtained on-therapy from 1557 subjects were available. For this population, the mean telithromycin plasma concentration was 1.08 ± 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 1 – Relationship between telithromycin plasma concentration and change in QTc



N=1611 data points from 1557 subjects
r2=0.003
P<0.05
Slope=0.98 ms/μg/mL
Mean concentration 1.08 ± 1.18 μg/mL

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

In summary, at therapeutic doses, telithromycin was associated with a 1.5 ms mean increase in QTc interval in the subset of all Phase III subjects for whom ECGs were performed systematically. QTc outlier values were uncommon and similar in frequency to those seen with clarithromycin and non-macrolide antibiotics.

4.5.8.5 Ex-US postmarketing safety data related to cardiac adverse events prior to FDA approval

Postmarketing spontaneous reports of cardiac AEs (including syncope) were followed up with the use of a special data collection form (AESI form) designed to standardize and maximize data collection for these reports. A copy of the cardiac AESI form is presented in *APPENDIX C: POSTMARKETING SAFETY METHODS* .

As of December 31, 2003, after an estimated worldwide marketed exposure of 6 million courses of treatment, 49 cardiac AESI cases had been reported to "sanofi-aventis". Ten of these 49 cardiac AESI cases involved a sudden or unexpected fatal or life-threatening cardiac event. These cases may be summarized as follows:

- Two of these cardiac AE cases lacked adequate information to assess the events, and 1 of these represented an unconfirmed rumor for which no hospital records could be identified by the patient's physician to confirm the occurrence of an arrhythmic event;
- Four of these cardiac AE cases had a normal QTc interval documented at the time of the event, making a drug-related repolarization effect unlikely;
- One of these cardiac AE cases was ventricular fibrillation, occurring in a patient with multiple risk factors for sudden cardiac death, described the onset of syncopal episodes prior to the first dose of telithromycin, thereby making the underlying cardiac disease a more likely cause for the event; and
- The remaining 3 cardiac AE cases were all confounded by the presence of underlying disease states (sepsis with hypokalemia, suspected pulmonary embolism, and severe and progressive idiopathic pulmonary fibrosis with chronic hypoxia and cyanosis), which possibly contributed to the development of the presumed arrhythmic event.

Thus, no signal for severe cardiac arrhythmic effects was identified based upon a review of ex-US postmarketing spontaneous reports obtained prior to FDA approval.

4.5.9 Adverse events of special interest: Visual adverse events

Visual AEs emerged as a signal during the Phase III clinical studies as an AE occurring more frequently in telithromycin-treated subjects than in comparator-treated subjects, which was confirmed in the early ex-US postmarketing reports. Further characterization of the nature of the visual events began with the development of a special data collection form for visual AEs from the large simple safety study, and utilization of this AESI form has continued during postmarketing spontaneous report data collection. As a result of this identified drug effect, preclinical studies were reanalyzed with a focus on potential visual effects, and 2 targeted Phase I clinical studies were performed to investigate potential mechanisms for this drug effect.

4.5.9.1 Preclinical studies related to visual adverse events

Nonclinical safety studies did not reveal any changes that could be of concern with respect to the human visual system during treatment with therapeutic doses of telithromycin.

The safety pharmacology studies provided no clear evidence of an effect of telithromycin on the visual system. Potential effects on the cholinergic system, which are of possible relevance for the visual function. The results are summarized below.

Receptor binding studies showed low affinity of telithromycin for muscarinic M1 and M2 receptors (38% and 30% displacement of ligand binding at 30 µM, respectively) and no affinity for M3 receptor up to 30 µM. A concentration of 30 µM corresponds to 24 µg/mL, which is approximately 30 times the maximal concentration (based on free drug) obtained in humans. In addition, RU 76363, the principal human circulating metabolite, had low affinity for M1 and M2 receptors (13% inhibition at 30 µM) and no affinity for M3 receptors (<10% inhibition).

There were no significant effects on acetylcholine release, reuptake, or metabolism. Telithromycin and RU 76363, at concentrations up to 80 µg/mL free drug, displayed only a trend to decrease the amplitude of contractions of isolated guinea-pig ileum induced by electric field stimulation with no potentiating effect, suggesting no atropinic or acetylcholine release effects. There were only weak effects at the choline uptake site of rat striatum with no inhibition of acetylcholinesterase activity.

A single dose of telithromycin given by the oral route to mice up to 300 mg/kg had no effect on the pupil size.

A pharmacological dose of the muscarinic agonist oxotremorine caused mortality when given in combination with oral doses of 100 and 300 mg/kg telithromycin. The similar effects were observed with roxithromycin, a macrolide marketed in the EU. The effects were not observed with intravenous doses of telithromycin up to 15 mg/kg. The mortality noted with the combination of telithromycin and oxotremorine was antagonized with the peripheral cholinergic antagonist, methylscopolamine, and the peripheral M1 muscarinic antagonist, pirenzepine. Furthermore, the association of telithromycin with several cholinergic agonists (tacrine, xanomeline, and carbachol) also induced toxicity and a potentiation of cholinergic symptoms. These data suggest that a peripheral muscarinic mechanism may be involved in this effect.

The ocular effects of telithromycin administration have been evaluated in pigmented and nonpigmented rats, beagle dogs and cynomolgus monkeys in repeated-dose toxicity studies.

In rats, no compound-related ocular changes were identified by ophthalmoscopy and light microscopy at oral doses up to 300 mg/kg/d, the highest dose level tested, which gives plasma exposures 14.3-fold higher than that at the therapeutic dose in humans (base on free drug levels).

In beagle dogs at doses of 150 and 300 mg/kg/d, which gives 13- and 33-fold higher plasma exposures than in humans at therapeutic dose, respectively, loss of reflectivity and color changes of the tapetal fundus were noted at ophthalmoscopy, with evidence of recovery after treatment discontinuation. Similar tapetal changes have been reported with other macrolide antibiotics, such as rosaramicin and azithromycin, where investigations in atapetal dogs showed this finding to be a unique change involving tapetal cells only [Fortner et al., 1993;Massa et al., 1984].

The tapetal fundus (also identified as tapetum lucidum) is a light-reflecting structure, between the choroid and retinal pigmented epithelium, which is not present in human eyes; therefore, this finding in dogs is not considered to be relevant for humans.

Further investigations were performed in the cynomolgus monkey, a species with a visual system that provides a better model of human vision. In a 4-week oral toxicity study, there were no compound-related ocular changes at ophthalmoscopy and light microscopy as well as on scotopic and photopic flash electroretinography (ERG) parameters up to the highest dose tested of 120 mg/kg/d, giving plasma exposure levels approximately 13-fold higher than the plasma exposures in humans at the therapeutic dose. In addition, further to a specific FDA request to pursue investigation of possible mechanisms of blurred vision in humans, a dedicated ERG study was recently performed in cynomolgus monkeys to evaluate potential effects of single oral doses of telithromycin on retinal adaptative processes. Preliminary data show that there were no telithromycin-related ERG changes during light or dark adaptation (evaluation of rod and cone system functions, respectively) up to the highest dose tested of 500 mg/kg.

In conclusion, toxicity studies did not identify any ocular pathology of relevance to humans, and electrophysiology studies in monkeys did not demonstrate any effects on retinal physiology.

4.5.9.2 Phase I studies related to visual adverse events

In Phase I studies, the effect of telithromycin on vision was rarely observed at the dose of 800 mg (1 case in 400 subjects), but was observed more consistently at supratherapeutic doses. A dose-dependent effect on vision (reported as blurred vision, abnormality of accommodation, diplopia, eye disorder, or abnormal vision) was reported by 11%, 26%, and 42% of subjects after administration of single doses of 1600 mg, 2400 mg, and 3200 mg of telithromycin, respectively (24 to 101 subjects per cohort).

Two ophthalmologic clinical pharmacology studies (A1059 and A1064) were conducted to better characterize visual events and to investigate the mechanism. Ophthalmic examinations in these 2 studies included examination of the lens, cornea and fundi, visual acuity, anterior chamber angle, intraocular pressure, refraction, accommodation, color vision and visual fields (left and right). In single dose Study 1059, no blurred vision occurred with telithromycin 800 mg but following a single dose of 2400 mg, 3 times the therapeutic dose, blurred vision was observed in 4/15 subjects under the age of 50. In Study 1064, blurred vision was reported in 12/24 subjects after a single supratherapeutic dose of telithromycin 2400 mg. Results from these studies showed:

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

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

Study PDY6571 is scheduled to start by December 2006 to assess if a supratherapeutic dose of telithromycin (2400 mg) induces changes in the visual pathways as measured by the evoked potentials on the retina and visual cortical junction using Ganzfeld ERG, mfERG, and visual evoked potentials (VEP). In this study, visual clinical signs and symptoms are also to be assessed, including blurred vision and ocular motility. This study is designed to possibly identify the mechanism of blurred vision and exclude the possibility that supratherapeutic dosing of telithromycin induces retinal toxicity or optic neuritis. This is a Phase I, double blind randomized, placebo-controlled, single-dose 2-way crossover study in a total of 24 healthy young male and female subjects (age 18 to 40 years).

4.5.9.3 Phase III safety data related to visual adverse events

The table below lists the visual TEAEs in Phase III studies by frequency.

Table 43 – Visual treatment-emergent adverse events in all Phase III studies, by decreasing frequency

Preferred Term	TEL (n=2702) No. of subjects (%)	COMP (n=2139) No. of subjects (%)	TEL open label (n=2078) No. of subjects (%)
Subjects with visual TEAEs	30 (1.1%)	9 (0.4%)	10 (0.5)
Vision blurred	17 (0.6)	3 (0.1)	5 (0.2)
Visual disturbance NOS	5 (0.2)	2 (0.1)	4 (0.2)
Photophobia	2 (0.1)	1(0.0)	0 (0.0)
Visual acuity reduced	2 (0.1)	0 (0.0)	0 (0.0)
Accommodation disorder	1 (0.0)	0 (0.0)	0 (0.0)
Vitreous floaters	0 (0.0)	1 (0.0)	0 (0.0)
Hallucination NOS	2 (0.1)	1 (0.0)	0 (0.0)
Hallucination, visual	0 (0.0)	1 (0.0)	0 (0.0)
Visual field defect NOS	1 (0.0)	0 (0.0)	0 (0.0)
Chromatopsia	0 (0.0)	0 (0.0)	1 (0.0)

TEL=telithromycin; COMP=comparator; TEAE=treatment-emergent adverse event; NOS=not otherwise specified.
This table does not include data from Study A3014.

The incidence of visual TEAEs in Phase III randomized controlled studies was higher in telithromycin-treated subjects (30/2702, 1.1%) than with comparator (9/2139, 0.4%). Across all Phase III studies, the incidence of visual TEAEs in telithromycin-treated subjects was 0.5% in noncomparative studies and 1.1% in controlled studies. One serious event of accommodation disorder was reported in a subject (Subject 3005/0197/021) receiving telithromycin, which was considered not related by the Investigator because the visual symptoms were present prior to enrollment in the study. The subject recovered without sequelae.

The incidence of blurred vision in Phase III randomized controlled studies was higher in telithromycin-treated subjects (17/2702, 0.6%) than with comparator (3/2139, 0.1%). In all Phase III studies, a total of 22 telithromycin-treated subjects reported blurred vision and this event was reported in 0.2% noncomparative studies vs. 0.6% in controlled. Of these 22 subjects, 17 had events considered possibly related to telithromycin by the Investigator. These events were generally mild in intensity and most frequently started within the first 2 days of treatment. Among the 17 telithromycin-treated subjects with possibly related blurred vision, 12 subjects were female (8 of whom were ≤36 years of age). All drug-related cases of blurred vision recovered fully. No specific pattern of medical history or concomitant medication was found in these subjects. Only 1 telithromycin-treated subject (Subject 3008/0209/005, a 30-year-old female in Study A3008) discontinued study medication due to mild blurred vision. The subject recovered without sequelae. One severe report was received, but was considered not related by the Investigator (no further information is available). Blurred vision started on Day 2 of treatment and resolved by Day 7 without sequelae. There were no blurred vision AEs reported as serious TEAEs in the integrated Phase III studies.

In summary, in Phase III studies:

- The incidence of visual TEAEs was higher in the telithromycin-treated than in the comparator-treated group (1.1% vs. 0.4% in randomized controlled studies). Most visual AEs were mild or moderate in severity.
- Blurred vision, which was generally mild, transient, and fully reversible, was infrequently reported (0.2 to 0.6%) in Phase III studies and appeared at higher incidence in subjects under 50 years of age and appears more common in women than in men. The mechanism of blurred vision is consistent with a transient delay in accommodation. The effect had a short duration (2-3 hours). There was no evidence of retinal toxicity or change in intraocular pressure or anterior chamber angle as explored in Phase I studies.

4.5.9.4 Integrated Overview of Visual Events

In September 2003, “sanofi-aventis” prepared the *Integrated Overview of Visual Events* to further investigate telithromycin’s visual adverse effects in response to the FDA Approvable letter dated January 24, 2003. This document reviewed preclinical information, 2 Phase I studies conducted to try to elucidate the mechanism for this event, clinical trial reports of visual AEs, and available postmarketing spontaneous reports of visual AEs (through January 31, 2003).

In this analysis, 207 postmarketing spontaneous visual AE reports were received after approximately 2.4 million exposures worldwide. Blurred vision was the most commonly reported event, followed by visual disturbance, accommodation disorder, diplopia, and reduced visual acuity. Approximately 82% of these reports involved nonserious AEs, and in 79% of cases, a resolution of the event was reported (approximately 11% of reports were assessed ongoing, and 10% had unknown outcome). A visual episode occurred a median of 1.5 hours after dosing, and lasted a median of 6 hours (range 0.02 to 48 hours). In the small subset of patients with examinations or testing performed (19 patients), no abnormalities were found other than a confirmation of impaired accommodative ability in 3 patients. In one-quarter of patients, an impact on activity was reported- most commonly an inability to read. Women reported visual events twice as often as men did, and events were more frequent in patients 21 to 40 years of age.

4.5.9.5 Ex-US postmarketing safety data related to visual adverse events prior to FDA approval

Eye disorders (vision blurred, visual disturbances NOS, accommodation disorder, diplopia were among the most frequent spontaneously reported AEs from ex-US markets as of December 31, 2003.

Although reported in approximately 1% of subjects in clinical trials and occurring less frequently than gastrointestinal events, visual AEs became the most common spontaneously reported AEs following the marketing authorization for telithromycin in the EU.

Through December 2003, a worldwide reporting rate for visual events of approximately 62 events per million exposures was observed. For the most part, these events were consistent with the mild and transient visual blurring described in the clinical studies.

Table 44 - Reports of visual adverse events through December 2003

MedDRA PT	No. of visual AE reports	Reporting rate (per 106 exposures)
Total visual AE reports	**371**	**62.2**
Vision blurred	268	45.0
Visual disturbance NOS	76	12.8
Accommodation disorder	39	6.5
Diplopia	37	6.2
Visual acuity reduced	16	2.7
Hallucination NOS	4	0.7
Hallucination, visual	3	0.5
Photophobia	3	0.5
Amaurosis fugax	2	0.3
Blindness	2	0.3
Photopsia	2	0.3
Vitreous floaters	2	0.3

Visual events reported in a single patient: blindness transient, chromatopsia, myopia, papilloedema, photophobia, presbyopia, and visual brightness.
MedDRA version 6.0.
NOS=not otherwise specified; PT=Preferred Term; AE=adverse event.

As shown above, very rare reports of severe visual AEs, including reports of transient amaurosis and blindness, were also described. Importantly, no evidence of objective eye injury permanent or persistent ocular sequelae had been observed with any of the visual AEs.

4.5.10 Adverse events of special interest: Exacerbation of myasthenia gravis

In February 2003, following the receipt of 2 postmarketing spontaneous reports of exacerbation of myasthenia gravis from France, the French Health Authority requested a review of exacerbation of myasthenia gravis with telithromycin. A total of 7 AE cases were identified, and were reviewed with external neuromuscular experts in order to determine whether this represented a drug effect. Subsequently, as part of this investigation, a re-assessment of preclinical data was undertaken, as well as a search in previously performed clinical studies. The result of these investigations was the inclusion of exacerbation of myasthenia gravis in the corporate labeling for telithromycin, prior to FDA approval, as described below.

4.5.10.1 Drug-induced exacerbation of myasthenia gravis

Myasthenia gravis is a neuromuscular disorder that results from an immune-mediated destruction of acetylcholine receptors at the neuromuscular junction of skeletal muscle. The prevalence of myasthenia gravis is estimated at 1 in 7500 with a female predominance [Harrison's, 2006]. The disorder is characterized by exacerbations, particularly during the early stages of the disease. These exacerbations are commonly precipitated by infections. Manifestations of myasthenic exacerbation may range from eyelid ptosis or mild muscular weakness to life-threatening respiratory failure and arrest. Acetylcholinesterase inhibitors, particularly neostigmine and pyridostigmine, are used to treat myasthenia gravis, along with supportive treatment of symptoms.

Exacerbations of myasthenia gravis have been reported in association with several classes of drugs, including anaesthetics, antibiotics, anticonvulsants, cardiovascular drugs, and psychotropics [Barrons, 1997]. Among the antibiotics, implicated drugs include the macrolides, β-lactams, fluoroquinolones, and aminoglycosides [Wittbrodt, 1997]. Among macrolides, erythromycin, clarithromycin and azithromycin treatment have been associated with aggravation of known myasthenia gravis or the unmasking of previously undiagnosed disease.

Published case reports of drug-induced myasthenia gravis exacerbations with antibiotic use are generally associated with symptom onset (eg, muscle weakness, ptosis, visual complaints, dysphagia, or respiratory distress) occurring within hours or days of drug administration and a rapid recovery following drug discontinuation. The presumed mechanism in these cases is drug-induced interference with neuromuscular transmission. This differs from penicillamine-induced myasthenia gravis, which occurs months after the start of drug treatment in patients without a history of myasthenia gravis, is associated with the development of anti-acetylcholine receptor antibodies, and resolved months after discontinuation of the drug. In this latter case, the syndrome has an autoimmune etiology.

4.5.10.2 Preclinical studies related to exacerbation of myasthenia gravis

As part of the nonclinical development plan for telithromycin, investigations were performed that assessed the potential for effects at the neuromuscular junction. The capacity of these studies to predict clinical outcomes in patients with myasthenia gravis is unknown.

The effects of high doses (100 and 500 μM) of telithromycin on neuromuscular transmission were investigated using a phrenic nerve/diaphragm preparation. No significant effects on the diaphragmatic muscle with either direct or indirect stimulation of the phrenic nerve were seen at 100 μM telithromycin. At 500 μM, telithromycin produced a facilitory effect on the diaphragmatic muscle that lasted up to 90 minutes, followed by an inhibitory effect with indirect phrenic nerve stimulation. However, it is noted that a similar degree of depression was apparent with both indirect stimulation via the phrenic nerve and direct stimulation of the muscle in the presence of d-tubocurarine, suggesting that an effect, if present, was occurring at the level of the muscle rather than at the neuromuscular junction. Similar effects were seen in comparative analyses with clarithromycin, azithromycin, and erythromycin, but at higher concentrations. The extremely high concentration required to produce this response, however, remains far above (81 times) the expected serum concentrations in man. In contrast, known neuromuscular blockers, such as d-tubocurarine and succinylcholine, produced rapid neuromuscular effects.

Overall, these preclinical findings neither support nor refute a potential for drug-induced exacerbation in patients with myasthenia gravis.

4.5.10.3 Phase III safety data related to exacerbation of myasthenia gravis

Following identification of a cluster of postmarketing reports of exacerbation of myasthenia gravis exacerbation, a retrospective review of Phase III data was undertaken to determine if additional information was available to provide further insight to the investigation of this topic. Myasthenia gravis AEs were defined using all PTs under the high-level term (HLT) Neuromuscular junction dysfunction in the MedDRA dictionary (version 6.0), which includes the following PTs: Eaton-Lambert syndrome, myasthenia gravis crisis, myasthenia gravis neonatal, myasthenia gravis, myasthenic syndrome, neuromuscular block prolonged, neuromuscular blockade, and ocular myasthenia. Additional fields in the safety database were also queried to identify subjects with possible pre-existing myasthenia gravis: Disease state coded with HLT Neuromuscular dysfunction or concomitant medications (generic or trade) containing pyridostigmine, neostigmine. There were no reports of exacerbation of myasthenia gravis nor were there any subjects with underlying myasthenia gravis identified in the Phase III program.

4.5.10.4 Ex-US postmarketing spontaneous reports of exacerbation of myasthenia gravis prior to FDA approval

While no cases of exacerbation of myasthenia gravis were reported during the clinical trials, rare cases of worsening of myasthenia symptoms – including respiratory failure – were received from treating physicians following the launch of telithromycin in the EU in 2001. These events typically occurred within a few hours of the first dose (thereby distinguishing it from an infection-related exacerbation), and generally resolved with discontinuation of telithromycin and supportive care.

In February 2003, exacerbation of myasthenia gravis was added to the corporate labeling for telithromycin, and the labeling was further revised to include a warning/precaution against use in patients with myasthenia gravis in May 2003. At that time, this labeling update was also communicated to prescribers in the EU via a Dear Healthcare Professional letter. Language describing the potential for exacerbation of myasthenia gravis was subsequently included in the current USPI for telithromycin at the time of US approval in 2004. Within the USPI, it is stated that telithromycin is not recommended for treatment in patients with myasthenia gravis unless no other treatment options were available, and when used, should be administered under close physician supervision.

As of December 31, 2003, a total of 19 reports of exacerbation of myasthenia gravis were identified by searching the safety database using the MedDRA HLT "neuromuscular junction dysfunction." One of these cases had a fatal outcome and 6 others resulted in life-threatening respiratory compromise. The reporting rate for exacerbation of myasthenia gravis prior to FDA approval was 2.9 reports per million exposures.

Table 45 – Postmarketing spontaneous reports of exacerbation of myasthenia gravis, received by December 31, 2003

MedDRA PT	No. of MG reports	Reporting rate (per 106 exposures)
All MG exacerbation reports	19	3.2
Fatal MG exacerbation reports	1	0.2
Myasthenic syndrome	7	1.2
Myasthenia gravis	5	0.8
Muscle weakness NOS	5	0.8
Diplopia	4	0.7
Dysphagia	4	0.7
Respiratory arrest	4	0.7
Dyspnoea NOS	3	0.5
Eyelid ptosis	3	0.5
Myasthenia gravis aggravation	3	0.5
Respiratory disorder	3	0.5
Dysphonia	2	0.3
Respiratory failure	2	0.3

Estimated ex-US postmarketing exposure (through December 31, 2003): 6.0 million courses of treatment.
Includes events reported in 2 or more patients. Events included in a single patient: asthenia, cardiac arrest, cardiopulmonary failure, death NOS, dysarthria, muscle fatigue, respiratory depression, and speech disorder.
Events not additive, as a single patient may have reported more than 1 event. Includes diagnoses and symptoms.
Reporting rate presented as cases per million exposures.
NOS=not otherwise specified; PT=Preferred Term; AE=adverse event.

Of note, all but 4 of the reports had been received prior to the inclusion of myasthenia gravis to the product information update in May 2003 and associated risk management activities concerning this issue (ie, "Dear Healthcare Professional" Letter issuance in the EU).

4.5.11 Summary of overall safety profile prior to FDA approval

- The incidence and nature of the most frequently reported TEAEs were, in general, similar between the telithromycin- and comparator-treated groups. Treatment-emergent adverse events of the Gastrointestinal disorders SOC (eg, diarrhea NOS, nausea and vomiting) were most frequently reported and were generally mild or moderate in intensity.
- The overall incidence of death was the same (0.4%) in both the telithromycin- and comparator-treated groups. None of the deaths were assessed by the Investigator as being possibly related to study medication.
- The incidence of SAEs was similar in both the telithromycin- and comparator-treated groups.
- Adverse events requiring discontinuation of study medications were uncommon and balanced between treatment groups: telithromycin (119/2702, 4.4%) and comparators (92/2139, 4.3%). The most frequently reported TEAEs leading to discontinuation in both telithromycin- and comparator-treated subjects were diarrhea NOS (0.9% vs. 0.7%, respectively), vomiting NOS (0.8% vs. 0.5%, respectively), and nausea (0.7% vs. 0.5%, respectively).
- The frequency and pattern of TEAEs in the Phase III open label studies did not differ significantly from those in the Phase III randomized controlled studies.
- At therapeutic dose, telithromycin was associated with a 1.5 ms mean increase in QTc interval. QTc outlier values were uncommon and similar in frequency to those seen with clarithromycin and non-macrolide antibiotics.
- The incidence of hepatic TEAEs was similar between treatment groups in all Phase III studies and hepatic laboratory values (such as combined total bilirubin and ALT increases and CNALVs for ALT and AST) were balanced between the telithromycin-treated and comparator-treated groups. Postmarketing surveillance as of December 31, 2003, revealed moderate and reversible reports of hepatic injury. There were no cases of drug-related hepatic failure or death, or hepatic injury resulting in transplantation.
- The incidence of visual TEAEs was higher in the telithromycin-treated group than in the comparator-treated group (1.1% vs. 0.4% in Phase III randomized controlled studies). Most visual AEs were mild or moderate in severity. Blurred vision, which was generally mild, transient, and fully reversible, was infrequently reported (0.6%) in Phase III studies. The mechanism of blurred vision is consistent with a transient delay in accommodation. In post-marketing reporting, visual AEs are the most commonly reported events. The characteristics of these events were generally similar to those observed in clinical trials.
- Postmarketing reports indicated a potential for telithromycin to induce exacerbations of myasthenia gravis. There were no reported cases of myasthenia gravis or worsening of pre-existing myasthenia gravis identified in the Phase III development program.

5 US – APPROVAL PROCESS

5.1 NEW DRUG APPLICATION

On February 28, 2000, sanofi-aventis submitted an application (NDA 21-144) for telithromycin for the treatment of RTIs to the FDA. The NDA included 36 Phase I studies (9 drug-drug interaction studies) and 10 Phase III studies (CAP Studies A3000, A3002, A3006, A3009; AECB Studies A3003 and A3007; ABS Studies A3002 and A3005; and T/P Studies A3004 and A3008).

5.2 ADVISORY COMMITTEE MEETING (APRIL 26, 2001)

In April 2001, the FDA Anti-Infective Drugs Advisory Committee (AIDAC) reviewed data relating to NDA 21-144. The Committee's recommendations included the collecting safety data from a larger sample of patients, particularly from older adults and subjects with comorbid conditions.

5.3 FIRST FDA APPROVABLE LETTER (DATED JUNE 1, 2001)

In the first Approvable Letter (dated June 1, 2001), the FDA deemed telithromycin "approvable" for the indications of CAP, AECB, and ABS, pending review of additional efficacy and safety data, and "not approvable" for T/P (the T/P indication was assigned NDA number 21-391) [*Amendment to Pending Application: Complete Response to the January 24, 2003, Approvable Letter*]. "Sanofi-aventis" filed a complete response to the first Approvable Letter on July 24, 2002.

5.4 ADVISORY COMMITTEE MEETING (JANUARY 8, 2003)

On January 8, 2003, the AIDAC reviewed the additional efficacy and safety data. At that time, the sanofi-aventis safety database included data from more than 4400 Phase III clinical trial subjects and more than 12,000 Study A3014 telithromycin-treated clinical trial subjects and postmarketing spontaneous reports following more than 1.5 million patient exposures. The AIDAC voted to approve telithromycin for the treatment of CAP, AECB, and ABS.

5.5 SECOND FDA APPROVABLE LETTER (DATED JANUARY 24, 2003)

- Subsequent to the second Advisory Committee meeting, sanofi-aventis received a second Approvable Letter (dated January 24, 2003), in which, following up on concerns over the integrity of Study A3014 data based upon then recent inspections by FDA's Division of Scientific Investigations, the FDA requested additional analyses and information relating to preapproval studies and postmarketing experience from other countries, prior to granting approval for marketing telithromycin in the US. "Sanofi-aventis" filed a complete response to the second Approvable Letter on October 17, 2003[*Amendment to Pending Application: Complete Response to the January 24, 2003, Approvable Letter*; submitted October 17, 2003].

5.5.1.1 5-month bridging safety update report

A 5-month bridging safety update report was submitted to the FDA on February 27, 2004 [*Five-Month Bridging Safety Update Report for Telithromycin*; submitted February 27, 2004]. This document presented a high-level summary of all AE/ADR cases received during the 5-month reporting period (August 1, 2003 to December 31, 2003). The report focused on the MedDRA SOC as well as trends in aggregate data following ~6 million patient exposures, comparing the 5-month cut of postmarketing safety data with the previous 24 months of data [*Six-Month Bridging Safety Update Report*, submitted November 26, 2003; *Postmarketing Spontaneous Reports in Amendment 3*; submitted October 17, 2003]. The purpose of this cumulative review of postmarketing safety data was to identify any new serious and unexpected events or events of increased frequency, which would signal a new risk with telithromycin. It was provided as a supplement to the incremental monthly safety update reports to facilitate the FDA's review of the growing body of postmarketing safety data.

5.5.1.2 Risk management plan

A proposal for a risk management plan for telithromycin [*Telithromycin: Proposal for a Risk Management Plan*; submitted July 24, 2002] was first written in July 2002 with the goals of (1) detecting unexpected and rare AEs; (2) regularly updating the telithromycin safety profile; and (3) facilitating access to relevant information for both prescribers and patients. At the time of this proposal, telithromycin had been on the market <1 year, with an estimated global marketing exposure of ~750,000 courses of treatment.

As sanofi-aventis had accumulated a large body of safety data, primarily through worldwide marketed use, which proved valuable in further defining the safety profile of this antibiotic (both with respect to identifying new events as well as confirming the recognized spectrum of AEs), the company took the opportunity to review the previously submitted risk management plan and revise it to reflect the current understanding of telithromycin and its safety profile [*Telithromycin Risk Management Plan (Revised March 2004)*; submitted March 1, 2004]. The revised risk management plan, submitted to the FDA on March 1, 2004, supports sanofi-aventis's commitment to maximizing the benefits and minimizing the risks associated with telithromycin administration. The plan includes a detailed description of the methods that sanofi-aventis utilizes to communicate potential risks to healthcare professionals and consumers.

5.6 FDA APPROVAL LETTER (DATED APRIL 1, 2004)

The FDA approved NDA 21-144 on April 1, 2004 [*APPENDIX D: FDA APPROVAL LETTER* ; FDA Summary Basis of Approval].

5.6.1 US labeling at approval

5.6.1.1 Treatment indications

The initial USPI (as presented in the FDA Approval Letter) included labeling for the following treatment indications in adults ≥18 years of age.

Community-acquired pneumonia (of mild to moderate severity) due to *S. pneumoniae*, (including multidrug-resistant isolates [MDRSP*]) *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *C. pneumoniae*, or *M. pneumoniae*;

Acute bacterial exacerbation of chronic bronchitis due to *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*; and

Acute bacterial sinusitis due to *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, or *S. aureus*.

MDRSP*, Multidrug-resistant *S. pneumoniae* includes isolates known as PRSP (penicillin-resistant *S. pneumoniae*), and are isolates resistant to 2 or more of the following antibiotics: penicillin, 2nd generation cephalosporins, eg, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

5.6.1.2 Warnings and precautions

The US labeling included the following WARNINGS and PRECAUTIONS (General) with respect to the AESIs (ie, hepatic AEs, cardiac AEs, visual AEs, and exacerbation of myasthenia gravis). The complete USPI (April 2004) is provided in
APPENDIX D: FDA APPROVAL LETTER .

WARNINGS

Cardiac adverse events

"Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (eg, quinidine and procainamide) or Class III (eg, dofetilide) antiarrhythmic agents.

No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical efficacy trials, including 204 patients having a prolonged QTc at baseline.

Exacerbation of myasthenia gravis

"Exacerbations of myasthenia gravis have been reported in patients with myasthenia gravis treated with telithromycin. This has sometimes occurred within a few hours after intake of the first dose of telithromycin. Reports have included life-threatening acute respiratory failure with a rapid onset in patients with myasthenia gravis treated for RTIs with telithromycin. Telithromycin is not recommended in patients with myasthenia gravis unless no other therapeutic alternatives are available. If other therapeutic alternatives are not available, patients with myasthenia gravis taking telithromycin must be closely monitored. Patients must be advised that if they experience exacerbation of their symptoms, they should discontinue treatment of KETEK and immediately seek medical attention. Supportive measures should be instituted as medically necessary."

PRECAUTIONS

Hepatic adverse events

"Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of KETEK. These events were generally reversible.

Caution should be used in patients with a previous history of hepatitis/jaundice associated with the use of KETEK. (See ADVERSE REACTIONS, Liver and biliary system.)

Telithromycin is principally excreted via the liver and kidney. Telithromycin may be administered without dosage adjustment in the presence of hepatic impairment. In the presence of severe renal impairment (CRCL [creatinine clearance] < 30 mL/min), the dose of KETEK has not been established. (See DOSAGE AND ADMINISTRATION.)"

Visual adverse events

PRECAUTIONS, General

"KETEK may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported. Patients should be cautioned about the potential effects of these visual disturbances on driving a vehicle, operating machinery or engaging in other potentially hazardous activities."

5.6.2 Postmarketing commitments

The FDA Approval Letter listed 3 postmarketing commitments:

- Provide information to support the pediatric use of telithromycin for the treatment of ABS in pediatric patients <18 years of age by March 31, 2008;
- Provide information to support the pediatric use of telithromycin for the treatment of CAP in pediatric patients <18 years of age by March 31, 2008; and
- Monitor and assess postmarketing spontaneous reports of visual AEs received during the 18 months after US launch from worldwide sources by March 31, 2006 (revised date: September 30, 2006).

5.6.2.1 Data to support pediatric use

During the drug development process, sanofi-aventis requested and received a deferral (on February 1, 2000) of the requirement under the Pediatric Research Equity Act to obtain pediatric data to include in the labeling for telithromycin until after approval in adults. Thereafter, and as required, sanofi-aventis structured pediatric assessments, in the form of data gathered from pediatric age groups, to assess the safety and efficacy of drugs in relevant pediatric subpopulations, and to support dosing and administration among pediatric patients.

The global pediatric development program includes 9 Phase I studies conducted to evaluate the tolerance, bioavailability, concentration in middle ear fluid (MEF), and the effect of food on the pediatric oral suspension formulations; and 3 Phase II studies in acute otitis media (AOM), CAP, and T/P. Following extensive discussion with the FDA, sanofi-aventis initiated 5 pediatric Phase III studies: 2 AOM studies, 1 CAP PK study, 1 T/P study in children, and 1 T/P study in adolescents (and adults).

During a meeting with the FDA on June 6, 2006, the FDA and sanofi-aventis discussed questions that have been raised regarding anti-infective drug development in pediatric populations. As a result of those discussions, on June 8, 2006, sanofi-aventis voluntarily paused enrollment in ongoing pediatric clinical trials, pending review and final confirmation that the pediatric development program for telithromycin is consistent with the current thinking of the FDA. No safety reason has been identified by sanofi-aventis to warrant suspension of the pediatric clinical trials.

Sanofi-aventis established an Independent Data Monitoring Committee (IDMC) to assess safety data emerging from pediatric studies for telithromycin and to advise the company on modifications or communications necessary for patient safety or to protect the scientific integrity of the studies. The IDMC is made up of a multidisciplinary group of clinicians and a biostatistician with experience in managing pediatric patients with infectious diseases and in conducting and monitoring clinical studies. In addition, an Independent Clinical Event Committee (ICEC) was established to evaluate all reports of visual disturbances in a blinded fashion and provide assessments of visual AEs to the IDMC.

6 US – POSTAPPROVAL DATA

6.1 POSTAPPROVAL: MICROBIOLOGY DATA

6.1.1 Epidemiologic surveys: the PROTEKT studies

The Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) studies – PROTEKT Global, an international study initiated in 1999, and PROTEKT US, initiated in 2000 – are longitudinal microbiological surveillance studies designed to evaluate the activity of telithromycin against *S. pneumoniae* and other common RTI pathogens and to compare its activity with that of other antibacterial agents. At the US level, only PROTEKT provides regular data on the activity of telithromycin on RTI pathogens. These studies are ongoing. As of September 15, 2006, PROTEKT results are available through Year 2004-2005. The summary below focuses on *S. pneumoniae* and *H. influenzae*, the pathogens most frequently implicated in mild to moderate CAP, AECB, and ABS.

The key findings of PROTEKT studies to be described in detail are as follows:

Streptococcus pneumoniae

- There has been relative stability in the prevalence of *S. pneumoniae* isolates with reduced susceptibility to penicillin (around 37%), with significant variation in the prevalence of penicillin-resistant S. *pneumoniae* from country to country. In the US, there has been a slight decrease of the prevalence of penicillin resistance (17.5% in 2004-2005), whereas strains of intermediate resistance tend to increase (20.1% in 2004-2005)
- There has been relative stability in the prevalence of *S. pneumoniae* isolates with resistance to macrolides, (around 30%), with significant variation in the prevalence of macrolide-resistant *S. pneumoniae* from country to country.
- There is a high prevalence of multidrug-resistant strains of *S. pneumoniae*; 40% at the global level and 29.1% in the US.
- There is a low prevalence of telithromycin-resistant *S. pneumoniae*, with no signal of increased resistance or clonal spread of resistance. Telithromycin remains active, irrespective of the resistance phenotype (ie, penicillin-resistant, macrolide-resistant, or multidrug-resistant), or their mechanism of resistance to macrolides. Overall, the prevalence of telithromycin-resistant *S. pneumoniae* is only 0.1%.

- In the US, the prevalence of macrolide-resistant *S. pneumoniae* is also stable (around 30%), but in the past few years there have been significant changes in the prevalence of different mechanisms of resistance to macrolides. In particular, the prevalence of *S. pneumoniae* isolates harboring *erm*(B) + *mef*(A) genes has increased from 9.7% in Year 1 to 20.1% in Year 5. This increase is linked to a clonal expansion. While this increase has been more pronounced in children, it has also been noted in adults. All *erm*(B) + *mef*(A) *S. pneumoniae* isolates collected in 2004-2005 are multidrug-resistant and highly resistant to amoxicillin-clavulanic acid (69.4% resistant). In contrast, the prevalence of telithromycin-resistant *S. pneumoniae* among these strains is low (0.7%).
- Results from PROTEKT US study, as also described by others, show an increase of 19A serotype (non covered by the PCV7 vaccine) in children and also elderly populations. In 2004-2005, serotype 19A has high resistance rates to penicillin (42.3%), azithromycin (63.5%) and amoxicillin-clavulanic acid (30%) while only 0.2% of these isolates are resistant to telithromycin. Part of these isolates belong to the *erm*(B) + *mef*(A) clone mentioned above.

Haemophilus influenzae

- Telithromycin has been shown to have a stable activity against *H. influenzae* in both PROTEKT Global and PROTEKT US. There is no signal of an increase in the prevalence of strains with high-level resistance. Telithromycin activity is not affected by β-lactamase production or other mechanisms of resistance to β-lactams.

6.1.1.1 Methodology of the studies

The objectives are to document the prevalence of antibiotic resistance phenotypes and genotypes, and the activity of a range of antibacterial agents, including telithromycin, against strains of *S. pneumoniae*, *H. influenzae*, *S. pyogenes*, and *L. pneumophila* (PROTEKT Global only) from patients with community-acquired RTIs. Isolates are collected from patients in the community or hospitalized for <48 hours presenting with 1 of the following infections: pneumonia, acute bacterial exacerbation of chronic bronchitis, acute exacerbation of other chronic obstructive airways diseases, acute/chronic sinusitis, acute/chronic T/P, or acute/chronic otitis media. Acceptable sources for isolates are: blood cultures, sputum cultures, bronchoalveolar lavage fluid, pus from MEF, nasopharyngeal swab or aspirate cultures, sinus aspirate cultures, and throat cultures. Duplicate or multiple isolates from the same patient are excluded. Minimum inhibitory concentrations are determined using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method. Minimum inhibitory concentrations are measured by 2 central labs: GR Micro (London) for PROTEKT Global and CMI (Portland, Oregon, USA) for PROTEKT US.

Susceptibility testing results are interpreted using CLSI breakpoints. For *S. pneumoniae*, multidrug resistance (MDR) is defined, according to the definition as resistance to ≥2 antibacterial classes (with penicillin, cefuroxime, erythromycin, tetracycline, cotrimoxazole, and levofloxacin being the class representatives). In addition, for PROTEKT Global, extended drug resistance (XDR) is the collective term used to describe *S. pneumoniae* isolates that are resistant to 5 or 6 classes of antibacterials. CLSI breakpoints are used to define susceptibility/resistance. Erythromycin-resistant strains are strains with an erythromycin MIC superior or equal to 2 mg/L. Penicillin-intermediate strains are strains with a penicillin MIC between 0.12 and 1 mg/L. Penicillin-resistant strains are strains with a penicillin MIC superior or equal to 2.0 mg/L. Levofloxacin-resistant strains are strains with a levofloxacin MIC superior or equal to 8 mg/L.

Testing for macrolide resistance mechanisms [*erm*(B), *mef*(A)], and *erm*(A) subclass *erm*(TR)] is performed using a Taqman™ polymerase chain reaction (PCR) assay. Serotyping is performed by Neufeld's Quellung reaction using Statens Serum Institute antiserum (SSI, Denmark). Genotyping and serotyping are performed at GR Micro, London.

PROTEKT results are stored on a restricted access website, hosted by GR Micro that allows interactive analysis. GR Micro loads results to the website site once the database has been validated and locked.

6.1.2 Streptococcus pneumoniae

6.1.2.1 PROTEKT Global

The number of sites/countries that participated in PROTEKT Global were: Year 1 – 71/26, Year 2 – 74/22, Year 3 – 112/33, Year 4 – 116/38, and Year 5 – 125/38.

A total of 7083 *S. pneumoniae* isolates were collected in Year 5; 57.1% were isolated from adults and 33.9% from children (0-15 years of age). For 9.1% of the isolates, there was no record of the patient's age.

The table below summarizes the activity of telithromycin and other antibiotics against the total number of *S. pneumoniae* isolates and particular phenotypes or populations

Table 46 - PROTEKT Global: Antibiotic activity against *Streptococcus pneumoniae*, Year 5

	SP	PEN-R SP	ERY-R SP	MDRSP	XDR SP
No. of *Streptococcus pneumoniae*	7083	1696	2638	2833	727
% of all *S. pneumoniae*	100	23.9	37.2	40	10.3
PEN-I/R %	13.4/23.9	0/100	20.8/50.2	20.3/59.9	0.3/99.7
ERY-R, %	37.2	78.1	100	83	99.7
TEL					
MIC_{90} (mg/L)	0.25	0.5	0.5	0.5	0.5
TEL-R, %	0.1	0.4	0.3	0.3	0.6
AZI					
MIC_{90} (mg/L)	≥128	≥128	≥128	≥128	≥128
AZI-R, %	37.1	77.7	99.3	82.6	99.3
AMC					
MIC_{90} (mg/L)	2	≥ 8	4	≥ 8	≥ 8
AMC-R, %	4	16.9	8.4	10.1	25.4
CEF					
MIC_{90} (mg/L)	8	≥ 16	8	8	≥ 16
CEF-R, %	28.7	99.9	60.2	70.5	100
LEV					
MIC_{90} (mg/L)	1	1	1	1	1
LEV-R, %	0.9	1.7	1.6	1.8	3.9

SP=*Streptococcus pneumoniae*; PEN-I=penicillin intermediately-resistant; PEN-R=penicillin-resistant; ERY-R=erythromycin-resistant; TEL-R=telithromycin-resistant; AZI-R=azithromycin-resistant; AMC-R=amoxicillin-clavulanic acid-resistant; CEF-R=cefuroxime-resistant; LEV-R=levofloxacin-resistant. MDRSP=multidrug-resistant *S. pneumoniae* (resistance to ≥antibacterial classes, with penicillin, cefuroxime, erythromycin, tetracycline, cotrimoxazole, and levofloxacin being the class representatives); XDR=extended drug resistance (ie, *S. pneumoniae* isolates that are resistant to 5 or 6 classes of antibacterials).
Year 5=2003-2004.

Overall, nearly 40% of the *S. pneumoniae* isolates collected during Year 5 of PROTEKT Global are resistant to macrolides and have reduced susceptibility to penicillin. Important variations are observed across different countries. At least 25% of *S. pneumoniae* isolates are resistant to macrolides and/or have reduced susceptibility to penicillin in France, Spain, Greece, Italy, the United Kingdom, Hungary, Turkey, Switzerland, Slovakia, the US, Brazil, Saudi Arabia, and Asian countries.

Overall, 40% of the *S. pneumoniae* isolates collected during Year 5 of PROTEKT Global are multidrug-resistant (ie, resistant to at least 2 classes of antibiotics) and 10% are XDR (ie, resistant to 5 or 6 classes of antibacterials). Telithromycin is active against *S. pneumoniae* isolates, irrespective of the phenotype of resistance; with MIC90 ≤0.5 mg/L and a prevalence of resistance <1%. The prevalence of levofloxacin-resistant *S. pneumoniae* is low, but higher than that of telithromycin-resistant *S. pneumoniae*. In contrast, 37.1% and 28.7% of the total number of *S. pneumoniae* isolates are resistant to azithromycin and cefuroxime, respectively. The prevalence of resistance to amoxicillin-clavulanic acid in the total number of *S. pneumoniae* isolates is 4%; this increases to nearly 17% for penicillin-resistant strains and 25% for XDR strains.

As shown in the table below, telithromycin, but not azithromycin, is shown to be active against erythromycin-resistant *S. pneumoniae* isolates.

Table 47 - PROTEKT Global: Telithromycin and azithromycin activity against the most frequent genotypes of erythromycin-resistant *Streptococcus pneumoniae*, Year 5

		Telithromycin				Azithromycin			
Genotype	N	MIC_{50} (mg/L)	MIC_{90} (mg/L)	TEL-S (%)	TEL-R (%)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	AZI-S (%)	AZI-R (%)
erm(B)	1452	0.03	0.25	99.0	0.3	≥128	≥128	0	100
mef(A)	808	0.12	0.5	100	0	8	16	0.3	98.4
erm(B)+*mef*(A)	317	0.5	0.5	99.4	0.6	≥128	≥128	0	100
Ribosomal mutation	52	0.06	0.25	100	0	≥128	≥128	3.9	86.5

TEL-S=telithromycin-susceptible; TEL-R=telithromycin-resistant; AZI-S=azithromycin-susceptible; AZI-R=azithromycin-resistant.
Year 5=2003-2004.

Over the past 5 years of PROTEKT Global, the prevalence of penicillin-, erythromycin-, and levofloxacin-resistant *S. pneumoniae* isolates has remained stable. The prevalence of telithromycin-resistant *S. pneumoniae* isolates was low prior to the EU launch in October 2001. A review of data from Years 1 to 5 does not demonstrate a trend toward increasing resistance to telithromycin. In France where there were more than 4.2 million prescriptions by the end of 2004, telithromycin resistance has not increased, with 0.5, 0.5, 0.9, 0.5, and 0.6% of resistant strains from Year 1 (prior to launch) to Year 5, respectively.

Table 48 - PROTEKT Global: Antibiotic-resistant *Streptococcus pneumoniae*, Years 1-5

Year	N	PEN-I/R (%)	ERY-R (%)	TEL-R (%)	LEV-R (%)
1	3435	14.1 / 21.7	31.4	0.1	1.1
2	4256	13.1 / 18	32.7	0.05	1
3	6320	13.6 / 24	36.9	0.1	0.7
4	6739	13.9 / 22.3	36.4	0.2	1
5	7083	13.4 / 23.9	37.2	0.1	0.9

PEN-I=penicillin intermediately-resistant; PEN-R=penicillin-resistant; ERY-R=erythromycin-resistant; TEL-R=telithromycin-resistant; LEV-R=levofloxacin-resistant.
Year 1=1999-2000; Year 2=2000-2001; Year 3=2001-2002; Year 4=2002-2003; Year 5=2003-2004.

6.1.2.2 PROTEKT US

A total of 191 sites participated in the PROTEKT US in Year 5 (2004-2005). Results for Year 5 and the evolution from Year 1 to 5 are summarized in the tables below. In 2004-2005, 17.5% of the strains of *S. pneumoniae* are penicillin-resistant, ranging from 13.8 to 31.6% across age groups. Since Year 1, nearly 40% of the strains are of decreased susceptibility to penicillin. However, during the 2 last years of the study, the prevalence of penicillin-resistant strains has decreased with a parallel increase in the prevalence of intermediate resistance strains. In 2004-2005, 30.9% of the strains of *S. pneumoniae* are erythromycin-resistant, ranging from 26.4 to 47% across age groups. Over the 5 years of PROTEKT US, the prevalence of telithromycin-resistant *S. pneumoniae* isolates has remained stable, being at 0.1% in 2004 to 2005. There is no evidence of any clonal spread of a telithromycin-resistant strain. Telithromycin is active against *S. pneumoniae* isolates, irrespective of the phenotype of resistance and in vitro is more active against multidrug-resistant strains than the other antibiotics. The prevalence of levofloxacin-resistant *S. pneumoniae* isolates is also stable at ~1%.

Table 49 - PROTEKT US: Antibiotic activity against *Streptococcus pneumoniae*, Year 5

	Total SP	PEN-R SP	ERY-R SP	MDRSP	SP from <2 years[a]	SP from 3-14 years[a]	SP from 15-64 years[a]	SP from >65 years[a]
No. of *Streptococcus pneumoniae*	9487	1658	2927	2765	1440	1149	4151	2576
% of SP	100	17.5	30.9	29.1	15.2	12.1	43.8	27.2
PEN I/R, %	20.1/17.5	0/100	39.6/43.3	34.4/59.9	25.2/31.6	22.7/18.8	18.9/13.8	17.8/14.8
ERY-R, %	30.9	76.5	100	83.7	47	32.7	26.4	28.2
TEL								
MIC_{90} (mg/L)	0.5	1	1	1	0.5	0.5	0.25	0.5
TEL-R, %	0.1	0.4	0.3	0.4	0.1	0.1	0.1	0.1
AZI								
MIC_{90} (mg/L)	≥256	≥256	≥256	≥256	≥256	≥256	64	≥256
AZI-R, %	30.8	76.4	99.6	83.4	46.7	32.7	26.4	28.1
AMC								
MIC_{90} (mg/L)	2	≥8	≥8	≥8	≥8	2	2	2
AMC-R, %	5.5	31.6	17.5	19	14.9	7.2	3.2	3.3
CEF								
MIC_{90} (mg/L)	8	≥16	≥16	≥16	≥16	8	4	4
CEF-R, %	19.9	99.4	47.9	65.6	35.6	20.7	16	16.8
LEV								
MIC_{90} (mg/L)	1	1	1	1	1	1	1	1
LEV-R, %	0.9	1.6	1.3	1.8	0.1	0.1	0.8	1.6

SP=*Streptococcus pneumoniae*; PEN-I=penicillin intermediately-resistant; PEN-R=penicillin-resistant; ERY-R=erythromycin-resistant; TEL-R=telithromycin-resistant; AZI-R=azithromycin-resistant; AMC-R=amoxicillin-clavulanic acid-resistant; CEF-R=cefuroxime-resistant; LEV-R=levofloxacin-resistant. MDRSP=multidrug-resistant *S. pneumoniae* resistance to ≥2 antibacterial classes (with penicillin, cefuroxime, erythromycin, tetracycline, cotrimoxazole, and levofloxacin being the class representatives); XDR=extended drug resistance (ie, *S. pneumoniae* isolates that are resistant to 5 or 6 classes of antibacterials).
Year 5=2003-2004.

[a] Age of the patient from whom the strain was isolated; this information is only available for a subset of the data.

Table 50 - PROTEKT US: Antibiotic-resistant *Streptococcus pneumoniae*, Years 1-5

Year	N	PEN-I/R (%)	ERY-R (%)	TEL-R (%)	LEV-R (%)
1	10103	12.5/26.3	31	0.04	0.8
2	10012	14.2/21.2	27.9	0.02	1.1
3	10886	15.3/20.2	29.2	0.01	0.8
4	8494	20/16.5	29.1	0.01	1
5	9487	20.1/17.5	30.9	0.1	0.9

PEN-I=penicillin intermediately-resistant; PEN-R=penicillin-resistant; ERY-R=erythromycin-resistant; TEL-R=telithromycin-resistant; LEV-R=levofloxacin-resistant.
Year 1=2000-2001; Year 2=2001-2002; Year 3=2002-2003; Year 4=2003-2004; Year 5=2004-2005.

When comparing PROTEKT US study to other US data, the rate of penicillin resistance has also decreased from 15% in 2001 to 9% in 2005 in strains obtained from invasive infections through the Centers for Disease Control (CDC) ABCs network (http://www.cdc.gov/ncidod/dbmd/abcs/survreports.htm), and the rate of macrolide-resistant strains appears also stable around 19% (2001 and 2005) in this study. Resistance rates reported by PROTEKT are higher than those of the CDC. This may be explained by the fact that both invasive and noninvasive isolates are collected in PROTEKT. The subgroup analysis of PROTEKT blood isolates (representing invasive strains) is consistent with the rates of resistance reported by the CDC for invasive infections in 2005: 11% vs. 9.5% for penicillin-resistant *S. pneumoniae*; and 23.2% vs. 19.4% for erythromycin-resistant *S. pneumoniae,* respectively.

The prevalence of penicillin-nonsusceptibility and of macrolide resistance and varies across the different regions in the US, as indicated in the table below.

Table 51 - PROTEKT US: Prevalence of penicillin and macrolide resistance in the different regions of US, Year 5

Region	Number of strains	PEN-I (%)	PEN-R (%)	ERY-R (%)
Total US	9487	20.1	17.5	30.9
North Central	1821	20	20.7	36.7
North East	3128	17.7	14.9	27.3
North West	525	14.7	14.3	20.8
South Central	1905	23.8	19.7	36.1
South East	1258	21.6	21	34.5
South West	850	21.7	11.9	20.7

PEN-I = intermediate resistance to penicillin; PEN-R = penicillin-resistant; ERY-R = erythromycin-resistant.

Although the prevalence of erythromycin-resistant *S. pneumoniae* isolates has remained stable over the 5 years of the PROTEKT US study, the distribution of resistance mechanisms has changed. The prevalence of *S. pneumoniae* isolates harboring *erm*(B) + *mef*(A) genes has increased from 9.7% in Year 1 to 20.1% in Year 5. This increase is more pronounced in children, but also noted in adults. Over the same time period, the prevalence of *S. pneumoniae* isolates harboring *mef*(A) alone, the most frequent mechanism of macrolide resistance in the US, has slightly decreased from 68.8% to 60.3%. The prevalence of *S. pneumoniae* isolates harboring *erm*(B) alone has remained stable, representing 17.3% of macrolide-resistant *S. pneumoniae* isolates in 2004-2005.

As *S. pneumoniae* isolates harboring *erm*(B) + *mef*(A) have increased in frequency, there has been a parallel increase in the development of resistance to amoxicillin-clavulanic acid of these strains in both children and adults. All *erm*(B) + *mef*(A) isolates collected in 2004 to 2005 are also multidrug resistant. In contrast, the prevalence of telithromycin-resistant *S. pneumoniae* among these strains is low (0 to 1.3% according to the years and age groups).

More than 95% of *erm*(B) + *mef*(A) strains isolated in 2004 to 2005 belong to the international Taiwan 19F-14 clonal complex 271 (CC271) [Jenkins, 2006] as already described in previous years [Farrell et al., 2005a]. Isolates belonging to this clone are mainly of 19F and 19A serotypes.

Table 52 - PROTEKT Global: Frequency of *erm*(B) + *mef*(A) among erythromycin-resistant *Streptococcus pneumoniae* isolates and susceptibility profile

Age group		Year 1	Year 2	Year 3	Year 4	Year 5
Total	**Frequency, %**	**9.7**	**12**	**16.4**	**18.4**	**20.1**
	AMC-R, %	29.9	34.3	43.9	54.2	69.4
	TEL-R, %	0	0.3	0	0.2	0.7
<2 years of age	**Frequency, %**	**10.7**	**18.4**	**23.9**	**31**	**34.9**
	AMC-R, %	44.3	39.8	46.5	57.1	79.7
	TEL-R, %	0	0.9	0	0.6	0.4
3-14 years of age	**Frequency, %**	**13.4**	**12.9**	**20.5**	**24**	**23.4**
	AMC-R, %	32.7	38.3	44.1	54.9	70.5
	TEL-R, %	0	0	0	0	1.1
15-64 years of age	**Frequency, %**	**8.9**	**9.8**	**12.9**	**13.8**	**14.1**
	AMC-R, %	23.5	32.6	39.1	54.8	61
	TEL-R, %	0	0	0	0	1.3
>65 years of age	**Frequency, %**	**8**	**9.3**	**12.3**	**12.1**	**14**
	AMC-R, %	20.7	25.7	46.9	46.1	55.9
	TEL-R, %	0	0	0	0	0

AMC-R=amoxicillin-clavulanic acid-resistant; TEL-R=telithromycin-resistant.

Following the introduction of the conjugate vaccine in the US, a decrease in the rate of invasive pneumococcal disease caused by penicillin nonsusceptible strains of *S. pneumoniae* has been observed in children and elderly adults (from 70.3 to 13.1 cases/100,000 in children <2 years of age, and from 16.4 to 8.4 cases/100,000 in patients >65 years of age, between 1999 and 2004) [Kyaw, et al., 2006]. However, an increase in infections caused by serotypes not included in the vaccine is noted, particularly due to the 19A serotype, which has increased by 238% (313% in children, 72% in elderly adults) [Kyaw, et al., 2006]. This serotype is particularly resistant to antibiotics as reported by Jacobs et al. [2006]: 87% of resistance to penicillin, 88% to amoxicillin, and 98% to erythromycin.

Results from PROTEKT US [Farrell, 2005b] also showed between Year 1 and Year 3 of the study an increase of 19A serotype in both children and elderly populations (from 4.7% to 11.7% in pediatric population and from 2.7 to 5 % in elderly patients). In 2004 to 2005, serotype 19A has high resistance rates at the whole US territory level, but slightly lower than those reported by Jacobs et al: 42.3, 63.5, and 30% of resistance for penicillin, azithromycin, and amoxicillin-clavulanic acid, respectively. Only 0.2% of these isolates are resistant to telithromycin. In addition, PROTEKT US study also evidenced that in children < 2 years old, 37.2% of 19A isolates belong to the same *erm*(B) + *mef*(A) clone [Farrell, 2006]. This clone, which belongs to the clonal complex CC271, has reached high levels of resistance to β-lactam antibiotics in 2004 to 2005 (100% and 83.1% of resistant isolates to penicillin and amoxicillin-clavulanic acid respectively). In contrast, only 0.7% of the isolates are resistant to telithromycin.

6.1.3 Haemophilus influenzae

6.1.3.1 PROTEKT Global

A total of 2834 *H. influenzae* strains were isolated in Year 5 of PROTEKT Global. Overall, 13.1% of *H. influenzae* isolates produce β-lactamase and are thus resistant to amoxicillin. As shown in the table below there has been no important change in the susceptibility of *H. influenzae* to antibiotics. Isolates resistant to cefuroxime and/or amoxicillin-clavulanic acid mainly come from Asia. Any increase in resistance to these β-lactam antibiotics should be monitored closely.

Table 53 - PROTEKT Global: Antibiotic activity against *Haemophilus influenzae*, Year 5

	Year 1	Year 2	Year 3	Year 4	Year 5
No. of *Haemophilus influenzae*	2986	3133	4294	4457	2834
TEL					
MIC_{90} (mg/L)	2	2	2	2	2
TEL-R, %	0	0.03	0.1	0.1	0.1
AZI					
MIC_{90} (mg/L)	2	2	2	2	2
AZI-R, %	0.2	0.3	0.3	0.6	0.3
AMC					
MIC_{90} (mg/L)	1	1	1	2	2
AMC-R, %	0.1	0.2	0.1	0.3	3.6
CEF					
MIC_{90} (mg/L)	2	2	2	2	4
CEF-R, %	0.1	0.4	0.4	0.4	5
LEV					
MIC_{90} (mg/L)	0.015	0.015	0.015	0.03	0.03
LEV-R, %	0	0.2	0.1	0.1	0

TEL-R=telithromycin-resistant; AZI-R=azithromycin-resistant; AMC-R=amoxicillin-clavulanic acid-resistant; CEF-R=cefuroxime-resistant; LEV-R=levofloxacin-resistant.
Year 5=2003-2004.

6.1.3.2 PROTEKT US

A total of 2706 *H. influenzae* strains were isolated in Year 5 of PROTEKT US. Overall, 27.3% of *H. influenzae* isolates produce β-lactamase and are thus resistant to amoxicillin. As shown in the table below there has been no change in the prevalence of ß-lactamase production of *H. influenzae* (28%, 27.5%, 30.3%, and 29% in Years 1, 2, 3, and 4, respectively).

Table 54 - PROTEKT US: Antibiotic activity against *Haemophilus influenzae*, Year 5

	Year 1	Year 2	Year 3	Year 4	Year 5
No. of *Haemophilus influenzae*	2706	3296	3367	2496	3529
TEL					
MIC_{90} (mg/L)	4	4	4	4	4
TEL-R, %	0.6	0.6	0.7	0.7	0.6
AZI					
MIC_{90} (mg/L)	4	2	2	2	2
AZI-R, %	0.6	0.5	0.4	0.7	1
AMC					
MIC_{90} (mg/L)	1	1	2	2	1
AMC-R, %	0.3	0.2	0.1	0.2	0.3
CEF					
MIC_{90} (mg/L)	4	4	2	4	4
CEF-R, %	0.5	0.6	0.4	0.2	0.5
LEV					
MIC_{90} (mg/L)	0.06	0.06	0.06	0.06	0.06
LEV-R, %	0.4	0.2	0.2	0.1	0.3

TEL-R=telithromycin-resistant; AZI-R=azithromycin-resistant; AMC-R=amoxicillin-clavulanic acid-resistant; CEF-R=cefuroxime-resistant; LEV-R=levofloxacin-resistant.
Year 5=2003-2004.

Telithromycin has been shown to have moderate and stable activity against *H. influenzae* in both PROTEKT Global and PROTEKT US. There is no signal of an increase in the prevalence of strains with high-level resistance. Telithromycin activity is not affected by β-lactamase production or other resistance mechanisms of resistance to β-lactams.

6.1.4 Mechanism of *Streptococcus pneumoniae* resistance to telithromycin

The mechanisms of *S. pneumoniae* resistance to telithromycin have been investigated in laboratory-generated mutants (selected by macrolides or telithromycin) and in clinical strains. Most of these mechanisms of *S. pneumoniae* resistance have been summarized by Hisanaga and colleagues [Hisanaga et al., 2005]. Various mutations have been identified in the upstream region of *erm*(B), the 23s ribosomal RNA, or the ribosomal proteins L4 and L22. Several alterations appear to be necessary to confer high-level resistance to telithromycin (MIC ≥16 mg/L) in clinical strains.

Another study performed by Al-Lahham and colleagues [Al-Lahham et al., 2006] identified 17 *S. pneumoniae* strains intermediate or resistant to telithromycin isolated in Europe between 2001 and 2005. The isolates showed a wide range of combination of resistance determinants including multiple alterations in the 23S rRNA (all strains), alteration in ribosomal protein L4 (9 strains), and *erm*(B) gene (all strains, including 14 N100 alterations). The role of each mutation in resistance to telithromycin was not established, and some may simply represent heterogeneity in *erm*(B) and its promoter region.

Rantala and coworkers [Rantala et al., 2006] described in 26 *erm*(B) strains isolated in Finland subpopulations that were resistant to telithromycin. These subpopulations were all detected by disc diffusion method only. The underlying mechanism of this phenomenon as well as its frequency all over the world and its clinical significance are unknown.

To date there have been a total of 3 published clinical case reports describing resistance to telithromycin under treatment.

- In the first case [Perez-Trallero et al., 2003], a telithromycin-resistant isolate of *S. pneumoniae* was selected under clarithromycin therapy in a patient who had never been exposed to telithromycin.
- The second case [Faccone et al., 2005] reports the isolation of a telithromycin resistant *S. pneumoniae* after azithromycin and telithromycin therapy.
- The third case [Goldstein et al., 2005] reports pneumonia with isolation of a telithromycin-resistant *S. pneumoniae* after treatment with telithromycin, while no bacterial documentation was available before treatment.

These 3 cases are detailed in *APPENDIX E: MICROBIOLOGY* .

6.1.5 Overall conclusion

The PROTEKT Global and PROTEKT US studies results show that telithromycin retains activity against S. *pneumoniae* and *H. influenzae*, the 2 bacterial pathogens most frequently implicated in CAP, AECB, and ABS, the indications for which the antibiotic is approved in the US. In particular, telithromycin displays potent in vitro activity against *S. pneumoniae* including strains resistant to antibiotics by a variety of mechanisms. No evidence of increased resistance to telithromycin or any clonal spread has been observed.

Telithromycin-resistant *S. pneumoniae* isolates, first described prior to launch of the product in October 2001, remain rare. Few cases of emerging resistance in clinical setting have been described. Several alterations (among *erm*[B], ribosomal RNA, or proteins) seem to be necessary to obtain strains with high level of resistance to telithromycin. Given its targeted spectrum activity on respiratory pathogens, telithromycin microbiological activity supports its use in the treatment of community-acquired RTI pathogens.

6.2 POSTAPPROVAL: EFFICACY DATA

A total of 10 Phase IV randomized controlled studies of telithromycin have been conducted by sanofi-aventis to expand on the efficacy database of telithromycin in approved indications in the US and have been completed (database locked): 3 in CAP; 4 in AECB; 3 in ABS. In addition, 1 proof of concept study was conducted in acute exacerbations of asthma. Another Sponsor conducted an AECB study [Perronne et al., 2005], using telithromycin as a comparator.

Postmarketing or Phase IV studies are often conducted at the local level and involve use of the drug consistent with approved labeling. These studies often assess objectives such as comparisons to other drugs in the market or to collect health outcome data. The information available on postmarketing studies varies, depending on the study and the sites and countries in which the study is conducted and have some limitations inherent in their design (eg, open label) or small size (eg, pilot studies). The information provided below is based upon currently available study data from studies with database locked.

6.2.1 Phase IV community-acquired pneumonia studies

A total of 3 Phase IV randomized controlled studies have been performed in the indication mild to moderate CAP in adults. In these studies, adult subjects were included if they had signs and symptoms of CAP, confirmed by chest X-ray. Two of these Phase IV CAP studies were local studies designed as noninferiority trials (Studies A4004 and A3502). One study was designed as a superiority study in countries with high levels of antibiotic resistance (Study A4015). Clinical cure rates at test of cure, which was the primary endpoint of these studies, are presented in the table below.

In the double-blind study conducted in Spain (Study A4004), telithromycin was shown to be noninferior to clarithromycin. Study A3502, a local Phase IV study performed in Brazil, showed telithromycin to be noninferior to amoxicillin-clavulanic acid in the treatment of CAP.

In the superiority Study A4015, telithromycin was compared to standard of care in the country where patients were recruited, based on clinical practice guidelines and Investigator's choice. In this study, the clinical cure rates at TOC in the telithromycin-treated group were statistically superior to that of the control group in the main analysis (ie, clinical efficacy at TOC in the mITT). However, in a sensitivity intent-to-treat (ITT) analysis, the difference between treatment groups was not statistically significant, although a trend in favor of telithromycin was still observed (83.2% vs. 77.1%, [-0.008, 0.130]; p=0.094).

Table 55 – CAP: Clinical cure rates at posttherapy/test of cure for telithromycin and comparator(s), by Phase IV study

	Telithromycin			Comparator			95% CI[a]
	N	n	(%)	N	n	(%)	
PPc population							
Study A4004[b]	92	88	95.7%	89	81	91.0%	[-2.6; 11.9]
Study A4015[c]	219	191	87.2%	219	175	79.9%	[0.4; 14.2]*[e]
Study A3502[d]	53	49	92.5%	53	45	84.9%	[-5; 20]
mITT population							
Study A4004	95	88	92.6%	97	81	83.5%	[0.06; 18.2]
Study A4015	242	208	86.0%	240	189	78.8%	[0.4; 14.0]*[f]
Study A3502	56	51	91.1%	56	46	82.1%	[-4; 22]

PPc=per protocol clinical; mITT=modified intent-to-treat.

[a] 95% confidence interval of the difference in cure rates between the treatment groups; * statistically significant difference

[b] Study A4004 was a randomized, double blind, national (Spain) study that compared 7-day telithromycin 800 mg qd to 10-day clarithromycin 500 mg bid.

[c] Study A4015 was a randomized, open, multinational (South Africa, Tunisia, Hong Kong, Korea, Taiwan, Thailand, Greece, Hungary and Spain) study that compared 7- to-10-day telithromycin 800 mg qd to local usual care regimen.

[d] Study A3502 was a randomized, open, national (Brazil) study that compared 7 days telithromycin 800 mg qd to 10 days amoxicillin-clavulanic acid 875 mg/125mg bid.

[e] Chi^2=4.255 p=0.0391.

[f] Chi^2=4.301 p=0.0381.

6.2.2 Phase IV acute exacerbation of chronic bronchitis studies

A total of 4 Phase IV randomized controlled studies have been performed in the indication AECB in adults.

In 2 of these studies, the primary endpoint was clinical efficacy at TOC (Studies A4007 and A4014). Patients were included in those studies if they had a chronic bronchitis and 2 or more of the following symptoms of exacerbation (increase of cough or dyspnea, sputum volume, or sputum purulence); in Study A4014, subjects had to have a forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio<75% in the last 12 months. Results of the main analysis of these 2 studies are presented in the table below, showing noninferiority to the control group. Time to relapse was also investigated in Study A4014, showing no difference between the 2 compounds (Quartile 25: 52 days for telithromycin vs. 58 days for azithromycin; logrank test: p= 0.791).

Table 56 - AECB: Clinical cure rates at posttherapy/test of cure for telithromycin and comparator(s), by Phase IV study

	Telithromycin			Comparator			95% CI[a]
	N	n	(%)	N	n	(%)	
PPc population							
Study A4007[b]	79	71	89.9%	78	74	94.9%	[-13.3; 3.3] [d]
Study A4014[c]	272	243	89.3%	274	246	89.8%	[-5.9; 5.1]
mITT population							
Study A4007	90	79	87.8%	92	87	94.6%	[-15.0; 1.4] [d]
Study A4014	321	277	86.3%	327	283	86.5%	[-5.8; 5.3]

PPc=per protocol clinical; mITT=modified intent-to-treat.

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

[b] Study A4007 was a National (Korea), multicenter, randomized, double-blind, double-dummy comparing 5 days telithromycin 800 mg qd to 10 days amoxicillin-clavulanic acid 500 mg tid.

[c] Study A4014 (STROBE) was a multicenter, multinational (Argentina, Australia, Belgium, Switzerland, Chile, Finland, France, UK, Italy, Mexico, New Zealand, Portugal, South Africa), randomized, double blind study comparing 5-day telithromycin 800 mg qd to 5-day azithromycin 500/250 mg qd.

[d] According to the statistical plan for this study 1- sided 95% CI was planned with a noninferiority accepted if the lower bound of the CI was ≥-15% (PPc= -11.9%, mITT= -13.7%); the 2-sided CI 95% has been calculated for consistency within this table.

In 2 additional studies, bacteriologic eradication was the primary endpoint.

Study A4002 was a pilot, randomized, national (UK), controlled, evaluator-blind study to compare the bacteriologic eradication rates of 5-day telithromycin 800 mg qd vs. 5-day azithromycin 500 mg on Day 1 then 250 mg once daily for Days 2-5 in the treatment of AECB in adults. A total of 163 subjects were randomized to treatment and all of these subjects took at least 1 dose of study medication (safety population) and had a causative organism isolated from their sputum. Continued bacteriologic eradication rates at the 3-month posttherapy visit was the primary efficacy analysis: a total of 27/44 subjects (61%) in the telithromycin-treated group vs. 35/50 subjects (70%) in the azithromycin-treated group were classified as successes (p=0.3779). Satisfactory bacterial outcome by pathogen at 3 months for telithromycin was 26% for *H. influenzae*, 78% for *S. pneumoniae*, and 64% for *M. catarrhalis*; and for azithromycin was 50% for *H. influenzae*, 75% for *S. pneumoniae*, and 64% for *M. catarrhalis*.

Study A4020 (PERSPECTIVE) was a multicenter, multinational (Turkey, France, Spain, Belgium, Tunisia, Morocco, Hungary, US) active-controlled, open, parallel group, randomized (ratio 1.4:1:1) study. Its primary objective was to demonstrate the superiority of telithromycin over azithromycin and over cefuroxime axetil in the reduction of macrolide-resistant or β-lactam-resistant strains of *S. pneumoniae* at the TOC visit in the sputum of patients with *S. pneumoniae* detected at baseline. A total of 3946 subjects were included in this study with 537 subjects with *S. pneumoniae* isolated from the sputum at entry. In the evaluable population of *S. pneumoniae* carriers at entry, results showed that the rate of patients who were carriers of a penicillin or macrolide-resistant *S. pneumoniae* (PERSP) at TOC visit was significantly lower in the telithromycin group (12.99%) than in the azithromycin group (28.3%) but not different from cefuroxime PERSP carriage (13.08%) [telithromycin vs. azithromycin p=0.0142].

There was an additional study published in the literature [Perrone et al., 2005] comparing 5-day telithromycin 800 mg qd to 5-day clarithromycin ER 1 g qd. The clinical success rate in the PPc population at Day 8 was 97% for each of the treatment groups (146/151 in the telithromycin-treated group vs. 161/166 in the clarithromycin-treated group, Fisher exact test F=0.564 n.s.). There was no significant difference between clinical cure rates in the 2 groups after 30 days (77% [116/151] for the telithromycin-treated group vs. 77% [129/166] for the clarithromycin-treated group; p=0.8502 n.s.]).

6.2.3 Phase IV acute bacterial sinusitis studies

A total of 3 Phase IV randomized controlled studies have been performed in the indication ABS in adults. In all 3 of these studies, the primary endpoint was clinical efficacy at TOC. Patients were included if they had signs and symptoms of acute sinusitis for more than 5 days (Studies A4013 and A4017) and 7 days (Study A4023), and a maxillary sinus X-ray showing total opacity, air-fluid levels, or mucosal thickening. Bacterial documentation at inclusion was obtained by endoscopy. Based on the primary analysis of clinical efficacy at TOC, it was concluded that telithromycin was noninferior to moxifloxacin in Study A4017, or to amoxicillin-clavulanic acid (875/125 mg bid) in Study A4023 (see table below). Time to symptom resolution, which was evaluated in both studies using a 5-item symptom score, was shown to be similar between telithromycin and moxifloxacin in Study A4017, and shorter with telithromycin than amoxicillin-clavulanic acid in Study A4023; the median time [95% CI] to reduction of 50% of baseline total symptom score in Study A4023 (mITT population) was 4.0 days [3.0; 5.0] in the telithromycin-treated group and 5.0 days [5.0; 6.0] in the amoxicillin-clavulanic acid group (p=0.044). In the third study, performed in Latin America (Study A4013), telithromycin was shown to be noninferior to amoxicillin-clavulanic acid (500/125 mg tid).

Results of the primary analysis of these studies are presented in the table below.

Table 57 - ABS: Clinical cure rates at posttherapy/test of cure for telithromycin and comparator(s), by Phase IV study

	Telithromycin			Comparator			95% CI[a]
	N	n	(%)	N	n	(%)	
PPc population							
Study A4017[c]	135	118	87.4%	137	119	86.9%	[-8.1; 9.2]
Study A4023[d]	123	109	88.6%	125	111	88.8%	[-8.9; 8.5]
mITT population							
Study A4013	231	228	98.7%	238	227	95.4%	[0.3; 6.4]
Study A4017	159	128	80.5%	163	125	76.7%	[-5.8; 13.4]
Study A4023	144	125	86.8%	146	128	87.7%	[-9.2; 7.5]

PPc=per protocol clinical; mITT=modified intent-to-treat.

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

[b] Study A4013 is a multicenter, multinational (Brazil, Mexico, Peru, Chile, Venezuela, Guatemala, Costa Rica, Santo Domingo, Colombia, Ecuador, and Argentina), open, randomized study that compared 5-day telithromycin 800 mg qd to 10-day amoxicillin-clavulanic acid 500/125 mg tid, results in the report are expressed in failure and OR; for the purpose of this table, results are expressed in cure rates (nonfailure).

[c] Study A4017 is a multicenter, national (US) double blind, randomized study that compared 5-day telithromycin 800 mg qd to 10-day moxifloxacin 400 mg qd.

[d] Study A4023 is a multicenter, multinational (Canada, Germany, Greece, Portugal, Turkey), open, randomized study that compared 5-day telithromycin 800 mg qd to 10-day amoxicillin-clavulanic acid 875/125 mg bid.

6.2.4 Phase IV acute exacerbation of asthma study

Given the potential role of atypical organisms in the pathogenesis of acute exacerbations of asthma, as well as the anti-inflammatory effect of macrolides, proof of concept Study A3503 (TELithromycin and Chlamydia in ASThma [TELICAST]) was performed in patients with mild or moderate asthma to evaluate the activity of telithromycin as an add-on to standard therapy, in acute exacerbations of asthma.

Study A3503 was a multicenter, multinational (Australia, Canada, France, Germany, Italy, UK) randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of oral telithromycin 800 mg (once daily for 10 days) as a supplement to the standard of care for patients with acute exacerbations of asthma.

A total of 278 adults with diagnosed asthma were enrolled within 24 hours after an acute exacerbation of asthma requiring short-term medical care. The primary endpoints were a change from baseline over the treatment period in symptoms (as recorded by subjects on a diary card) and in the peak expiratory flow in the morning at home. The presence of *C. pneumoniae* or *M. pneumoniae* was ascertained by serologic analysis, PCR, and culture.

Of the 2 prespecified primary outcomes, only asthma symptoms showed a significantly greater reduction among subjects receiving telithromycin than among those receiving placebo. Mean (±SD) scores on a test of asthma symptoms (on a 7-point scale, with 0 denoting no symptoms and 6 denoting severe symptoms) were 3.0±1.4 at baseline and 1.7±1.1 at the end of treatment for the telithromycin-treated group and 2.8±1.3 at baseline and 2.0±1.0 at the end of treatment for the placebo-treated group. The mean decrease in symptom scores during the treatment period was 1.3 for the telithromycin- and 1.0 for the placebo-treated group (mean difference, -0.3; 95% CI, -0.5 to -0.1; p=0.004). There was no significant treatment effect on the other primary outcome measure, a change in morning peak expiratory flow. Nausea was more common among subjects in the telithromycin-treated group than in the placebo-treated group (p=0.01). Although 61% of subjects had evidence of infection with *C. pneumoniae*, *M. pneumoniae*, or both, there was no relationship between bacteriologic status and the response to asthma treatment. This study provides evidence of the benefit of telithromycin in patients with acute exacerbations of asthma; the mechanisms of benefit remain unclear.

6.2.5 Conclusion

Results of these Phase IV studies are consistent with preapproval experience demonstrating that telithromycin is effective in the treatment of CAP, AECB, and ABS. Data show potential clinical benefits in 3 areas. A trend toward superior efficacy was observed in the treatment of CAP in countries with high prevalence of *S. pneumoniae* resistance to antibiotics. In subjects with AECB, focusing on the population of subjects with *S. pneumoniae* at baseline, a significant decrease in carriage of *S. pneumoniae* resistant to penicillin or macrolides was observed. In subjects with ABS, evaluation of time to symptom resolution showed that telithromycin was comparable to moxifloxacin and potentially better than treatment with amoxicillin-clavulanic acid, both recognized as highly effective treatments in this indication.

6.3 POSTAPPROVAL: SAFETY DATA

6.3.1 General safety: Phase IV studies

To date, a total of 12 Phase IV studies including a comparator antibiotic have been completed; 10 clinical efficacy studies for the approved indications (CAP, AECB, and ABS) and 2 clinical pharmacology studies to evaluate the effect on normal flora in healthy subjects. These studies enrolled a total of 3136 telithromycin- and 3846 comparator-treated subjects.

In addition, there was 1 placebo-controlled study (Study A3503) for acute exacerbation of asthma.

The table below summarizes the rates of AEs for the 12 Phase IV comparator studies that enrolled a total of 3142 telithromycin- and 3852 comparator-treated subjects.

Table 58 - Summary of adverse events in Phase IV comparator studies for all treatment indications

Study ID	Telithromycin		Comparator	
	No. of subjects	(%)	No. of subjects	(%)
Safety population	3142		3852	
Adverse events	660	(21.0%)	691	(18.0%)
Possibly related AEs[a]	412	(13.1%)	374	(9.7%)
SAEs	64	(2.0%)	63	(1.7%)
Possibly related SAEs[a]	9	(0.3%)	9	(0.2%)
AEs leading to death	4	(0.1%)	5	(0.1%)
Possibly related AEs leading to death[a]	0	(0%)	0	(0%)
AEs leading to discontinuation	53	(1.7%)	73	(1.9)

AE=adverse event; SAE=serious adverse event.

[a]Possibly related per Investigator.

Overall, the incidence of all AEs and SAEs was similar between the 2 treatment groups.

There were a total of 274 safety evaluable subjects enrolled in Study A3503. The frequency of AEs was similar between treatment groups (39.9% in telithromycin vs. 39.7% in the placebo treatment group). There were 2 SAEs in each treatment group; none were considered related to study medication. The incidence of AESIs was low in the telithromycin treatment group (eg, hepatic AEs 1.4% and visual AEs 2.2%). There were no AESIs in the placebo treatment group (see *APPENDIX F: PHASE IV SAFETY DATA*).

Table 59 - Summary of adverse events in Phase IV placebo-controlled in acute exacerbation of asthma (Study A3503)

Study ID	Telithromycin		Placebo	
	No. of subjects	(%)	No. of subjects	(%)
Safety population	138		136	
Adverse events	55	(39.9%)	54	(39.7%)
Possibly related AEs[a]	28	(20.3%)	19	(14.0%)
SAEs	2	(1.4%)	2	(1.5%)
Possibly related SAEs	0	(0%)	0	(0%)
AEs leading to death	0	(0%)	0	(0%)
Possibly related AEs leading to death	0	(0%)	0	(0%)
AEs leading to discontinuation	11	(8.0%)	8	(5.9%)

AE = adverse event; SAE = serious adverse event

[a] Possibly related per Investigator.

6.3.1.1 Deaths in Phase IV studies

There were a total of 23 deaths in the 13 Phase IV studies (including Study A3503), 13 in the telithromycin-treated vs. to 10 in the comparator-treated group. There is no evidence for any treatment-related death in any of these cases, based on information available. None of the deaths in either group were considered related to study medication by the Investigator.

An overview table of the cases involving deaths as well as brief narratives appear in *APPENDIX F: PHASE IV SAFETY DATA* .

6.3.2 General safety: Worldwide postmarketing surveillance

The estimated worldwide marketed exposure to telithromycin from July 2001 through August 31, 2006, is 28 million courses of treatment; the corresponding exposure in the US (from May 2004 through August 2006) is 5.8 million prescriptions.

In the period from July 2001 through September 15, 2006, a total of 5579 postmarketing spontaneous reports of AEs have been received worldwide by sanofi-aventis, giving an overall reporting rate for postmarketing spontaneous AEs of approximately 199 reports per million exposures.

Reporting rates in the first 29 months since approval in the US (269 reports per million exposures) were generally similar to those seen worldwide in the 29-month period (July 2001 through December 2003) reviewed prior to FDA approval (207 reports per million exposures). The current ex-US decrease seen when compared to the December 2003 worldwide reporting rate (all worldwide reports through 2003 were ex-US) likely reflects the decrease in overall reporting expected with the Weber effect [Weber, 1984].

Table 60 - Postmarketing spontaneous reports, Worldwide, US, and ex-US

Worldwide 09-Jul-01 to 31-Dec-03		Worldwide 09-Jul-01 to 15-Sep-06		US 15-May-04 to 15-Sep-06		Ex-US 09-Jul-01 to 15-Sep-06	
No. of AE reports	Reporting rate (per 10^6 exposures)	No. of AE reports	Reporting rate (per 10^6 exposures)	No. of AE reports	Reporting rate (per 10^6 exposures)	No. of AE reports	Reporting rate (per 10^6 exposures)
1231	207	5579	199	1554	269	4025	181

AE=adverse event.

The most frequently reported individual AEs are presented in the table below. All of these events are listed in the current USPI (June 2006) for telithromycin.

Table 61 - Most commonly reported adverse events in postmarketing spontaneous reports, received by September 15, 2006

	Worldwide 09-Jul-01 to 31-Dec-03		Worldwide 09-Jul-01 to 15-Sep-06		US 15-May-04 to 15-Sep-06		Ex-US 09-Jul-01 to 15-Sep-06	
MedDRA PT	No. of AE reports	Reporting rate (per 10^6 exposures)	No. of AE reports	Reporting rate (per 10^6 exposures)	No. of AE reports	Reporting rate (per 10^6 exposures)	No. of AE reports	Reporting rate (per 10^6 exposures)
Vision Blurred	268	45.0	904	32.3	264	45.7	640	28.9
Dizziness	121	20.3	559	20.0	148	25.6	411	18.5
Nausea	140	23.5	518	18.5	155	26.8	363	16.4
Diarrhea	84	14.1	362	12.9	98	17.0	264	11.9
Visual disturbance	76	12.8	276	9.9	107	18.5	169	7.6
Rash	33	5.5	327	11.7	57	9.9	270	12.2
Vomiting	65	10.9	278	9.9	82	14.2	196	8.8
Headache	83	13.9	253	9.0	64	11.1	189	8.5
Dyspnoea	28	4.7	156	5.6	76	13.1	80	3.6
Diplopia	37	6.2	154	5.5	71	12.3	83	3.7
Abdominal pain	51	8.6	151	5.4	44	7.6	107	4.8
Malaise	43	7.2	147	5.3	38	6.6	109	4.9

Estimated worldwide exposure (through August 2006): 28.0 million courses of treatment.
Estimated US exposure (through August 2006): 5.8 million courses of treatment.
Estimated ex-US exposure (through August 2006): 22.2 million courses of treatment.
MedDRA version 9.0.
Reporting rate presented as cases per million exposures.
AE = adverse event; PT = Preferred Term.

6.3.3 Adverse events of special interest: Phase IV studies

- In the 12 Phase IV studies with a comparator antibiotic, the incidence of hepatic AEs was similar between the 2 treatment groups.
- There were a total of 3 Phase IV clinical trial reports of cardiac AEs in the telithromycin-treated group and none in the comparator-treated group. There were 5 reports of syncope in the telithromycin-treated group and 1 report of vasovagal syncope in the comparator-treated group. Of the syncope cases in the telithromycin-treated group, 2 were described by Investigator as lipothymia and 1 as mild syncope in a context of endocarditis.
- Consistent with the Phase III studies, the incidence of visual AEs in the Phase IV studies was higher in the telithromycin- than in the comparator-treated group. Blurred vision was the most commonly reported visual AE, and was more frequently reported in association with telithromycin than comparators.

Table 62 - Adverse events of special interest in Phase IV studies

Category/MedDRA Preferred Term	Telithromycin (N=3142) n (%)	Comparator (N=3852) n (%)
Hepatic	13 (0.4%)	15 (0.4%)
Liver function test abnormal	2	3
Changed ALT/AST	2	3
Transaminases increased	9	9
Cardiac (QTc-related)	3 (0.1%)	0 (0.0%)
Tachycardia	1	0
Sudden death	1	0
Heart failure	1	0
Visual	20 (0.6%)	5 (0.1%)
Blurred vision	16	3
Visual acuity reduced	2	0
Visual field defect	0	1
Abnormal vision	2	0
Visual disturbance	0	1
Myasthenia gravis	0	0
Syncope [a]	5 (0.1%)	1 (0%)
Syncope	5	0
Vasovagal syncope	0	1

[a] Two of the syncope cases were reported as lipothymia (near syncope) and 1 as mild syncope.

6.3.4 Adverse events of special interest: Hepatic adverse events

Following the launch of telithromycin in the US in April 2004, sanofi-aventis continued intensified monitoring for hepatic AE reports, both in clinical studies and with postmarketing spontaneous reports.

6.3.4.1 Postmarketing safety data related to severe hepatic adverse events received by September 15, 2006

From April 2004 to April 2005, interval and cumulative postmarketing reports of hepatic AEs were assessed at 2 separate intervals in the 6-monthly PSURs, submitted September 2004 and January 2005. These reviews of hepatic postmarketing safety data noted no changes from the preapproval assessments. As noted previously, postmarketing spontaneous reports of hepatic AEs were followed up using the AESI forms.

In April 2005, sanofi-aventis received 3 reports of hepatic failure occurring in the Charlotte, NC, region. A review of the database at that time revealed that 2 additional reports involving significant hepatic injury or hepatic failure had been received in recent weeks, coming from New Jersey and Puerto Rico, and bringing the total of recent cases of concern to 5.

As a result, sanofi-aventis began intensive follow-up of these 5 cases, contacting the reporting physicians. A preliminary review of the data, finalized in May 2005, revealed that, of these 5 cases, 2 cases were in fact reversible hepatitis, 1 had another confounding alternative explanation (overwhelming sepsis), and 1 lacked adequate information to assess for possible causality; in the remaining case, an association could not be excluded but further case details and records were still needed to fully assess the case. A review of cumulative cases, submitted to worldwide health Agencies (including the FDA) in June 2005, confirmed this initial assessment that no change in the hepatic safety profile had been demonstrated despite the receipt of these reports.

Subsequently, additional cumulative reviews of reported hepatic cases were performed in September 2005 (for the scheduled PSUR) and December 2005 (as part of the regulatory submission for 5-year renewal of marketing authorization in the EU), and each confirmed the prior assessments.

In January 2006, the *Annals of Internal Medicine* published a brief communication concerning the 3 case reports received in March 2005 from North Carolina, which resulted in a substantial increase in spontaneous AE reports, primarily in the US.

Two additional cumulative reviews, both of which were submitted to worldwide health authorities, were then completed in February 2006, following this influx in cases, to determine whether substantial differences in the safety profile were evident based upon this newly received information. This review included identification of ASLI and ALF, as previously defined. Subsequent changes were made to worldwide labeling documents to include language regarding the potential for hepatic failure with telithromycin administration.

This was followed in the US by several meetings with the FDA and external hepatic experts to interpret this issue in the face of the stimulated reporting and to ascertain its meaning in the context of overall antibiotic use. These discussions led to further modifications of the USPI in June 2006 to include hepatic failure in this document as well.

However, the stimulated reporting of hepatic AEs, primarily coming from the US in the wake of the *Annals of Internal Medicine* communication, distorts the assessment of comparative reporting of hepatic events for telithromycin versus other antibiotics, making unclear the relative positioning of this drug with respect to others used in the treatment of RTIs. For this reason, as explained below in the epidemiology assessments, sanofi-aventis has performed studies using claims data for telithromycin and other commonly-used antibiotics to investigate the comparative risk for hepatic AEs.

Through September 15, 2006, a total of 443 spontaneous hepatic AE reports have been received by sanofi-aventis, giving a spontaneous reporting rate of 15.8 hepatic reports per million exposures worldwide, as shown in the table below.

Table 63 – Worldwide postmarketing reports of hepatic adverse events, received by September 15, 2006

Parameter	Assessment
Hepatic AEs	966
Hepatic AE cases	443
Hepatic reporting rate (cases per million exposures)	15.8
Hepatic AE proportional reporting ratio	0.072

AE=adverse event.
Proportional reporting ratio defined as: number of hepatic AEs/ total number of AEs

This represents an increase in the reporting rate for hepatic AEs from December 2003, and is primarily due to an increase in reporting of hepatic events in the US (including increases in both ASLI and ALF cases), as shown below. The reporting rates for ex-US hepatic cases were similar to the rates observed in December 2003.

Table 64 – Postmarketing reports of hepatic adverse event reports: Worldwide, domestic (US), and ex-US

	Worldwide 09-Jul-01 to 31-Dec-03		Worldwide 09-Jul-01 to 15-Sep-06		US 15-May-04 to 15-Sep-06		Ex-US 09-Jul-01 to 15-Sep-06	
	No. of hepatic AE reports	Reporting rate (per 10^6 exposures)	No. of hepatic AE reports	Reporting rate (per 10^6 exposures)	No. of hepatic AE reports	Reporting rate (per 10^6 exposures)	No. of hepatic AE reports	Reporting rate (per 10^6 exposures)
Total hepatic AE reports	58	9.7	443	15.8	212	36.7	231	10.4
ASLI reports	16	2.7	136	4.9	57	9.9	79	3.6
ALF reports	1	0.2	16	0.6	12	2.1	4	0.2

Estimated worldwide exposure (through August 2006): 28.0 million courses of treatment.
Estimated US exposure (through August 2006): 5.8 million courses of treatment.
Estimated ex-US exposure (through August 2006): 22.2 million courses of treatment.
Reporting rate presented as cases per million exposures.
AE=adverse event; ASLI=acute severe liver injury; ALF=acute liver failure.

Sixteen reports of ALF have been reported worldwide, 12 of which have been reported in the US.

Table 65 - Worldwide reports of acute liver failure

Case ID Age/sex	Indication Duration of treatment	Clinical course/ *sanofi-aventis comment*	Outcome
200415044FR 75/M	AECB 5 days	Hospitalized for fever, jaundice and right upper quadrant pain 2 days after completing course with TEL. Clinical deterioration over 24 hours, requiring intubation. Developed DIC and multi-organ failure during laparotomy. Hepatitis A IgM positive and *C. Burnetti* (IgM positive, confirming acute hepatitis A and Q fever. Patient died 5 days after admission. *Unlikely related to telithromycin. Confirmed acute hepatitis A and Q fever as likely causes for fulminant hepatic failure.*	Died
200413245JP 78/F	Acute bronchitis 4 days + 4 days + 2 days	History of cardiac and ESRD on hemodialysis. Given 3 consecutive courses of TEL (third course with lincomycin and fosfomycin for presumed lack of effect with increase in WBC to 14,800. AST 1200 with acidosis; AST increased to 18,000. Assessed unrelated to TEL; due to circulatory collapse. *In agreement with reporter, most likely due to septic shock.*	Died

Case ID Age/sex	Indication Duration of treatment	Clinical course/ *sanofi-aventis comment*	Outcome
200413505JP 82/M	CAP 3 days	History cardiac failure (EF 20%). Hospitalized for CAP and TEL begin as in-patient. Two days later, ALT 1800U/L, AST 3410 U/L, LDH 4400 U/L, BUN 78, Creat 2.5 (all normal 2 days prior). Followed by mental status decrease and elevated ammonia level (99) with INR 2.9. Improvement in mental status and liver enzymes (AST 1240, ALT 1570) 1 day later. Full recovery noted. *Fulminant ALF with reversibility. Rapid onset and recovery, combined with poor cardiac function, supports ischaemic injury to liver. Unlikely association to TEL.*	Recovered
200510416FR 46/M	CAP 16 days	History of epidermoid lung cancer; treated with chemotherapy (cisplatin, amifostine, and gemcitabine on Day 2 of TEL treatment. Developed hepatocellular jaundice with encephalopathy/ALF, renal failure, and septic shock 3 days after last dose. *Confounded by concurrent chemotherapy, pneumonia and septic shock. Unlikely association to TEL.*	Died
200513250US 51/F	URTI 5 days	Presented with jaundice and ascites 1 week after completing treatment. Anti smooth muscle antibody positive. Subacute course noted, ending in transplantation after several months. Explanted liver with extensive, non-specific necrosis. *Liver failure leading to transplantation. Subacute progression to liver failure atypical for acute drug injury with short course medication. Significance of anti-smooth muscle antibody unknown (not repeated). Cannot exclude drug cause.*	Sequelae (transplant)
200513491US 26/M	Sinusitis 10 days	Presented to Emergency Department with 8-day history of jaundice, tachycardia (114 bpm), tachypnea (20-40 breaths per minute), and firm, tender abdomen. ALT 2200 U/L, AST 3638 U/L, AP 535 U/L, WBC 22,000, platelets 39000, INR 25.7. Developed cardiac arrest during EGD performed for hematemesis. Deep peritoneal lavage with non-bloody ascetic fluid. Developed persistent acidosis despite ventilatory and vasopressor support, dialysis and bicarbonate infusion. Developed asystole and died on hospital Day 3. *Fulminant liver failure with fatal outcome- cause unknown. Lacks information regarding medical history and concomitant medications. Presented in extremis, cannot exclude acute abdomen. Cannot exclude drug as cause for the hepatic event with limited information available, but iatrogenic cause for rapid deterioration and death seems likely.*	Died
200520456US 45/F	CAP 3 days	Decreased level of consciousness on Day 3. ALT and AST > 5000 U/L, TB 4.4, INR 1.4, creatinine 2.4. Neurologic improvement next day, with ALT 3700 and AST 2300. Patient discharged after 2 days in hospital. *Reversible fulminant hepatic failure, cause unknown. Rapid and dramatic onset and recovery suggestive of an ischaemic injury, rather than a drug effect, but blood pressure monitoring not available.*	Recovered

Case ID Age/sex	Indication Duration of treatment	Clinical course/ *sanofi-aventis comment*	Outcome
200611392US 26/F	Sinusitis 1 day	Feeling "run down" several days prior to first dose of TEL. Concomitant use of acetaminophen and Nyquil (dextromethorphan, acetaminophen, pseudoephedrine, and doxylamine). Developed mental status changes 2-3 hours after first dose of TEL. Taken to Emergency Department; found to be afebrile without rash; (+) pedal edema. Tylenol level "normal." Transaminases > 3000 U/L, with progression to 24,000 U/L; elevated PT and "signs of DIC". Developed brain edema requiring shunt. *ALF; outcome unknown. Lacks plausible temporal relationship to single dose of TEL. Etiology unknown.*	Unknown
200611473US 69 F	URTI 4 days	Developed abdominal pain on Day 3, so TEL replaced with trimethoprim-sulfamethoxasole. Developed jaundice and severe fluid retention requiring hospitalization 1 month later. ALT 690 U/L, AST 286 U/L, alkaline phosphatase unknown, TB 13.8, INR 1.9. Liver biopsy showed cirrhosis of unknown etiology (4-5 weeks after TEL). Discharged on prednisone. Readmitted 2 weeks later with recurrent increase in LFTs. Died during surgery for perforated duodenal ulcer. *Acute on chronic liver failure with fatal outcome. Unlikely related to 3 doses of TEL. More proximal timing to treatment with trimethoprim-sulfamethoxasole, and recurrence suggests possible underlying chronic disease (eg, autoimmune hepatitis).*	Died
200615076US 80/M	AECB 3 days	Treated in week prior to TEL with amoxicillin 1500 g daily with clinical worsening. Presented with continued fever (102-103°F), chills, sweats, and productive cough. WBC 5.85 with 90% segs, AST 88 U/L, ALT 55 U/L. Begun on ceftriaxone, metronidazole, normal saline (for azotemia) atrovent, and nebulized albuterol. ALT increased to 1200 U/L, AST 800 U/L; alkaline phosphatase 550 U/L and bilirubin 5.4 mg/dL. Abdominal US and viral hepatitis serologies NOS negative. Antibiotics held for suspected viral infection. Day 4, developed hypotension, tachycardia and increased respiratory distress with hypoxia. Course complicated by acidosis and presumed myocardial injury (increased troponin T). Developed multi-organ failure (ARDS, hepatic failure, ARF) and died. *ALF with fatal outcome. Progressive infection/sepsis as likely alternative explanation for events.*	Died
200615086US 49/F	RTI 1 day	History of polycystic kidney disease on chronic ambulatory peritoneal dialysis (CAPD). Two-week history of fever, chills, aches and diarrhoea. Took 1 or 2 doses TEL, but stopped due to nausea and vomiting. ALT 1399 U/L, AST 3510 U/L; subsequent peaks at 2489 U/L and 9112 U/L, respectively. Total bilirubin peak at 3.1 and alkaline phosphatase normal. Developed progressive respiratory failure, DIC and liver failure. Care withdrawn and patient expired in hospice. *ALF with fatal outcome. Unlikely related to 1-2 doses TEL. Events consistent with sepsis in at-risk patient.*	Died

Case ID Age/sex	Indication Duration of treatment	Clinical course/ *sanofi-aventis comment*	Outcome
200616091US 41/F	Lower RTI 5 days	History of 2-3 alcoholic drinks daily. Presented back to MD's office 3 months later with abdominal pain, 11 lb weight gain, icterus, and hepatomegaly. (Course in intervening 3 months unknown to MD, as patient without insurance). Large volume paracentesis (5L) performed. Subsequent re-admission for recurrent fluid overload and variceal GI bleeding. Liver failure with cirrhosis. Lacks intervening clinical symptoms. Cannot exclude acute hepatitis, but cirrhosis more likely secondary to chronic alcoholic liver disease.	Ongoing
200616174US 79/M	Whooping cough 5 days/ 5 days	Consumer report. Previous hospitalization for whooping cough; treated with TEL for persistent symptoms; 2nd course begun 3 weeks later. Developed hepatic failure 1 month later, and died of renal failure. *Lacks adequate information, including medical confirmation.*	Died
200616195US 70/M	Unknown Unknown	Medical history and medications unknown. Patient developed a "liver issue" requiring hospitalization. Subsequently died of liver failure and DIC. Lacks adequate information.	Died
200616365US 60's/M	Unknown Unknown	Elderly man developed sepsis and liver failure 2 months after treatment. Reporting physician assessed liver failure as unrelated to TEL; due to viral sepsis. *Minimal information, but sepsis as possible explanation, as reported.*	Ongoing
200617796US 19/M	CAP Unknown	19 year-old man with history of transposition of great vessels and VSD (both surgically repaired at 5 months). Surgery complicated by postoperative cerebrovascular accident with chronic unilateral weakness and spasticity. Treated with TEL for X-ray confirmed pneumonia. Following treatment, patient with persistent dyspnea and fatigue. Six weeks later, developed nausea, vomiting and RUQ pain. CT with "normal looking liver" and small pleural and pericardial effusions. Treated following month with 5-day course of azithromycin. Admitted to hospital for edema on Day 4, and found to have ALT 356 U/L, AST 350 U/L, TB 4.8 mg/dl, and LDH 504 U/L. ALT/AST peaked 2 days later at 3218 U/L and 5279 U/L, respectively. LDH 4752 U/L and total bilirubin 9.4 mg/dL. Developed progressive hepatic and renal failure, and died of ventricular fibrillation/ pulseless electrical activity on Day 5 of hospitalization. *Delayed time to onset from TEL administration makes association unlikely; closer temporal relationship to azithromycin. While full details lacking, presence of effusions and oedema on admission suggests underlying cardiac contribution (recent cardiac status not reported).*	Died

TEL=telithromycin; M=male; F=female; AECB=acute exacerbation of chronic bronchitis; CAP=community-acquired pneumonia; RTI=respiratory tract infection (unspecified).

Of these 16 cases, 10 cases are heavily confounded or otherwise explained by underlying infection or other concurrent states, 2 lack adequate information to make a causal assessment, and 2 lack a reasonable drug exposure or temporal association. However, an association cannot be excluded in the remaining 2 cases. Based upon the worldwide exposure, ALF would appear to be a rare event reported with telithromycin administration.

Importantly, the hepatic reports, particularly those involving ALF, were discussed extensively with leading hepatic experts external to sanofi-aventis. These experts provided their assessment of the hepatic effects observed with telithromycin in the subsequent discussions with the FDA in June 2006.

6.3.4.2 Summary of postapproval hepatic findings

Close surveillance of hepatic effects has been implemented by sanofi-aventis via the use of intensified case follow-up, and regular reviews of available case data from clinical trials and spontaneous reports. The available preapproval data in 6 million treatment courses administered outside of the US revealed no evidence for severe hepatic injury or liver failure. However, rare reports of severe hepatic injury and hepatic failure have been identified with continued marketed use involving an estimated 28.0 million postmarketing prescriptions both in and outside of the US. Based upon these findings, severe hepatic injury and hepatic failure were added to the USPI in June 2006.

6.3.5 Adverse events of special interest: Cardiac adverse events

Cardiac AEs continued to be monitored in the post-US approval period, with the continued use of the cardiac AESI form for spontaneous report follow-up. Additionally, cardiac events continued to be regularly monitored in the 6-monthly PSURs that were submitted to worldwide agencies, including the FDA.

In March 2006, a review was performed of all events reflecting QT prolongation at the request of the EMEA. In total, 13 cases of QT prolongation were identified. OF these cases, 5 lacked adequate information to establish whether a plausible timing from telithromycin administration existed, and a 6th lacked any QT interval information to confirm the reported ECG abnormality. Two additional cases occurred 3 days and 2 months after the last dose of telithromycin, thereby excluding this drug as a cause given it's 9-hour half-life. While the remaining 5 cases all were confounded by the presence of underlying disease or other administered drugs which may have contributed to the observed events and the lack of positive rechallenge information to establish a probable drug relationship, a change was proposed to the corporate labeling to include QTc prolongation into the labeling. Of note, this change was made more on the potential for such an event to occur, based upon the small effect observed in clinical studies and the observance of such events with related macrolides, rather than the strength of any of the cases received to date. However, it is equally important to note that this assessment did not change the overall benefit-risk for telithromycin when used as directed in the treatment of respiratory tract infections.

A review of the spontaneous reports received through September 15, 2006, reveals isolated reports of torsades de pointes and ventricular fibrillation after 28 million exposures. However, as these various cases of malignant ventricular arrhythmia, reported collectively at rates of approximately 1 case per million exposures, either lack information to establish the diagnosis, are confounded by the coadministration of other medications known to affect cardiac repolarization, or occur in patients with significant underlying cardiac disease or concurrent illness which may otherwise explain the event onset .The overall risk profile remains consistent with the pre-approval cardiovascular risk assessment.

6.3.6 Adverse events of special interest: Visual adverse events

Since May 2003, visual AEs from worldwide postmarketing reports have been followed up using the special AESI form to enhance the collection of standard data regarding the visual events. Items on the AESI form included time to event onset from dosing, descriptive characteristics of the event, impairment of activity, history of visual events or diseases, plus specific questions designed to attempt to elucidate possible mechanistic considerations (see *APPENDIX C: POSTMARKETING SAFETY METHODS*).

In addition, as part of the FDA Approval Letter for telithromycin, sanofi-aventis was required to perform a worldwide surveillance of postmarketing visual AEs reported with telithromycin over the 18 months after launch in the US. The subsequent visual safety update report covered the period from May 2004 through January 2006[5] and was submitted to the FDA on October 2, 2006.

[5] The review period was expanded beyond 18 months to include a "pre-launch" period wherein telithromycin was available for prescription in the US by medical specialists.

This section on postmarketing spontaneous reports of visual AEs presents the cumulative postmarketing report information received from initial EU launch through September 15, 2006. This overview is followed by a summary of the findings from the 18-month visual safety update report, which provides additional characterization of the visual AEs as obtained through these intensified postmarketing activities.

6.3.6.1 Postmarketing safety data related to visual adverse events received by September 15, 2006

Sanofi-aventis has received a cumulative total of 1262 postmarketing spontaneous reports of visual AEs.

Table 66 - Postmarketing spontaneous reports of visual adverse events, received by September 15, 2006

	Worldwide: December 2003		Worldwide: September 2006		US: September 2006		Ex-US: September 2006	
	No. of visual AE reports	Reporting rate (per 10^6 exposures)	No. of visual AE reports	Reporting rate (per 10^6 exposures)	No. of visual AE reports	Reporting rate (per 10^6 exposures)	No. of visual AE reports	Reporting rate (per 10^6 exposures)
All visual AE reports	**371**	**62.2**	**1262**	**45.1**	**347**	**60.0**	**915**	**41.3**
Vision blurred	268	45.0	904	32.3	264	45.7	640	28.9
Visual disturbance	76	12.8	276	9.9	107	18.5	169	7.6
Diplopia	37	6.2	154	5.5	71	12.3	83	3.7
Visual brightness	1	0.2	20	0.7	17	2.9	3	0.1
Photopsia	2	0.3	23	0.8	11	1.9	12	0.5
Accommodation disorder	39	6.5	125	4.5	9	1.6	116	5.2
Visual acuity reduced	16	2.7	36	1.3	7	1.2	29	1.3
Colour blindness	1	0.2	19	0.7	8	1.4	11	0.5
Hallucination	4	0.7	15	0.5	7	1.2	8	0.4
Hallucination, visual	3	0.5	10	0.4	4	0.7	6	0.3
Blindness	2	0.3	7	0.3	2	0.3	5	0.2
Blindness transient	1	0.2	5	0.2	4	0.7	1	<0.1

Includes MedDRA PTs with reporting rates greater than 0.5 reports per million exposures.
AE=adverse event.

In general, the visual AE reporting rate has decreased worldwide. The visual AE reporting rate in the US is similar to that seen worldwide in December 2003 (ie, after some 2 years on the market).

Although the individual coded terms vary somewhat between regions, the visual AE profile between the US and ex-US were generally comparable, with vision blurred, visual disturbance, and diplopia as the most commonly reported events. Although accommodation disturbance was a relatively frequently reported event (diagnosis or symptom) worldwide, visual AEs from the US were reported this way less frequently. Conversely, MedDRA PTs visual brightness, photopsia, and visual brightness were reported almost exclusively in the US. The relative differences in these latter, specific reporting terms, which were explicitly queried on the visual AESI form, may have been stimulated in part by the use of this "Checklist" form (see *AESI checklist for visual adverse events*).

There have been rare postmarketing spontaneous reports of amaurosis or blindness since launch. Most of these cases were either not confirmed as loss of vision because the patients still had functioning vision on follow-up (events appeared more consistent with severe blurred vision) or other causes appeared as the more likely cause of the events than the treatment with telithromycin (eg, temporal arteritis). In only a handful of these cases, an association to telithromycin appeared possible. Of note, however, none of these isolated reports had an ophthalmology examination performed at the time of the event that confirmed the reported transient vision loss. With the exception of the temporal arteritis case, all of these events were fully reversible.

6.3.6.2 Postmarketing commitment: 18-Month visual safety update report

In general, the visual events were comparable to those observed in the clinical trials and consistent with findings from the analyses provided in response to the second FDA Approvable Letter. The most commonly reported events were vision blurred, visual disturbance, diplopia, and accommodation disturbance, events generally consistent with the current USPI for telithromycin. Less frequently, more severe visual disturbances were experienced, including isolated cases reporting a transient vision loss, followed by a gradually resolving visual blurring to full recovery. However, none of the patients was examined at the time of the reported vision loss – in those with subsequent examinations, the assessment could not confirm actual vision loss.

While the day of onset was not reported in 1/3 of all cases, the events occurred most commonly on Day 1 or 2 of treatment (38.9% and 14.3% of all patients with visual AEs, respectively). As shown in the following tables, the timing to onset from dosing was most commonly a few hours after dosing, and the events frequently lasted between 3 and 7 hours, although durations >12 hours after dosing were also seen in approximately 11% of cases.

Table 67 – Visual adverse event time to onset from most recent dose of telithromycin

Time to onset from dosing	Number of visual AEs
< 1 hr	52
1 to < 3 hrs	178
3 to < 7 hrs	52
7 to 12 hrs	8
> 12 hrs	24
Unknown	377

Table 68 – Duration of visual AEs

Duration of visual AE	Number of visual AEs
< 1 hr	27
1 to 3 hrs	60
3 to 7 hrs	90
7 to 12 hrs	61
> 12 hrs	75
Unknown	376

In the vast majority of cases, the events resolved after discontinuation or completion of telithromycin treatment. No consistent pathology was observed in patients seeking a specialist examination (most cases did not report a specialist referral).

The events frequently resulted in some impact in daily activities, most commonly reading, and led to discontinuation in 62% of patients. A single report was received of a motor vehicle accident occurring in a patient with blurred vision; however, it is unclear whether the visual event, or the underlying balance disorder due to the ear infection, was the primary cause for the accident.

No definitive groups at increased risk for the development of visual events could be identified. While visual events were most commonly reported in females and younger (31 to 50 years of age) patients, it is not clear whether reporting biases could account for at least some of the observed differences (ie, it is unclear whether females vs. males are more likely to report a generally mild event, or whether these events are more notable in otherwise active, young patients). A review of medical history and concomitant medication use revealed no patterns of risk.

6.3.7 Adverse events of special interest: Exacerbation of myasthenia gravis

6.3.7.1 Postmarketing safety data related to exacerbation of myasthenia gravis received by September 15, 2006

Given the variable ways in which exacerbation of myasthenia gravis can be reported, the search of the database was performed to identify potential myasthenia gravis cases by identifying: (1) cases in which myasthenia gravis was explicitly reported as the AE (MedDRA HLT "Neuromuscular junction dysfunction"); (2) cases in which the patient had a medical history of myasthenia gravis, irrespective of the reported ADR; and (3) patients reported to be taking neostigmine or pyridostigmine, even if no history of myasthenia gravis was specifically reported. All identified cases were then reviewed to determine which cases reported symptoms consistent with myasthenia gravis exacerbation.

Using this search criteria, which was broader than that used in previous analyses, a total of 60 reports of exacerbation of myasthenia gravis were identified through September 15, 2006; 7 of which had a fatal outcome reported. Of note, 2 of these fatal cases lacked a plausable, temporal relationship to telithromycin administration, as the deaths occurred approximately 2 weeks and 5 weeks after the last dose was given.

Table 69 - Postmarketing spontaneous reports of exacerbation of myasthenia gravis, received by September 15, 2006

	Worldwide 09-Jul-01 to 31-Dec-03		Worldwide 09-Jul-01 to 15-Sep-06		US 15-May-04 to 15-Sep-06		Ex-US 09-Jul-01 to 15-Sep-06	
	No. of MG AE reports	Reporting rate (per 10^6 exposures)	No. of MG AE reports	Reporting rate (per 10^6 exposures)	No. of MG AE reports	Reporting rate (per 10^6 exposures)	No. of MG AE reports	Reporting rate (per 10^6 exposures)
All MG AE reports	19	3.2	60	2.1	29	5.0	31	1.4
Fatal MG AE reports	1	0.2	7	0.3	3	0.5	4	0.2
Myasthenia gravis[a]	8	1.3	30	1.1	19	3.3	11	0.5
Dyspnoea	0	0	13	0.5	9	1.6	4	0.2
Myasthenic syndrome	7	1.2	13	0.5	1	0.2	12	0.5
Asthenia	1	0.2	8	0.3	5	0.9	3	0.1
Myasthenia gravis crisis	1	0.2	3	0.1	2	0.3	1	< 0.1

	Worldwide		Worldwide		US		Ex-US	
	09-Jul-01 to 31-Dec-03		09-Jul-01 to 15-Sep-06		15-May-04 to 15-Sep-06		09-Jul-01 to 15-Sep-06	
Respiratory failure	2	0.3	10	0.4	4	0.7	6	0.3
Respiratory arrest	4	0.7	8	0.3	4	0.7	4	0.2
Dysphagia	4	0.7	7	0.3	3	0.5	4	0.2
Eyelid ptosis	3	0.5	4	0.1	1	0.2	3	0.1
Acute respiratory failure	0	0	1	< 0.1	1	0.2	0	0
Cardiopulmonary failure	1	0.2	1	< 0.1	0	0	1	<0.1
Speech disorder	1	0.2	2	< 0.1	1	0.2	1	<0.1
Dysphonia	2	0.3	3	0.1	0	0	3	0.1
Cardiac arrest	1	0.2	2	< 0.1	0	0	2	<0.1
Respiratory disorder	3	0.5	3	0.1	0	0	3	0.1
Respiratory depression	1	0.2	2	< 0.1	1	0.2	1	<0.1
Respiratory distress	0	0	2	< 0.1	2	0.3	0	0
Diplopia	4	0.7	11	0.4	4	0.7	7	0.3
Death	1	0.2	2	< 0.1	1	0.2	1	<0.1
Muscle fatigue	1	0.2	2	< 0.1	0	0	2	<0.1
Muscular weakness	5	0.8	6	0.2	1	0.2	5	0.2

MG=(exacerbation of) myasthenia gravis; AE=adverse event; PT=Preferred Term.

[a]MedDRA 6.0 PT Myasthenia gravis aggravation changed to PT myasthenia gravis in version 9.0

The reporting rate for myasthenia gravis in the US is higher than the ex-US rate. However, as the US is the most recent major country to launch telithromycin, part of this higher reporting rate may reflect the Weber effect. While a similar peak in reporting was observed in the EU prior to the initial and updated labeling changes in 2003, the issuance of a "Dear Healthcare Professional" Letter at the time of the labeling update led to a rapid decrease in reporting of these events.

6.3.8 Adverse events of special interest: Syncope/loss of consciousness

As discussed previously, syncope was not a signal in the pre-US approval data for telithromycin. Following the approval in the US, however, reports of syncope began to be received from worldwide sources, thereby launching a re-investigation of preclinical and clinical trials findings, and resulting in a labeling change.

6.3.8.1 Preclinical studies

As part of the investigation of the pathogenesis of the syncope/loss of consciousness (LOC) potentially related to telithromycin administration in patients, a tilt study was recently performed in dogs to evaluate the effects of telithromycin on the orthostatic response. The objective of this study was to evaluate, in chronically instrumented conscious mongrel dogs, the effects of a single 15-minute intravenous infusion of telithromycin at 2.4 and 15 mg/kg on the adaptation of cardiovascular parameters to a postural change according to a tilt procedure. These effects were compared to those of azithromycin (15 mg/kg), clarithromycin (15 mg/kg), and levofloxacin (5 mg/kg). Prazosin at 0.01 and 0.03 mg/kg was used as a reference compound for orthostatic hypotension. All treatments were sequentially and randomly given to dogs as 15-minute intravenous infusions with a washout period of at least 3 days between administrations. The tilt procedure consisted of changing for 1 minute the usual horizontal position of the dog on its 4 limbs to a vertical position with the head upwards. The tilt procedure and measurements of the cardiovascular parameters (arterial blood pressure, heart rate and carotid blood flow velocity) were performed 15 minutes before intravenous infusion and 10, 30, and 60 minutes after the beginning of the infusion. Blood sampling was performed before and 7, 14, and 35 minutes after the beginning of the intravenous infusion in all animals. Evaluation of drug plasma exposure was made after telithromycin and levofloxacin infusion.

A 15-minute intravenous infusion of telithromycin at 2.4 and 15 mg/kg had no effects on cardiovascular parameters (arterial blood pressure, heart rate and carotid blood flow) in conscious dogs subjected to a rapid postural change. Relative to exposure levels in man at the therapeutic dose, the dose of 15 mg/kg gave a ratio of approximately 9.7, based on free fractions of drugs. Azithromycin at 15 mg/kg, clarithromycin at 15 mg/kg and levofloxacin at 5 mg/kg, administered under the same conditions and used as comparators, presented no effects on cardiovascular parameters during the tilt procedure. Prazosin, given at 0.01 and 0.03 mg/kg as a 15-minute intravenous infusion and used as a positive reference compound, induced a dose-related orthostatic hypotension associated with an increase in heart rate during the tilt procedure. These results exclude a primary orthostatic effect of telithromycin, but do not exclude potential secondary effects (eg, vasovagal hypotension associated with gastrointestinal symptoms such as nausea and vomiting).

6.3.8.2 Phase I studies

In Phase I studies, a total of 6 AEs of syncope were reported, 2 of which were reported as SAEs. The first serious case, 199710105RUPV, occurred in Study A1018, an open label Phase I trial assessing the acceptability of the aqueous oral telithromycin solution during the pretest study at a dose <1 mg (actual cumulative doses of 92.5 µg). This report involved a 21-year-old man who experienced a vasovagal attack preceded by nausea, vomiting, malaise, and blurred vision. The event occurred 6 hours and 30 minutes after dosing, after the patient had left the testing site. Examination at the emergency department shortly following the event revealed a systolic blood pressure of 90 mmHg and a normal ECG; heart rate was not provided. The Investigator considered the event unrelated to the administration of study medication, citing that it was a hot day and the environmental conditions likely led to the development of vasovagal syncope. In this case, the delayed time to onset (several hours past the expected peak plasma levels) and the recurrence of vasovagal syncope 2 weeks later without drug administration suggests the possibility of an underlying vasovagal reflex tendency in this subject.

In the second case, 200020069EU (Study A1049), a 71-year-old female developed epigastric pain, nausea, and flatulence following a 1600 mg dose. She had a syncopal episode 15 minutes after the onset of gastrointestinal symptoms (4 hours and 35 minutes after dosing), followed by diarrhea. While an ECG was not performed at the time of the event, she was undergoing continuous Holter monitoring at the time of the event. The Holter revealed bradycardia in the period around the time of the event, with heart rate dropping as low as 35 beats per minutes for a brief period (approximately 90 seconds). This event was deemed consistent with a vasovagal reaction by the expert cardiologist involved with the study analysis. The severity/significance of the gastrointestinal complaints may in part be related to the supratherapeutic dosing in this case. Additionally, the underlying aortic stenosis may have made the transient bradycardia poorly tolerated in this particular subject.

6.3.8.3 Phase III studies related to syncope/loss of consciousness

In Phase III randomized controlled studies, 3 out of 2702 subjects (0.1%) in the telithromycin-treated group reported syncopal TEAEs compared to 3 out of 2139 (0.14%) subjects in the comparator-treated group. None of these syncopal TEAEs were considered related to study medication by the Investigator. There were no syncopal TEAEs in Phase III open label studies.

Syncopal events were defined using the PTs Loss of consciousness, depressed level of consciousness and PT terms containing the term ‘syncope’ (see table below).

Table 70 - All syncope/loss of consciousness treatment-emergent adverse events, Phase III randomized controlled studies

Preferred Term	TEL (n=2702)	COMP (n=2139)
Syncope	1	2
Syncope vasovagal	1	1
Loss of consciousness	1	0

TEL=telithromycin; COMP=comparator.

One event in the telithromycin-treated group was considered serious. This involved an 83-year-old male subject who was wheelchair bound and had a syncopal episode on Day 9 of treatment. The subject had multiple comorbid conditions including Parkinson's disease, cardiac failure, respiratory insufficiency, and atrial fibrillation, and the Investigator considered the event unrelated to telithromycin. The narrative for this case is in *Narratives for serious syncope cases* .

The remaining cases were nonserious. Few details were provided. One of the telithromycin cases was clearly vasovagal and occurred while the subject was taking a shower. The second case was described as a "brief" loss of consciousness. In both cases no treatment was required and the subjects recovered without sequelae. The events were considered unrelated by the Investigator.

In Phase I and III there were a total of 12 subjects with syncopal events, 8 of which occurred in telithromycin-treated subjects. Most events appeared to be vasovagal in nature (due to vomiting, posture, etc.) and not considered directly related to telithromycin treatment.

In summary, the overall incidence of syncope was low in Phase III studies and had similar incidence between treatment groups (0.1% in both telithromycin- and comparator-treated groups). Most AE cases were mild or moderate in severity. None of the AE cases were considered related to study medication by the Investigator.

Syncopal events were also analyzed in a previous submission titled *Analysis of a Population of Pooled MedDRA terms for Syncope/Loss of Consciousness or Dizziness-Related Adverse Events in Clinical Trials of Telithromycin*, submitted in March 2005. This analysis used a broader set of pooled MedDRA terms to identify syncopal events and used data from 12 completed Phase III studies as well as Study A3014. This analysis did not reveal a consistent mechanism for syncope/LOC in subjects taking telithromycin or comparator. Available data suggests that the mechanism of syncope/LOC is no different from that observed with other widely prescribed antibiotics and is likely multifactorial. None of these events were associated with a fatal outcome and did not suggest excess risk of higher morbidity.

6.3.8.4 Cumulative review of syncope/loss of consciousness reports (July 2004)

In July 2004, a review of the sanofi-aventis safety database was performed to identify all reports of syncope or LOC. A total of 44 reports were identified, 6 of which were from Japan, giving an

overall reporting rate for syncope of 4.5 reports per million exposures (irrespective of likely association to drug). None of these reports spontaneous cases were reported from the US.

While approximately half of the postmarketing cases lacked adequate information to establish a minimal temporal relationship to drug, the remaining reports could be classified into the following categories: cases confounded by underlying disease states or concomitant medications that might otherwise explain the event (39%); cases with a probable vagal association due to the presence of associated gastrointestinal complaints or dizziness associated with bradycardia and hypotension (29%); cases with suggestive association to telithromycin but unknown mechanism (18%); and cases lacking adequate detail to medically assess the nature of the event (14%). Importantly, there was no information to suggest a cardiac origin for the observed syncope.

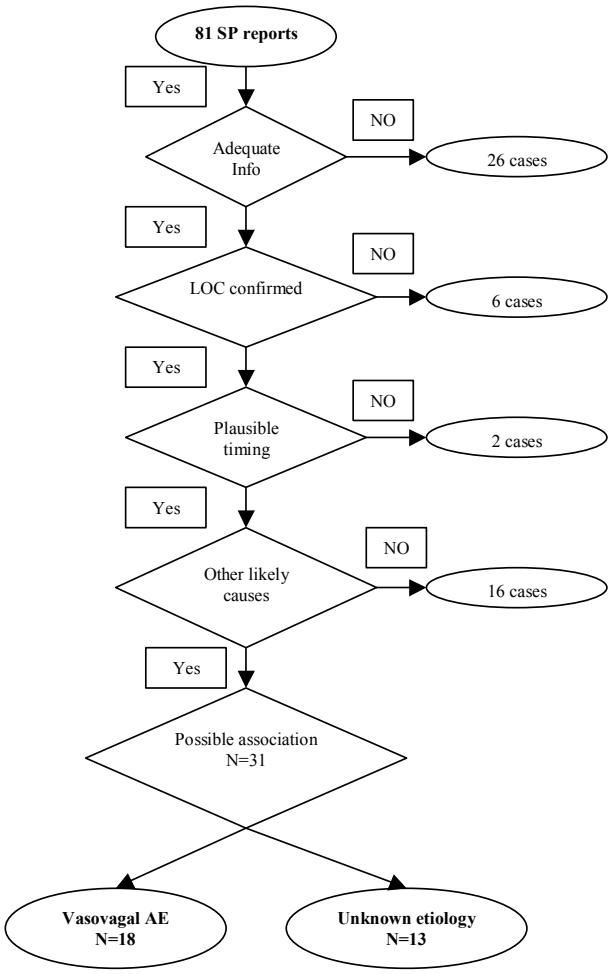
Based upon this assessment, modifications were made to the corporate labeling for telithromycin to include syncope in the AE section.

In Japan, this labeling change, implemented in November 2004, was followed by the posting of the labeling change by the Japanese Ministry of Health, Labor and Welfare (MHLW), which was then reported in the local medical and lay press, as well as a local television news broadcast in December 2004, leading to an additional stimulation of Japanese reports of syncope.

Following the receipt of these additional cases, an updated review was performed on January 18, 2005, in order to assess whether any significant changes had been identified from the new cases and to investigate potential mechanisms for the event. This review revealed 81 spontaneous cases in the database, increasing the reporting rate to 5.8 reports per million exposures.

The findings of the re-assessment were consistent with the prior analysis, despite the increase in cases. As shown below, of the cases with adequate information provided, the largest subgroup of reports appeared consistent with a secondary vasovagal phenomenon.

Figure 2 – Assessment of loss of consciousness reports



In addition, an analysis of the FDA Freedom of Information (FDA FOI) database (extracted from the FDA Adverse Event Reporting System database) was performed, looking at reporting rates of events likely to cause an abrupt "Global impairment" (defined as reports involving syncope, seizure or anaphylaxis) to determine whether there was an increased risk in impairment with telithromycin vs. other marketed antibiotics used in the treatment of RTIs when compared in the first year after launch[6]. While direct comparisons are complicated by potential differences in data collection and coding across industry, timepoint initially on the market, and secular trends in reporting, the results revealed that telithromycin appeared comparable to other prescribed antibiotics with respect to global impairment, although the specific nature of the impairment may vary by drug. Additionally, reporting rates in general were higher for newer antibiotics (moxifloxacin, gatifloxacin, and telithromycin) as compared to the older drugs (clarithromycin, azithromycin, and levofloxacin), likely reflecting an overall increase in AE reporting in recent years (ie, secular trends in reporting).

Table 71 - Reporting rates for adverse events impacting driving in the first year following launch

	TEL	MOX	GAT	CLA	AZI	LEV
"Global impairment"[a] case reporting rate	5.6	33.1	26.4	2.7	1.05	6.5
Anaphylaxis reporting rate	1.6	18.1	5.8	0.4	0.4	2.9
Seizure reporting rate	0.6	7.6	12.4	1.1	0.4	3.1
Syncope reporting rate	3.7	10.3	7.2	1.2	0.3	0.8

TEL=telithromycin; MOX=moxifloxacin; GAT=gatifloxacin; CLA=clarithromycin; AZI=azithromycin; LEV=levofloxacin.
Reporting rate defined as case reports per million prescriptions.
Reporting rates are presented for the period over the first year after launch for each antibiotic.
[a]Global impairment cases are defined as anaphylaxis, seizures, and syncope

6.3.8.5 Postmarketing safety data related to syncope/loss of consciousness received by September 15, 2006

A total of 154 postmarketing spontaneous reports of syncope/LOC have been received by sanofi-aventis in the 5 years that the drug has been on the market worldwide.

[6] This time period after launch, generally seen as the period of most active reporting by physicians, was used so as to minimize the potential Weber effect.

Table 72 – Postmarketing spontaneous reports of syncope/loss of consciousness, received by September 15, 2006

Source	Worldwide		US		Ex-US (excluding Japan)		Japan	
	No. of syncope AE reports	Reporting rate (per 10^6 exposures)	No. of syncope AE reports	Reporting rate (per 10^6 exposures)	No. of syncope AE reports	Reporting rate (per 10^6 exposures)	No. of syncope AE reports	Reporting rate (per 10^6 exposures)
Syncope reports	154	5.5	31	5.4	61	3.2	62	20.5

Estimated exposure, in millions (through August 2006): Worldwide=27.97; US =5.78; ex-US/JP=19.16; Japan=3.03.
Reporting rate presented as cases per million exposures.
AE=adverse event.

The reporting rate for syncope in the US after approximately 2 years on the market (5.4 reports per million exposures) is comparable to the rate seen worldwide in the initial 3 years after launch in the EU, when the first analysis of syncope was performed (5.2 reports per million exposures, as described previously). Consistent with the Weber effect, the worldwide reporting rate has decreased over the 5 years (to 3.2 reports per million exposures excluding Japan). Media coverage is a significant contributor to the high reporting rates seen in Japan, as this issue was not so prominently discussed anywhere else in the world. Other possible reasons for the increased reporting in Japan remain unknown.

Each of the syncopal reports was also reviewed to establish the possible etiology of the event. As with prior assessments, 38% of reports either were confirmed on follow-up to be consistent with LOC, or lacked adequate information to establish a clear etiology; for these cases, a drug etiology cannot be clearly established or excluded. Of the remainder, 21% were consistent with a vasovagal cause, and in 19% the syncope was a complication of another well-defined syndrome, rather than a primary drug-related cause. In 5% of subjects, a possible cardiac arrhythmic cause was suggested; in all of these cases, the patient had a history of cardiovascular disease or risk factors. In the final 17%, the cause of the syncope was unknown and a drug effect could not be excluded.

6.4 POSTAPPROVAL: LABELING CHANGES

6.4.1 Postmarketing surveillance

As growing information from marketed product use is routinely reviewed and analyzed, and as is customary in the evolution of product labeling, sanofi-aventis periodically submitted additional information to Health Authorities and changes were made to the labeling in both the US and EU, based upon information from postmarketing studies or postmarketing surveillance activities.

6.4.2 Labeling history

The US and EU labeling changes resulting from review of postmarketing safety data are summarized in *Post approval labeling modifications, US and EU (01-Apr-04 to 15-Sep-06)* . The current USPI together with the "Dear Healthcare Professional" Letter related to the June 2006 labeling modifications regarding severe hepatic AEs exacerbation of myasthenia gravis with fatal outcome as well as the current EU Summary of Product Characteristics (SPC) dated October 2006 are also provided for reference *APPENDIX G: LABELING*).

The following US labeling modifications occurred following FDA approval of the USPI (April 1, 2004):

- Information regarding dose reduction in patients with severe renal impairment and multiple impairments – added to the CLINICAL PHARMACOLOGY, PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the USPI (submitted as a Prior Approval Labeling Supplement April 9, 2004);
- Clinical safety information on a potential drug-drug interaction with oral anticoagulants – added to PRECAUTIONS section of the USPI (submitted as a Changes Being Effected [CBE-0] Labeling Supplement August 3, 2004);
- Clinical safety information on postmarketing reports of pancreatitis, palpitations, and syncope (transient LOC) – added to the ADVERSE REACTIONS and PRECAUTIONS sections of the USPI (submitted as a CBE-0 November 12, 2004); and
- Clinical safety information on postmarketing reports of severe hepatic AEs and exacerbation of myasthenia gravis with fatal outcome added to the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE REACTIONS sections of the USPI as well as the PPI (submitted and approved as a CBE-0 June 29, 2006).

6.5 EPIDEMIOLOGY

6.5.1 Background

The risk management plan for telithromycin calls for continued monitoring of AESIs to further characterize them in clinical practice environments and to compare their occurrence with other antibiotics that are prescribed for similar indications. As part of the risk management effort, an assessment of the FDA FOI database (an extract of the FDA AERS database obtained via the FOI Act) was done periodically to assess similarities and dissimilarities across these comparable antibiotics. In addition, when a safety signal emerges, sanofi-aventis will perform more rigorous epidemiological investigations with a medical claims database to both quantify the risk, and to compare those risks across comparable drugs.

Thus, the epidemiologic investigations included the following:

- FDA FOI database analyses: The database contains mainly spontaneous reports, which is a good source for detecting signals of rare AEs. Since all methods that may be used to analyze the FDA FOI database have both advantages and disadvantages, sanofi-aventis did both the disproportionality analysis and the reporting rate analysis.
- Retrospective epidemiologic studies using 2 independent medical claims databases in the US. Based on the review of the spontaneous reports and the FDA FOI database analysis, severe hepatic injury was detected as a potential safety signal that should be further confirmed or refuted by epidemiological studies. Therefore, epidemiological studies using medical claims databases were done to evaluate the safety signal.

In addition, in order to capture all ALF cases that may be attributable to telithromycin use, sanofi-aventis requested national liver transplant data from the United Network for Organ Sharing (UNOS)

The details of these investigations are described below.

6.5.2 FDA Freedom of Information database

The FDA FOI database is an extract from the FDA's Adverse Events Reporting System surveillance system, which relies on voluntary reporting of AEs to the FDA by healthcare professionals and consumers, as well as required reporting by pharmaceutical manufactures. The objective of the analysis based on this database was to assess how the various AEs were spontaneously reported with the use of telithromycin in the context of similar reports with the use of other antibiotics in the FDA FOI database. Two types of analyses were undertaken to achieve this objective: (1) relative disproportionality analysis of spontaneous reports for telithromycin and competing antibiotics, as well as for reference, over-the-counter (OTC) medications; (2) evaluation of AESIs for telithromycin and other antibiotics using a reporting rate analysis.

6.5.2.1 Relative disproportionality analysis of spontaneous reports for various antibiotics

The FDA FOI database was queried using QScan® (a proprietary data analyses software by DrugLogic, Reston, VA) to identify disproportionality amongst the spontaneously reported AEs for antibiotics from different classes and OTC medications utilizing the following case definitions (i.e., the numerators):

- The events retained for the analysis were events related to the drug, ie, when the role of drug was coded as 'Suspect'.
- Foreign cases and study cases recorded in the variable "report source" were excluded as per the QScan program, as globally only a subset of these cases are included in this database.
- Duplicate cases, defined as cases with the same manufacturer and control codes, were excluded from the analyses, as per the QScan program.

- The antibiotic agents used as the comparators included Augmentin, cefuroxime, clarithromycin, erythromycin, azithromycin, moxifloxacin, and levofloxacin, which were each evaluated separately.
- Antibiotics known to be non-oral (eg, injectable, topical) were excluded from the analyses.

Two types of background comparators (ie, the internal denominator) were used in the analyses, the full FDA FOI background (ie, all reported events meeting the same case definitions as the numerators, but for all drugs) and all FDA FOI cases with a fatal outcome for all drugs.

Analyses of OTC medications were performed to provide context validation for this type of assessment. The results of these analyses provided AE profiles that are consistent with what is known for these agents (eg, the hepatotoxicity associated with acetaminophen). The results of the disproportionality analyses for OTC medications provided some reassurance of the sensitivity in this type of analyses, despite their overall crudeness. See *APPENDIX H: EPIDEMIOLOGY TABLES* for details and tables.

The MGPS method has been developed and employed by some regulators and some pharmaceutical companies to detect potential safety signals from spontaneous reporting schemes. This statistical method, which is used to identify drug-event combinations that occur more frequently than expected (based upon the overall patterns in the database), has been widely used and is more robust in the instance of small numbers. The statistical parameter used in the MGPS is the Empirical Bayesian Geometric Mean (EBGM), which is the adjusted ratio of the observed vs. expected count for pair-wise combinations. The signal score (EBGM05), defined as the lower 90% confidence interval limit of the EBGM, is used to screen the relative disproportionality indicating safety signals. When used as an active signaling method, threshold of 2 is commonly used, which means for any drug-event combinations that are disproportionate by more than a factor of 2, are referred to as potential signal and require confirmation and assessment. Age, sex, and year of report received by the FDA were adjusted in the MGPS calculation. Overall, the disproportionality analysis represents a sophisticated method to detect events that are observed more than they are expected as a signal detection tool.

In the following analysis sanofi-aventis is using these statistics to profile the antibiotics of interest to demonstrate their disproportionalities within the specified internal denominators, or backgrounds. The resulting displays show the major characteristic safety issues with these antibiotics.

The table below shows the selected disproportionalities that are associated with each of the comparable drugs. It is easily noticeable that these results show the types of safety issues that are known with these drugs. Many of the safety signals that arose for telithromycin in the clinical development program are confirmed in these analyses. A full listing of events on HLTs and PT levels are shown in *APPENDIX H: EPIDEMIOLOGY TABLES* .

For telithromycin, a disproportionality in hepatic AEs was observed, including MedDRA 9.0 HLT "hepatic failure and associated disorders" and "hepatocellular damage and hepatitis NEC". A disproportionality at an HLT level does not necessarily mean that all PTs within that HLT are disproportionate. Details of the disproportionality on HLT and PT levels are shown in the table below and *APPENDIX H: EPIDEMIOLOGY TABLES* . Other antibiotics with a disproportionality in hepatic AEs were Augmentin and erythromycin. Other disproportionalities observed in telithromycin included the HLTs "Visual disorders NEC" and "Neuromuscular junction dysfunction", both of which supported the safety signals raised either in clinical development or in ex-US postmarketing surveillance prior to FDA approval.

The table below also shows that, in general, different antibiotics have different events that appear disproportionate. Augmentin and levofloxacin, for example, are disproportionate in the HLT "Bullous conditions" (including PT "Stevens-Johnson syndrome" and "Toxic epidermal necrolysis"). These very serious events were not found to be disproportionate for telithromycin. "Clostridia infections" were disproportionate for Augmentin, moxifloxacin, cefuroxime, and levofloxacin; and "Anaphylactic responses" was a signal for β-lactams and quinolones. These results clearly suggest differing safety profiles for the antibiotics that are used in similar indications.

Table 73 - Selected disproportionality in the nature of spontaneous reports for different antibiotics using the full FDA FOI database as a background: FDA FOI database through March 2006

High Level Term	Preferred Term	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
Hepatic failure and associated disorders		X	-	-	-	-	-	-	-
	Hepatic failure	X	-	-	-	-	-	-	-
Hepatocellular damage and hepatitis NEC		X	X	-	-	X	-	-	-
	Hepatitis	X	X	-	-	X	-	-	-
	Hepatocellular damage	-	X	-	-	-	-	-	-
	Cytolytic hepatitis	-	X	-	-	-	-	-	-
	Hepatitis fulminant	-	X	-	-	-	-	-	-
Visual disorders NEC		X	-	-	-	-	-	-	-
	Diplopia	X	-	-	-	-	-	-	-
	Vision blurred	X	-	-	-	-	-	-	-
	Photopsia	X	-	-	-	-	-	-	-
	Visual brightness	X	-	-	-	-	-	-	-
	Visual disturbance	X	-	-	-	-	-	-	-
Neuromuscular junction dysfunction		X	-	-	-	-	-	-	-
	Myasthenia gravis	X	-	-	-	-	-	-	-
	Myasthenia gravis crisis	X	-	-	-	-	-	-	-
Bullous conditions		-	X	-	-	-	-	-	X
	Stevens-Johnson syndrome	-	X	-	-	-	X	-	X
	Toxic epidermal necrolysis	-	X	-	-	-	-	-	X
	Dermatitis bullous	-	X	-	-	-	-	-	-
Clostridia infections		-	X	X	-	-	-	X	X

High Level Term	Preferred Term	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
	Clostridium difficile colitis	-	X	X	-	-	-	-	-
	Clostridium colitis	-	X	X	X	-	-	-	X
	Colitis pseudomembranous	-	X	X	-	-	-	X	X
Anaphylactic responses		-	-	-	-	-	-	-	X
	Anaphylactic reaction	-	-	X	-	-	-	X	X
	Anaphylactoid reaction	-	-	-	-	-	-	X	X
	Anaphylactic shock	-	X	X	-	-	-	X	-
Ventricular arrhythmias and cardiac arrest		-	-	-	-	-	-	X	-
	Torsade de pointes	-	-	-	X	X	X	X	X
Muscle, tendon and ligament injuries		-	-	-	-	-	-	X	X
	Tendon rupture	-	-	-	-	-	-	X	X
	Tendon injury	-	-	-	-	-	-	-	X
Hearing losses		-	-	-	X	X	X	-	-
	Deafness	-	-	-	X	X	X	-	-
	Deafness transitory	-	-	-	-	X	-	-	-
Interactions		-	-	-	X	X	X	-	-
	Drug interaction	-	-	-	X	X	X	-	-
Olfactory nerve disorders		X	-	X	X	-	X	X	X
	Anosmia	-	-	-	X	-	X	X	X
	Parosmia	X	-	-	X	-	X	-	-
Sensory abnormalities NEC		-	-	-	X	-	X	-	-
	Ageusia	-	-	X	X	-	X	X	-
	Dysgeusia	X	-	-	X	-	-	-	-

Note: X means a signal for a specific antibiotic; a signal is defined as an EBGM of at least 2.0. Tel=telithromycin; Aug=Augmentin; Cef=cefuroxime; Cla=clarithromycin; Ery=erythromycin; Azi=azithromycin; Mox=moxifloxacin; and Lev=levofloxacin.

The table below shows the selected disproportionalities for cases with fatal outcome in the FDA FOI database. The full FDA FOI database of cases with fatal outcomes was used as a background. All disproportionate results shown on an HLT and PT level are in *APPENDIX H: EPIDEMIOLOGY TABLES* .

A disproportionate finding for "Hepatocellular damage and hepatitis NEC" with a fatal outcome was observed for telithromycin and Augmentin, but not for other antibiotics. On the PT level, however, none of the PTs within the HLT "Hepatocellular damage and hepatitis NEC" was disproportionate for telithromycin. For Augmentin, on the other hand, several PTs with fatal outcome remained disproportionate within the HLT "Hepatocellular damage and hepatitis NEC": "Hepatocellular damage", "Hepatitis", "Cytolytic hepatitis", "Hepatitis acute", "Hepatitis fulminant", and "Hepatitis neonatal" (*APPENDIX H: EPIDEMIOLOGY TABLES*). The HLT "Hepatic therapeutic procedures" was not disproportionate for other antibiotics but moxifloxacin.

Similar to the results in the table above, the table below also shows that different antibiotics had different events that were disproportionate and had fatal outcomes. “Anaphylactic responses”, for example, were found to be disproportionate only for Augmentin and cefuroxime, but not for telithromycin or other antibiotics. “Bullous conditions” were noted to be disproportionate for Augmentin, cefuroxime, and levofloxacin. “Clostridia infections” was disproportionate for Augmentin, cefuroxime, and levofloxacin but not for other antibiotics. A disproportionality for “Hearing losses” was found only for erythromycin and a disproportionality for “Interactions” was found for erythromycin, and azithromycin. It is important to note that an event with a fatal outcome does not necessarily mean that the event caused the death. The death itself may be caused by another event experienced by the same patient. For example, although “Hearing loss” mentioned above has a fatal outcome, the death itself may not be caused by “Hearing loss”, but may be caused by other events reported together with “Hearing loss”.

Briefly, the results showed that there was a disproportionality of reporting of hepatic events in telithromycin, Augmentin and moxifloxacin for the reports with fatal outcomes. Notably, the hepatic events for telithromycin include cases both from the enhanced data submission and from the stimulated reporting that followed the *Annals of Internal Medicine* publication in January 2006, so it must be interpreted with caution. The results also showed disproportionalities of other AEs with fatal outcomes for other antibiotics.

Table 74 - Selected disproportionality in the nature of the spontaneous reports for adverse events with fatal outcomes for different antibiotics using full FDA FOI cases with fatal outcomes as a background: FDA FOI database through March 31, 2006

High Level Term	Preferred Term	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
Hepatic therapeutic procedures		-	-	-	-	-	-	X	-
	Liver transplant	-	-	-	-	-	-	X	-
Hepatocellular damage and hepatitis NEC		X	X	-	-	-	-	-	-
	Hepatocellular damage	-	X	-	-	-	-	-	-
	Hepatitis	-	X	-	-	-	-	-	-
	Cytolytic hepatitis	-	X	-	-	-	-	-	-
	Hepatitis acute	-	X	-	-	-	-	-	-
	Hepatitis fulminant	-	X	-	-	-	-	-	-
	Hepatitis neonatal	-	X	-	-	-	-	-	-
Anaphylactic responses		-	X	X	-	-	-	-	-
	Anaphylactic shock	-	X	-	-	-	-	-	-
	Anaphylactic reaction	-	-	X	-	-	-	-	-
Bullous conditions		-	X	X	-	-	-	-	X
	Stevens-Johnson syndrome	-	X	X	-	-	-	-	X
	Toxic epidermal necrolysis	-	X	-	-	-	-	-	X
	Dermatitis bullous	-	X	-	-	-	-	-	-
Clostridia infections		-	X	X	-	-	-	-	X
	Clostridium colitis	-	X	X	-	X	-	-	X
	Colitis pseudomembranous	-	X	X	-	-	-	-	-
Hearing losses		-	-	-	-	X	-	-	
Interactions		-	-	-	-	X	X	-	-

High Level Term	Preferred Term	Tel	Aug	Cef	Cla	Ery	Azi	Mox	Lev
Hepatic therapeutic procedures		-	-	-	-	-	-	X	-
	Liver transplant	-	-	-	-	-	-	X	-
	Drug interaction	-	-	-	X	X	X	-	-

Note: X means a signal for a specific antibiotic; a signal is defined as an EBGM of at least 2.0. Tel=telithromycin; Aug=Augmentin; Cef=cefuroxime; Cla=clarithromycin; Ery=erythromycin; Azi=azithromycin; Mox=moxifloxacin; and Lev=levofloxacin.

The relative disproportionality analysis (eg, MGPS) based on the FDA FOI database has its strengths. Rare AEs usually cannot be detected until the drug is exposed to a larger heterogeneous patient population during the postmarketing period. The analysis of spontaneous report database using the MGPS can provide us the opportunity to evaluate safety signals that were impossible to be detected from clinical trials that often being conducted in a controlled environment among a selectively small patient population for a shorter duration. The MGPS analysis provides a computational evaluation of the very large database to detect drug safety signals.

Relative disproportionality analysis also has known limitations. The potential limitations include those inherent from the FDA FOI database, such as under-reporting, reporting biases, incomplete, unverified data, a lag time for release of data, and the presence of duplicate reports. Results of our relative disproportionality analysis might not be identical to those performed by others. The observed discrepancies could be partly due to the differences between datasets provided by various vendors (eg, QScan vs. Lincoln) because each vendor uses a different algorithm to eliminate duplicate reports. The FDA FOI dataset also lacks standardization of drug names. Different software vendors use various approaches to retrieve the drug information that could also yield different results.

Several factors can affect the EBGM scores for drugs from a given class. The various scores could be due to differences from the age of the drug, the MedDRA coding practices utilized by different pharmaceutical companies when submitting case reports, the labeling status of a particular event, the postmarketing activities (eg, survey), etc. Stimulated reporting of an AE of interest for a drug due to the publicity or media coverage could also alter the results of the relative disproportionality analysis.

Currently there is a lack of gold standard or guidelines for interpretation of the relative disproportionality results. Because of this limitation, the signals detected from the relative disproportionality analysis do not necessarily reflect a valid and true-positive drug-event association. The findings of the relative disproportionality analysis should not be over-interpreted. No causality can be implied for the hypotheses generated from this relative disproportionality analysis without subsequent detailed clinical case reviews and other investigations (eg, pharmacoepidemiologic study). However, the relative disproportionality analysis does provide an objective and quantitative assessment of risks to help detect potential drug safety signals.

6.5.2.2 Evaluation of adverse events of special interest for telithromycin using reporting rate analysis

The objective of this analysis was to estimate and compare the reporting rates of AEs of special interest for telithromycin with that of selected antibiotics: Augmentin, cefuroxime, clarithromycin, azithromycin, moxifloxacin, and levofloxacin. Adverse events of special interest for telithromycin included hepatic AEs, visual AEs, exacerbation of myasthenia gravis, and syncope/LOC. The case definitions of the AESIs used in this analysis were shown in *APPENDIX H: EPIDEMIOLOGY TABLES* . The reporting rates were calculated based on the FDA FOI data in the first 2 years post launch. Reports of the AESIs for the first 2 years after launch were assessed for all comparator drugs, so as to minimize the effects of time on the market on the reporting rate (i.e. the Weber effect). However, this method does not control for secular trends in AE reporting over time. Data from the FDA FOI database were used to identify cases reported for telithromycin and the comparator drugs for the reporting rate analysis. Although sanofi-aventis intended to include only U.S. spontaneous reports in the investigation, the QScan program may not identify all foreign and/or study cases if the "report source" is not checked as "foreign" and/or "study" in the database, therefore there may be a variable number of foreign/study cases included in the analysis. Exposure was estimated using IMS prescription data for all drugs. The reporting rates of the AESIs per drug are displayed in the table below.

Table 75 - Number of spontaneous reports and reporting rate (reports per million prescriptions) of AESI by antibiotics during the first 2-year period after launch (FDA FOI database as of Q1 2006)

AESI	N / Rate	Tel	Aug	Cef	Cla	Azi	Mox	Lev
Broadly-defined hepatic injury	N	153	19	17	123	31	51	64
	Rate	29.4	5.5	4.0	17.0	10.1	20.5	12.6
Critical hepatic injury	N	30	1	0	7	3	4	11
	Rate	5.8	0.3	0.0	1.0	1.0	1.6	2.2
Visual events	N	330	0	1	47	6	46	54
	Rate	63.3	0.0	0.2	6.5	1.9	18.5	10.7
Myasthenia gravis	N	16	0	0	5	3	7	1
	Rate	3.1	16	0.0	0.7	1.0	2.8	0.2
Syncope	N	81	0	5	20	5	53	13
	Rate	15.5	0.0	1.2	2.8	1.6	21.3	2.6

. Tel=telithromycin; Aug=Augmentin; Cef=cefuroxime; Cla=clarithromycin; Azi=azithromycin; Mox=moxifloxacin; and Lev=levofloxacin

For both broadly defined hepatic events and critical hepatic events, the reporting rate for telithromycin appeared to be higher than the comparator drugs. Part of the higher reporting rate associated with telithromycin therapy might be due to the number of foreign cases that were submitted to the FDA by sanofi-aventis but not identified as such in the FDA FOI database. The misclassification of foreign cases is especially a problem for telithromycin. By FDA regulation (CFR 314.80), only serious and unexpected (that is, not listed in the product label) foreign cases should be reported to the FDA. However, as part of our risk management activities, sanofi-aventis has been supplementing the normal US reporting requirements to FDA by additionally providing all foreign serious hepatic AEs (both listed and unlisted) to FDA. Thus, the FDA FOI database may contain disproportionately a higher number of foreign hepatic AEs for telithromycin. In addition, it should be noted that prior to launch, telithromycin was subject to increased publicity of hepatic events after the 2 FDA AIDAC meetings, and post-launch there has been stimulated reporting following the publication of the 3 case reports in the Annals article in January 2006. Sanofi-aventis also employed an augmented postmarketing surveillance program for hepatic events including the use of an AESI form, potentially leading to possible focus or enhanced reporting of these events.

Moxifloxacin had higher reporting rates for syncope than other antibiotics, followed by telithromycin. The reporting rates for visual AEs and myasthenia gravis AEs appeared to be higher for telithromycin than for other antibiotics.

It is important to stress that these reporting rates are calculated based upon reported terms and do not reflect confirmed reports. Furthermore, reporting rates must be interpreted with extreme caution, due to varying times on the market and differences in secular trends in reporting over the years in which the various drugs were granted marketing authorization.

Of note, the total number of spontaneous domestic AE reports included in the FDA FOI database has doubled from the year 2000 to 2005. Although drug use in the general US population has increased as well during the same time period, it does not account for the majority of the increase in AE reporting in the past 5 years. In fact, according to IMS Health and the National Association of Chain Drug Stores, the number of prescription drugs increased about 14% from 2000 to 2004. Therefore, the data indicates a general trend of a significant increase in spontaneous AE reporting to the FDA in the past 5 years. All antibiotics included in the investigation, except telithromycin, were marketed in the US prior to the year 2000. Since telithromycin was the only antibiotic in this comparison that was marketed after the year 2000, the timing for the product launch may account for some of the differences in the reporting rates between telithromycin and other antibiotics.

For all these reasons, sanofi-aventis considers these and all reporting rate analyses to be the least reliable and least rigorous of those analyses that were being presented in this postmarketing section.

6.5.2.3 Summary of assessments using the FDA FOI database

Two different analyses were performed (a disproportional analysis and reporting rate analysis) to assess potential differences in spontaneous reporting for telithromycin vs. other commonly prescribed antibiotics with similar indications. The MGPS/disproportionality method showed that hepatic AEs, visual AEs, and exacerbation of myasthenia gravis may be associated with telithromycin therapy. All of these signals were identified preapproval in the US, and have been monitored closely since approval. Known safety signals for other antibiotics were confirmed as well, including anaphylaxis for Augmentin, moxifloxacin, cefuroxime, and levofloxacin; bullous condition (Stevens-Johnson syndrome and toxic epidermal necrolysis) for Augmentin and levofloxacin; clostridia infections (including colitis) for Augmentin, moxifloxacin, cefuroxime, and levofloxacin; hearing losses and interactions (with other drug) for erythromycin, azithromycin, and clarithromycin; and ventricular arrhythmias and cardiac arrest, including torsades de pointes, and tendon disorders for moxifloxacin. This analyses when conducted on selected OTC drugs, showed the expected disproportionalities for hepatic AEs as safety signals for acetaminophen and thus validated these types of analyses.

The reporting rate of critical hepatic events appeared to be higher in association with telithromycin use than with other antibiotics, but the secular trend of increased spontaneous AE reporting in recent years and nature of the AERS databases may partly explain the differences. Reporting rates of visual events were higher in telithromycin than in other antibiotics.

Nonetheless, this disproportionality analysis is generally used as a signal detection tool. Reporting rate analysis is only a gross instrument to generate hypothesis. Signals detected from spontaneous reports using either method is not an evidence of an association, but rather raise a safety issue that requires further clinical and epidemiological investigation.

6.5.3 Epidemiologic studies using 2 independent US data sources

As described above in the spontaneous report analysis, the signal of hepatic injury remains unclear. Risk of a rare event is difficult to be measured by any type of analysis of the Phase III studies. The hypothesis of no difference in severe liver injury among users of antibiotics for similar indications cannot be tested by spontaneous report analysis.

In order to evaluate the association between telithromycin use and severe hepatic injury, we conducted studies based on systematic datasets that have complete capture of medical service data including severe hepatic injury events in a well-defined population. Therefore, separate pharmacoepidemiologic studies evaluating the risk of severe hepatic injury have been implemented. These studies are designed to better evaluate the risk of severe hepatic injury following telithromycin use and are outlined below.

The primary objective of these investigations was to conduct a population-based pharmacoepidemiologic study to evaluate the risk of severe hepatic injury among telithromycin users, and to compare the risk estimates with those following use of comparator antibiotics with similar indications. Due to the nature of observational studies, the effects of bias, confounding, and effect modification cannot be ignored. Pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. However, agreement of the results from more than one study helps to provide reassurance that the observed results are robust. Therefore, a pharmacoepidemiologic study was proposed based on the 2 largest independent data sources identified in the US: the PHARMetrics Integrated Outcome Database and the Ingenix proprietary research database.

6.5.3.1 PHARMetrics Integrated Outcome Database

A retrospective cohort study was designed to evaluate the risk of severe hepatic injury requiring hospitalization among users of telithromycin, compared with users of other comparator antibiotics with similar indications. The study report is included in *APPENDIX H: EPIDEMIOLOGY TABLES* . Comparator antibiotic agents included drugs in the class of macrolide, penicillin, and quinolone antibiotics. All patients were required to be 18 years of age or older and have at least one year of claims history prior to dispensing of the antibiotic to be eligible for this study. The risk window for identification of severe hepatic injury was defined as the 40-day period from the start date of the anti-infective claim. All eligible patients were followed for the occurrence of a hospitalization for severe hepatic injury during the risk window. Severe hepatic injury was defined as a diagnosis of acute or subacute necrosis of the liver including acute hepatic failure (ICD-9 570), hepatic coma (ICD-9 572.2), toxic (non-infectious) hepatitis (ICD-9 573.3), or a procedure code for liver transplant (any of the listed CPT codes 47135, 47136, 47140, 47141, 47142, or 00796). The primary analysis was the calculation of the estimated risk of severe hepatic injury requiring hospitalization following the use of telithromycin or comparable antibiotics.

Between July 1, 2004 and December 31, 2005, the following users were identified from the PHARMetrics database that met the pre-specified study criteria and had had at least 1 claim: 124,413 (telithromycin), 93,871 (Augmentin), 202,456 (clarithromycin), and 111,336 (moxifloxaxin). The baseline characteristics (eg, age, diagnosis associated with claims 14 days prior to and including the start date of each anti-infective agent dispensing, percentage of users with a prior history of liver disease) were similar between telithromycin users and users of comparator antibiotics. Moxifloxacin users in general were slightly older and had a slightly higher percentage of users with comorbid diseases. The risk of severe hepatic injury requiring hospitalization in telithromycin, Augmentin, clarithromycin, and moxifloxacin was 8.01 (95% CI [3.28, 12.75]; 5.83 [1.17, 10.50]; 11.65 [7.17, 16.13]; and 16.93 [9.69, 24.16] cases per 100,000 prescriptions, respectively.

To evaluate potential confounding by prior history of hepatic injury, the risk (prescription-level) of severe hepatic injury requiring hospitalization for each antibiotic agent, stratified by prior history of hepatic injury, was calculated (see table below). As some patients may have had more than one prescription, the numbers in the table differ slightly from the numbers above. Consistent with the results mentioned above (nonstratified analyses), among patients with no prior history of hepatic injury, the risk of severe hepatic injury requiring hospitalization among telithromycin users was within the range of the other antibiotics, with Augmentin having the lowest risk and moxifloxacin having the highest risk. For all four anti-infective agents, the risk of severe hospitalized hepatic injury appeared to be greater among patients with a history of hepatic disease and seemed to be higher among patients prescribed clarithromycin and moxifloxacin

Table 76 - Risk of severe hepatic injury requiring hospitalization (cases per 100,000 prescriptions) stratified by prior history of hepatic injury: PHARMetrics Database

Without a prior history of liver disorder				
	Telithromycin	Augmentin	Clarithromycin	Moxifloxacin
Number of events	8	5	18	16
Number of prescriptions	134613	100737	218063	120882
Risk (95% CI)	5.94 (1.82-10.06)	4.96 (0.61-9.31)	8.25 (4.44-12.07)	13.24 (6.75 –19.72)
With a prior history of liver disorder				
	Telithromycin	Augmentin	Clarithromycin	Moxifloxacin
Number of events	3	1	8	5
Number of prescriptions	2686	2116	5032	3196
Risk (95% CI)	111.69 (0-238.08)	47.26 (0-139.89)	158.98 (48.81-269.15)	156.45 (19.31-293.58)

Generalized estimating equation (GEE) models were used to evaluate the potential association between telithromycin use and severe hepatic injury requiring hospitalization adjusted for age, gender, Charlson Index, and prior history of hepatic disorders. The GEE method was used to handle dependent observations from the same patient. “Augmentin users” was treated as the reference group in the GEE models. After adjusting for age, gender, Charlson Index, and prior history of hepatic disorders in the GEE models, there was no increased risk of severe hepatic injury requiring hospitalization associated with telithromycin use compared to other antibiotics with similar indications.

The crude risks of severe hepatic injury requiring hospitalization among antibiotics users from the current analysis was between 5.8 to 16.9 cases per 100,000 prescriptions. If we conservatively assume a background incidence rate of severe hepatic injury as five cases per 100,000 prescriptions, with an alpha level of 5%, the current study has a power of 94% to rule out a 4-fold increase in risk of severe hepatic injury requiring hospitalization for patients following use of telithromycin.

6.5.3.2 Ingenix Proprietary Research Database

It was originally planned and agreed to apply the same study protocol (as described above for the PHARMetrics database analysis) to the Ingenix database. A preliminary exploration was conducted using the i3 Aperio system, an active drug safety surveillance system derived from the Ingenix proprietary research database, to estimate the number of cases that were present in the Ingenix proprietary database. No severe hepatic injury case that met the prespecified criteria (ie, an occurrence of a hospitalization for severe hepatic injury as specified in Section 6.5.3.1 during the 40-day risk window) was identified in the Ingenix proprietary research database. Therefore the original study protocol could only be conducted using the PHARMetrics data and not the Ingenix database. Instead, a separate study protocol was prepared by i3 Drug Safety to focus on the validation of the potential cases of severe liver injuries. Thus, the Ingenix study complemented the findings of the PHARMetrics study where medical record access is not feasible.

The potential cases of severe hepatic injury that were selected for medical record review were identified not only through data from the primary inpatient diagnoses as originally planned with the 2 database analyses, but also from other inpatient diagnoses, the outpatient diagnoses, as well as diagnoses made during emergency room visits. In addition, the follow-up period criteria for case identification were relaxed to increase the sensitivity of detecting severe liver injuries in the Ingenix study. Any cases of hepatic injury that were identified within 1- year period following either telithromycin or clarithromycin use were selected for validation by medical record review. However, the medical record review was focused only on cases with a diagnosis code of hepatic coma (ICD-9 572.2) or acute/subacute necrosis of the liver including acute hepatic failure (ICD-9 570), a subset of the diagnosis codes used in the PHARMetrics study. Following medical record review, liver injury events with an onset within 60 days of last drug use were pre-specified as the outcome events of interest for the study.

The preliminary results of the medical record review of the Ingenix study has found no case of ALF associated with telithromycin use. There were 2 cases of ALF confirmed in the 60-day window following clarithromycin use. I3 drug safety is currently evaluating all types of hepatic injury. The analysis of this study is still ongoing. Sanofi-aventis expects to receive the study report before the advisory committee meeting.

The current preliminary findings of the Ingenix study showed that severe hepatic injury is a very rare event among patients taking either telithromycin or clarithromycin.

6.5.3.3 Summary of epidemiological studies using medical claim databases

The results from the epidemiologic study using PHARMetrics indicate that, compared to other antibiotics with similar indications, there is no evidence of an elevated risk of severe hepatic injury associated with telithromycin use. The Ingenix study confirmed that the risk of severe hepatic injuries is very rare, with no case of ALF identified within 60 days following prescription of telithromycin in more than 100,000 patients.

6.5.3.4 Liver transplantation data from the United Network for Organ Sharing

Liver transplantation data were requested by sanofi-aventis to further investigate the frequency of liver failure requiring liver transplant due to drug toxicity. The data were provided by the UNOS. The UNOS is a national network consisting over 250 centers that are divided into 11 geographic regions nationwide in the US. It contains data on every single solid organ transplant event occurring in the US. Data are collected on many aspects of a patient's health, medications, ability to pay, graft survival, risk factors pre- and post-transplant, and etc. The physicians from each center decide which drugs to enter as the cause of organ failure. There is no predefined algorithm/sequence for entering the suspect drug.

Search was performed to look for any drugs mentioned in the text fields where member centers enter their data. After the drugs were isolated from other causes of liver failure they were classified into categories (eg, Tylenol, methotrexate).

Between the year 2004 and October 27, 2006, there were 316 patients undergoing liver transplantation and 328 patients on the waiting list due to drug toxicity. About 69%of the 316 patients who underwent liver transplantation fell under the category of 'alcohol' (N = 115) or 'Tylenol' (N= 104). Of the 328 patients on the waiting list for liver transplantation, 99 were categorized as 'alcohol' and 176 patients were categorized as 'Tylenol'. Among the 316 patients who underwent liver transplantation, 14 transplant cases attributed to 12 anti-infective agents since 2004. One of the 14 cases was attributed to telithromycin. Also, 4 of the 14 cases were specifically attributed to comparators used in sanofi-aventis's FDA FOI database analyses including 1 case each for amoxicillin-clavulanate, clarithromycin, levofloxacin and moxifloxacin. Other anti-infective agents cited as causative drug for transplant cases since 2004 include trimethoprim-sulfamethoxazole (2 cases), minocycline (2 cases), amoxicillin (1 case), ciprofloxacin (1 case), macrodantoin (1 case), nitrofurantoin (1 case), and dapsone (1 case). None of the 328 patients on the waiting list had liver failure due to telithromycin.

6.5.4 Conclusions of epidemiology analysis

Results from the FDA FOI database indicate signals of hepatic AEs, visual AEs, and exacerbation of myasthenia gravis in association with telithromycin use, while other safety signals were associated with other antibiotics. It is important to stress that results from the spontaneous reports signal detection analyses should be interpreted with caution because the reports are not confirmed and the biased nature of spontaneous reporting. Results from a more rigorous method for evaluation of safety signals, the epidemiologic study using PHARMetrics database, indicate that, compared to other antibiotics, there is no evidence of an increased risk of severe hepatic injury in telithromycin compared to antibiotics with similar indications. The data from both the preliminary Ingenix medical record review and the UNOS confirmed that ALF is a rare event following telithromycin use.

7 BENEFIT/RISK ASSESSMENT

7.1 INTRODUCTION

Telithromycin is the first of a new class of antibacterial agents, the ketolides, developed for the treatment of community-acquired RTIs. In the US, telithromycin is approved for 3 indications: CAP, AECB, and ABS.

Community-acquired RTIs are among the most frequent infectious diseases encountered in the ambulatory care setting and are associated with significant morbidity. The key organisms associated with these infections include common bacterial pathogens such as *S. pneumoniae* (including penicillin- and/or macrolide-resistant strains), *H. influenzae*, and *M. catarrhalis* (including their β-lactamase-producing strains), *S. aureus*, and *S. pyogenes*. In addition, atypical and intracellular pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* represent important causes of CAP that may be clinically refractory to the β-lactam antibiotics.

7.2 MEDICAL NEED

Community-acquired RTIs are among the most frequent infectious diseases encountered in outpatients, with an estimated US incidence of ~5 million, 9 million, and 30 million cases per year for CAP, AECB, and ABS, respectively. These infections are associated with significant morbidity and, in the case of CAP and to a lesser extent AECB, a risk of increased mortality.

In the US, CAP, AECB, and ABS are most often treated empirically with the following antibiotics: β-lactams (eg, amoxicillin, amoxicillin-clavulanic acid, oral cephalosporins), macrolides (eg, clarithromycin, azithromycin, and erythromycin), ketolides (telithromycin), and quinolones (eg, levofloxacin, moxifloxacin). To a lesser extent, tetracyclines, trimethoprim-sulfamethoxazole, and clindamycin are also used in the treatment of RTIs.

Each of the antibiotics currently used in the treatment of RTIs has at least 1 of the following limitations, thus creating an ongoing medical need for therapeutic options:

- Decreased in vitro activity against key RTI pathogens, thereby exposing patients to an increased risk of complications due to inadequately treated infection (eg, macrolides, β-lactams)
  - In RTIs, the prevalence of penicillin-resistant *S. pneumoniae* is stable at ~15%, the prevalence of macrolide-resistant *S. pneumoniae* is ~25%, and the prevalence of MDRSP (ie, resistance to >2 classes of antibiotics) is ~30%. According to the CDC, in invasive streptococcal infections, the prevalence of penicillin-resistant *S. pneumoniae* is ~9%, the prevalence of macrolide-resistant *S. pneumoniae* is ~19.4%. The estimated case fatality rate for invasive infections due to *S. pneumoniae* rises from 1.1% for patients in the 35-49 year old age range to >6% for patients older than 65 years of age;
  - The widespread use of the anti-pneumococcal vaccine has been associated with an overall decrease in the number of invasive *S. pneumoniae* infections and antibiotic resistance. In the US, *S. pneumoniae* strains with high-level resistance – including those serotypes that are not covered by the current vaccine – have recently emerged, evoking a possible future escape from the beneficial impact of the vaccine; and
  - The clinical relevance of antibiotic resistance has not been established in all populations, but several recent studies seem to concur, providing indirect evidence that macrolide resistance may be associated with a higher rate of treatment failure in CAP.
- Collateral effects on nonrespiratory tract pathogens from the normal antimicrobial flora when the antibiotic spectrum is not specifically targeted to RTI pathogens (eg, fluoroquinolones, β-lactams). This may:
  - Result in the selection of antibiotic resistance in nonrespiratory pathogens (eg, enteric Gram-negative bacteria), which decreases the value of these antibiotics in infections due to these pathogens and leads to an increase in the use of broader-spectrum antibiotics that are normally reserved for more severe infections or
  - Favor the overgrowth of other bacteria such as *C. difficile*. *Clostridium difficile* strains, "hyperproducers" of toxins and associated with fluoroquinolone resistance, have recently been associated with an increase in pseudomembranous colitis infections of high morbidity.

7.3 BENEFITS

7.3.1 Telithromycin is active against key respiratory bacterial pathogens

In contrast to macrolides, telithromycin binds tightly to 2 sites on the ribosome, domains II and V of the 23S rRNA on the 50S subunit. The affinity of telithromycin for the 50S ribosomal subunit is ten-fold higher than that of erythromycin. Because of its novel mechanism of action, telithromycin is active against bacteria that harbor a macrolide-lincosamide-streptogramin$_B$ (MLS_B)-inducible type of resistance and does not induce MLS_B resistance in vitro. It is active in vitro against *S. pneumoniae* resistant to the macrolides via an efflux mechanism, is 2-4 times more active than clarithromycin, and is 4-8 times more active than azithromycin against Gram-positive cocci susceptible to macrolides. Unlike most macrolides, telithromycin also demonstrates concentration-dependent bactericidal activity against *S. pneumoniae*. Occurrence of *S. pneumoniae* resistance to telithromycin is less than 1%. Telithromycin remains active in vitro against strains of *S. pneumoniae* with multiple mechanisms of resistance to macrolides, ie, *erm*(B) + *mef*(A); these strains are associated with high-level macrolide resistance and even β-lactam resistance, and have been recently on the rise in the US.

Overall, the antibacterial spectrum of telithromycin is targeted against RTI pathogens: *S. pneumoniae* (including multidrug-resistant strains), *H. influenzae* (including β-lactamase-positive strains), *M. catarrhalis* (including ß-lactamase-positive strains), *S. pyogenes* (susceptible to macrolides or resistant to macrolides by the presence of *mef* or *erm*TR genes), *S. aureus* (susceptible to macrolides or resistant to macrolides by an inducible mechanism), and atypical and intracellular pathogens *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. Telithromycin's weak in vitro activity against enteric Gram-negative rods makes it less likely than fluoroquinolones or β-lactams to contribute to the development of clinically significant antibiotic resistance among enteric pathogens of concern.

7.3.2 Pharmacokinetic profile of telithromycin

Telithromycin's half-life of approximately 10 hours and extensive distribution in human tissue permits once daily dosing. Relative to macrolides such as azithromycin, telithromycin achieves high mean maximum plasma concentrations (Cmax of approximately 2.27 µg/mL) after repeated doses of 800 mg once daily. Telithromycin achieves useful concentrations in pulmonary epithelial lining fluid. Pulmonary epithelial lining fluid levels achieved by telithromycin are higher than the MIC_{90} for *S. pneumoniae* (MIC_{90}=1 µg/mL, 15 times higher), *H. influenzae* (MIC_{90}=4 µg/mL, 4 times higher), and *M. catarrhalis* (MIC_{90}=0.25 µg/mL, 60 times higher). Food has no significant effect on the rate or extent at which telithromycin is absorbed.

Telithromycin is eliminated by multiple pathways. Telithromycin excreted unchanged in urine and in the feces and after metabolism by both CYP450-dependent and CYP450-independent pathways. Studies have shown that the renal pathway is compensatory when metabolism is impaired. Therefore, there is limited risk for excessive drug exposure when 1 of the pathways is impaired due to hepatic insufficiency, mild to moderate renal insufficiency, or drugs that inhibit the CYP450 3A4 pathway.

Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system and is a mild inhibitor of CYP2D6.

7.3.3 Clinical outcomes

7.3.3.1 Community-acquired pneumonia

Among telithromycin-treated clinical trial subjects with CAP, the overall cure rate for telithromycin is 93.7% (312/333) for *S. pneumoniae*. In Phase III double-blind randomized controlled CAP studies the cure rates were 93.6% (73/78) for *S. pneumoniae.* The overall cure rates in the Phase III studies were 87.9% (29/33) for macrolide-resistant *S. pneumoniae*, 87.0% (20/23) for penicillin-resistant *S. pneumoniae*, 91.9% (34/37) for MDRSP, and 88.2% (67/76) for pneumococcal bacteremia. In the same studies, the overall cure rates were also satisfactory for *H. influenzae (*89.3% 226/253), *M. catarrhalis (*85.5%, 47/55), and the atypical pathogens *M. pneumoniae* (*97.1*%, 33/34) and *C. pneumoniae* (94.3%, 33/35).

Phase IV studies confirmed the high clinical efficacy of telithromycin in CAP, with a trend for superior efficacy in 1 study where telithromycin was tested against the locally prescribed regimen in countries with high levels of antibiotic resistance.

7.3.3.2 Acute exacerbation of chronic bronchitis and acute bacterial sinusitis

The bacterial pathogens for the AECB and ABS indications are similar to those for CAP. Among telithromycin-treated clinical trial subjects with AECB, the overall cure rates for bacteriologically proven disease is 81.5% (22/27) for *S. pneumoniae*, 73.3% (44/60) for *H. influenzae*, and 93.1% (27/29) for *M. catarrhalis*. Among telithromycin-treated clinical trial subjects with ABS, the cure rates for bacteriologically proven disease is 87.1 % (27/31) for *S. pneumoniae*, 82.4% (28/34) for *H. influenzae*, 93.1% (27/29) for *C. pneumoniae*, 7/7 for *M. catarrhalis*, and 8/8 for *S. aureus*.

Phase IV data also showed a potential benefit of telithromycin in the population of AECB patients with infection due to penicillin- or macrolide-resistant *S. pneumoniae*, in eradicating resistant strains. In subjects with ABS, evaluation of time to symptom resolution showed that telithromycin was comparable to moxifloxacin and potentially better than amoxicillin-clavulanic acid, both recognized as highly effective antibiotic treatments in this indication.

Therefore, the clinically demonstrated activity of telithromycin for the CAP indication is also confirmed for the AECB and ABS indications with 5 days of treatment.

7.4 RISKS

The estimated worldwide marketed exposure to telithromycin through August 31, 2006, is 28 million courses of treatment. The overall AE profile of telithromycin is comparable to commonly prescribed antibiotics for community acquired RTIs, including β-lactams, macrolides, and fluoroquinolones.

7.4.1 Clinical trial safety data

The AE profile in Phase III pivotal efficacy and safety studies has been examined in 4780 telithromycin-treated and 2139 comparator-treated subjects. In addition, 12,159 subjects in the telithromycin treatment group of Study A3014 were safety evaluable. FDA raised concerns about good clinical practice violations at several clinical study sites; they did not rely on Study A3014 as a basis for approval. Information on this study is not referenced in the US labeling, and the data are not included in the Phase III safety database information provided in this document.

In clinical trials, the vast majority of TEAEs associated with telithromycin are of mild to moderate intensity and are related to the gastrointestinal tract, with diarrhea being the most common AE. The incidence of SAEs was similar in both telithromycin and comparator groups. Discontinuation rates were low and similar to those of comparators, and were most commonly associated with AEs related to the gastrointestinal tract.

Preclinical data and known class drug effects for macrolides suggested hepatic and cardiac AEs as areas for increased postmarketing surveillance. These topics were monitored closely throughout product development.

Evaluation of hepatic effects in all Phase III studies included detailed review of hepatic laboratory values and hepatic AEs. Hepatic laboratory values (such as combined total bilirubin and ALT increases and CNALVs for ALT and AST) were balanced between telithromycin and comparators, and the incidence of hepatic AEs was similar between treatment groups. No cases of drug-related fulminant hepatitis, hepatic failure, liver transplant, or primary hepatic death were observed in Phase III investigations

Extensive ECG and AE analyses in Phase I and Phase III studies demonstrated no significant difference from comparators. At therapeutic dose, electrocardiographic analyses in the clinical development program revealed a minimal increase of 1.5 milliseconds in the QTc interval (corrected for heart rate by the Bazett formula). QTc outlier values were uncommon and similar in frequency to those seen with clarithromycin and non-macrolide antibiotics. No excess in risk for significant QTc interval prolongation was noted, even in at-risk populations. Similarly, cardiac AEs and death rates are also comparable between telithromycin and comparators.

During clinical trials, the review of clinical AE data in controlled studies revealed the incidence of visual TEAEs was higher in the telithromycin-treated than in the comparator-treated groups (1.1% vs. 0.4%). The visual AEs most commonly were described as blurred vision, which was generally mild or moderate in severity, transient, and reversible. The effect typically had a short duration (2 to 3 hours). This AE was further evaluated through 2 clinical pharmacology studies to investigate potential mechanisms. Based on the clinical descriptions and objective findings from these 2 studies, the mechanism for the reported blurred vision is most consistent with a transient effect on the ciliary body delaying relaxation of the lens and hence accommodation. Importantly, potentially more serious and irreversible causes, such as retinal toxicity or angle closure glaucoma, have been excluded.

Overall, Phase IV safety data did not reveal any new safety signals as compared to Phase III studies.

Telithromycin being an inhibitor of CYP3A4 increases the plasma levels of compounds metabolized by this cytochrome P450; therefore, caution should be exercised when using these compounds concomitantly with telithromycin although the duration of treatment with telithromycin is rather short. Simvastatin, lovastatin, or atorvastatin should be avoided in patients receiving telithromycin. If telithromycin is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be stopped during the course of telithromycin treatment. Studies have also clarified that telithromycin is eliminated by multiple pathways, both as unchanged drug and after metabolism by CYP450-dependent and CYP450-independent pathways. Therefore, there is limited risk for excessive drug exposure when one of the pathways is impaired either due to mild to moderate renal insufficiency, hepatic insufficiency, or drugs that inhibit the CYP3A4 pathway.

7.4.2 Postmarketing safety data

The AE profile of telithromycin, including rare events of concern with previously approved antibiotics, has been thoroughly examined with clinical trials, intensified monitoring, and postmarketing surveillance.

Postmarketing safety data collection and analysis have continued to regularly review these safety signals on an ongoing basis, as well as search for new relevant safety information in order to refine characterization of the known AE profile and to detect rare previously unidentified risks. These activities, based on worldwide spontaneous reporting, epidemiologic analyses, and periodic signal detection approaches, have confirmed the safety profile of telithromycin characterized during the clinical development program. Postmarketing safety data from an estimated marketed exposure to telithromycin of 28 million courses of treatment in countries where telithromycin is currently marketed (as of August 31, 2006) supports the safety profile observed in clinical trials. Among the most commonly reported AEs are gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, abdominal pain), visual events, headache, dizziness, and allergic events (eg, rash, urticaria).

The postmarketing data have also identified some new important safety information for rare AEs. Ex-US (ie, EU) postmarketing spontaneous reports received prior to FDA approval, identified reports of exacerbation of myasthenia gravis in patients receiving telithromycin that led to a labeling modification. Exacerbations of myasthenia gravis exacerbations also have been reported in association with several other classes of drugs, including anesthetics, antibiotics, anticonvulsants, cardiovascular drugs, and psychotropics [Barrons, 1997]. Among the antibiotics, implicated drugs include the macrolides, β-lactams, fluoroquinolones, and aminoglycosides [Wittbrodt, 1997].

Similarly, several months after FDA approval, worldwide reports of syncope led to another product information update. Detailed analysis of the reports suggested that some of the reports could be linked to a secondary vasovagal mechanism occurring in conjunction with gastrointestinal AEs, which were the most common AE noted in clinical trials. There was no evidence for a cardiac arrhythmic etiology for syncope, consistent with prior clinical study QTc analyses, but the labeling was updated to highlight the risk of syncope particularly in patients experiencing gastrointestinal symptoms. Other ADRs (ie, angioedema, anaphylaxis, pancreatitis, and palpitations) that have been reported have also been added to the labeling for telithromycin.

Particular attention has been given to the evaluation of postmarketing reports of hepatic, cardiac, and visual AEs.

Reports of hepatic AEs with telithromycin most commonly include asymptomatic transaminase elevations or mild to moderate clinical liver injury. These hepatic AEs were described in the initial US labeling and have been reinforced with respect to rare severe events in the current US labeling for telithromycin (June 2006). Isolated reports of ASLI, including ALF requiring transplantation or with fatal outcome have also been received, most recently in the US. In the vast majority of these cases, when the relevant information was available, it was not possible to establish a causal relationship between the ALF and the administration of telithromycin; the cases being confounded by an underlying disease involving the liver, sepsis, severe circulatory failure, or cardiac failure. The stimulated reporting of hepatic AEs primarily coming from the US in the wake of the Annals of Internal Medicine communication in early 2006, combined with Weber effect and secular trend biases for a new drug, distort assessment of comparative reporting rates of hepatic events for telithromycin vs. other antibiotics, and obscure the relative positioning of this drug with respect to others used in the treatment of RTIs. For this reason, sanofi-aventis has performed 2 epidemiologic studies to investigate the comparative risk for hepatic events. Unlike disproportional analysis methods dependent upon spontaneous reports subject to the biases noted above and with incomplete numerators and grossly estimated denominators, these studies evaluate the association between telithromycin use and severe hepatic injury based on systematic datasets that have complete capture of severe hepatic injury events in a well-defined population. Based on the review of currently available clinical and epidemiologic data, including the 2 epidemiologic studies performed in the PHARMetrics and Ingenix databases, there is no evidence that the risk of hepatotoxicity with telithromycin is more frequent or more severe than that with other marketed antibiotics used in the treatment of RTIs, including macrolides.

A small dose-related effect on cardiac repolarization was observed during the clinical development program. Since initial marketed product launch in the EU in October 2001, isolated reports of torsades de pointes or ventricular fibrillation have been received, however all either lack information to establish the diagnosis, are confounded by the coadministration of other medications known to affect cardiac repolarization, or occur in patients with significant underlying cardiac disease or concurrent illness which may otherwise explain the event onset. The overall risk profile remains consistent with the pre-approval cardiovascular risk assessment.

Most reports of visual AEs describe mild and transient visual blurring, diplopia, and difficulty in focusing. Several analyses have focused on characterization of the visual events through detailed data gathering methods applied to the spontaneous reports. The most recent cumulative analysis has confirmed the prior overall characterization of visual events from clinical trials, with event onset typically within the first few doses, with short duration of several hours, and is reversible. Postmarketing surveillance has also identified isolated reports of transient blindness or amaurosis. Most of these cases were either not confirmed as loss of vision because the patients described some visual functioning on follow-up questioning (events appeared more consistent with severe blurred vision) or other causes appeared as the more likely cause of the events than the treatment with telithromycin (eg, temporal arteritis). None of these isolated reports had an ophthalmology examination performed at the time of the event that confirmed the reported transient vision loss. With the exception of the temporal arteritis case, all of these events were fully reversible.

To further elucidate the safety profile of telithromycin, analyses from the FDA Freedom Of Information (FOI) database were performed for telithromycin as well as for other oral antibiotics typically used to treat community-acquired respiratory tract infections (β-lactams, macrolides, and fluoroquinolones). These analyses demonstrate the characteristic safety profile of telithromycin showing signals of hepatic AEs, visual AEs, and exacerbation of myasthenia gravis. Since characteristic safety profiles of drugs are unique, other marketed antibiotics show different signals (eg, pseudomembranous colitis, anaphylactic reactions, tendon rupture), which are not signals for telithromycin.

The results from these signal generation methods should be interpreted with caution because the spontaneous reports of AEs are subject to multiple biases, including stimulated reporting, incomplete unverified data, secular trends in reporting, and the Weber effect.

8 CONCLUSIONS OF BENEFIT/RISK ASSESSMENT

Telithromycin is active against *S. pneumoniae*, including strains with various mechanisms of antibiotic resistance (eg, multidrug-resistant *S. pneumoniae*) and an antibacterial spectrum specifically targeted to respiratory tract infection pathogens. Both features are of particular importance in the context of bacterial resistance. Several US regions have reached significant levels of *S. pneumoniae* resistance, with a growing number of strains that are highly resistant to numerous antibiotics. In addition, resistance of non-respiratory pathogens has been favored by the use of antibiotics with a broader spectrum of activity and maybe associated with difficult-to-treat infections of high morbidity and mortality.

Clinical trials in community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute bacterial sinusitis have consistently demonstrated the clinical efficacy of telithromycin. A short treatment duration of 5 days is effective for the treatment of patients with acute exacerbation of chronic bronchitis and acute bacterial sinusitis. A 7- to 10-day treatment period is effective for the treatment of community-acquired pneumonia. The short treatment duration of 5 days may enhance compliance and further reduce development of resistance.

Overall, the risks associated with telithromycin appear to be comparable to those of other marketed antibiotics prescribed for the treatment of community-acquired respiratory-tract infections, including β-lactams, macrolides, and fluoroquinolones. Each antibiotic has a different benefit/risk profile. By understanding the attendant benefits and the risks, healthcare professionals are better able to choose the appropriate treatment based on the infection, local resistance pattern, patient history, and concomitant medications. Therefore, telithromycin is an important therapeutic option for its approved indications in the treatment of community-acquired respiratory tract infections.

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